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Research

Formulation And Evaluation Of Ondansetron Hcl Transdermal Patch

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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.

INTRODUCTION

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 term controlled release has a meaning that goes beyond scope of sustained release. The release of drug ingredients from a controlled release drug delivery advances at a rate profile that is not only predictable kinetically, but also reproducible from one unit to other[1].the difference between sustained release and controlled release is shown by Fig.1.

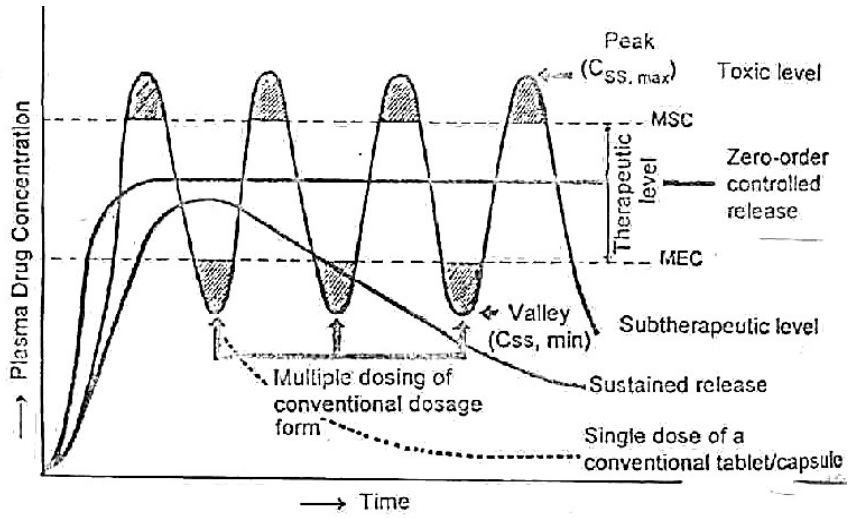

Fig 1: Comparative graphs of conventional, sustained- and controlled release delivery systems

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.

1.1 Transdermal drug delivery: An Introduction

The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation.

Until recently, the use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen.

Definition

Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness. The Transdermal device is a membrane-moderated system. The membrane in this system is a microporous polypropylene film. The drug reservoir is a solution of the drug in a mixture of mineral oil and polyisobutylene. This study release is maintained over a one-day period. Non-medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists of two major sub-categories — therapeutic and cosmetic), aroma patches, and weight loss patches, and patches that measure sunlight exposure. Transdermal drug delivery has many advantages over conventional drug delivery and can be discussed as follows.

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

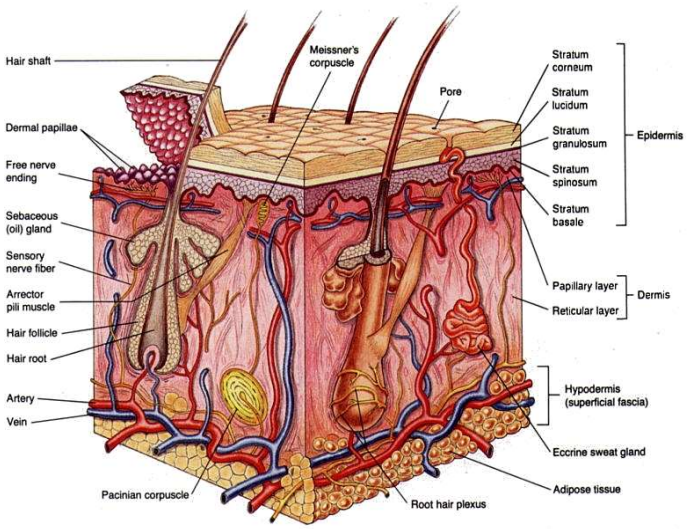

Fig 2: Structure of skin

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.

The Epidermis

The outer (epidermal) layer of the skin is composed of stratified squamus epithelial cells. The multilayered envelope of the epidermis varies in thickness, depending on cell size and then number of cells and then number of cell layers, ranging from about 0.8mm on the palms and the soles down to 0.66mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs provide epithelial tissue differ from those of all other organs in that as they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein.

Stratum germinativum (basal layer)

The basal cells are nucleated, columnar, and about 6 microns wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges. Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit. The junction serves three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction.

Stratum spinosum (prickle cell layer)

As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. These polygonal cells are called as prickle cells because they interconnect by fine prickles.

Stratum granulosum (granular layer)

As the Keratinocytes approach the surface, they manufacture basic staining particles, the keratohyalin granules. It was suggested that these granules represent an early form of keratin 3, 4. The term transitional zone is convenient region between living cells and dead keratin.

Stratum lucidum

In the palms and the soles an anatomically distinct, poorly staining hyaline zone forms a thin, translucent layer immediately above layer immediately above the granular layer. This region is the stratum lucidum.

Stratum corneum (horny layer)

As the final stage of differentiation, epidermal cells construct the most the superficial layer of the epidermis, the stratum corneum. On general body areas the membrane provides 10-15 layers of much flattened, keratinized dead cells (corneocytes). Ultimately these cells are sloughed off through desquamation. A keratinocyte's journey from basal layer to horny layer takes about 14 days. The cell travels through the layers of stratum corneum for another 14 days before it is finally shed. So the normal turnover rate of the epidermis is atleast 28 days. The stratum corneum plays a crucial role in controlling the percutaneous absorption of drug molecules.

The barrier nature of stratum corneum depends critically on its unique constituents; 75-80% is protein, 5-15% is lipid with 5-10% unidentified on a dry weight basis. The protein is located primarily within the keratinocytes and is predominantly alpha-keratin (around 70%) with some beta-keratin (approximately 10%) and a proteinaceous cell enveloping (around 5%). Enzymes and other proteins account for approximately 15% of the protein component. The cell envelop protein is highly insoluble and is very resistant to chemical attack. This outer keratinocytes protein has a key role in structuring and ordering the intercellular lipid lamella of the stratum corneum; the keratinocytes is bound to a lipid envelop through glutamate moieties of the protein envelop. The lipid envelop thus provides an anchor to the keratinocytes and links the proteinaceous domains of the keratinocytes to the intercellular lipid domains. Human stratum corneum is a unique mixture of lipids and, for most permeates; the continuous multiply bilayered lipid component of the stratum corneum is key component in regulating drug flux through the tissue. It is clear that the lipid content of the stratum corneum varies between individuals and with body site, but major components of the domain include ceramides, fatty acids, cholesterol, and cholesterol sulfate and sterol/wax esters.

MATERIALS

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.

METHODOLOGY

Analytical method development

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.

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.

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.

Preformulation study

Colour, Odour, Taste and Appearance

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

Melting point determination

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

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.

Formulation of transdermal patches

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.

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. the formulation table is given in table no. 6.3.

Table 1: 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**

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.

Analysis of drug

UV scan

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

Construction of calibration curve

Table 2: 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

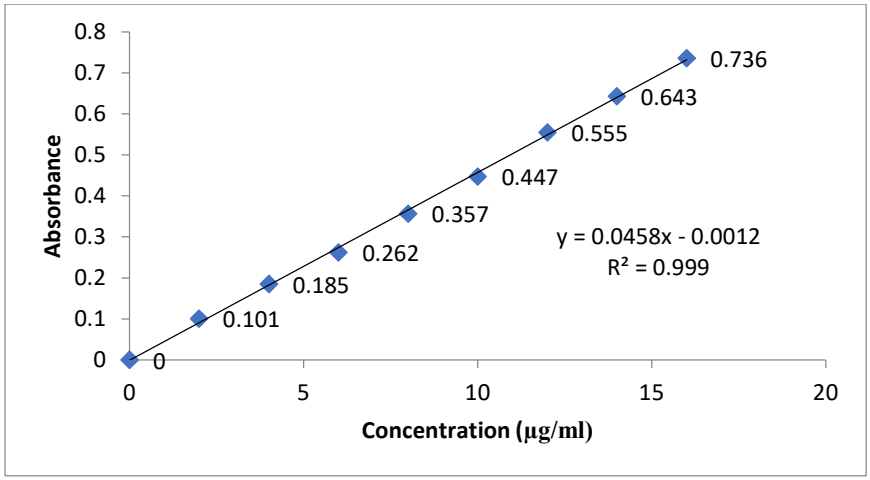

Fig 3: Standard calibration curve of ondesartan hydrochloride

Compatibility studies

IR Spectroscopy

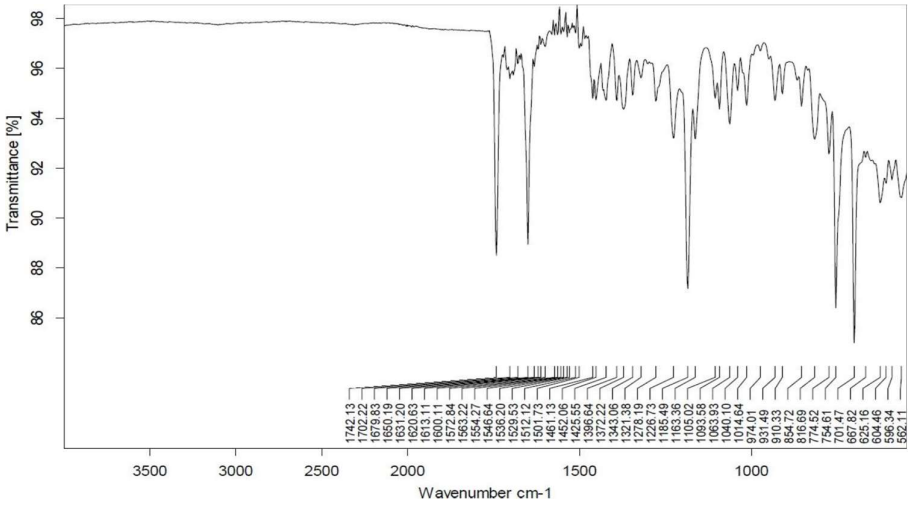

Fig 4: FTIR Spectrum of pure Ondesartan hydrochloride drug

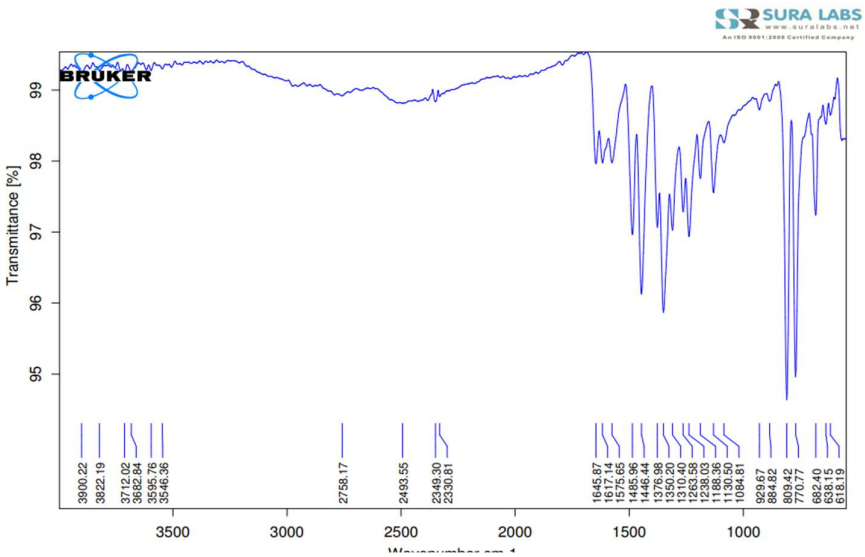

Fig 5: FTIR of Optimized formulation

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

Preformulation study

Totally, Eleven formulation trials (OND-1 to OND-6) were done with the aim to achieve the successful matrix type Ondesartan hydrochloride transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

Colour, odour, taste and appearance

Table 3: Results of identification tests of drug

Parameter	Ondansetron hydrochloride
Color	white
Odor	odorless
Taste	bitter
Appearance	A whity powder

Melting point determination

Table 4: Results of melting point determination tests of drug

Drug	Reported melting point
Ondansetron hydrochloride	178.5 ^{0}c to 179.5 ^{0}c

Determination of solubility

Table 5: Solubility Determination

solvent	Drug solubility(mg/ml)
Distilled water	55.03
Ph 7.4 phosphate buffer	78.3

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 6: 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

***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 ºC. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table 7: *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

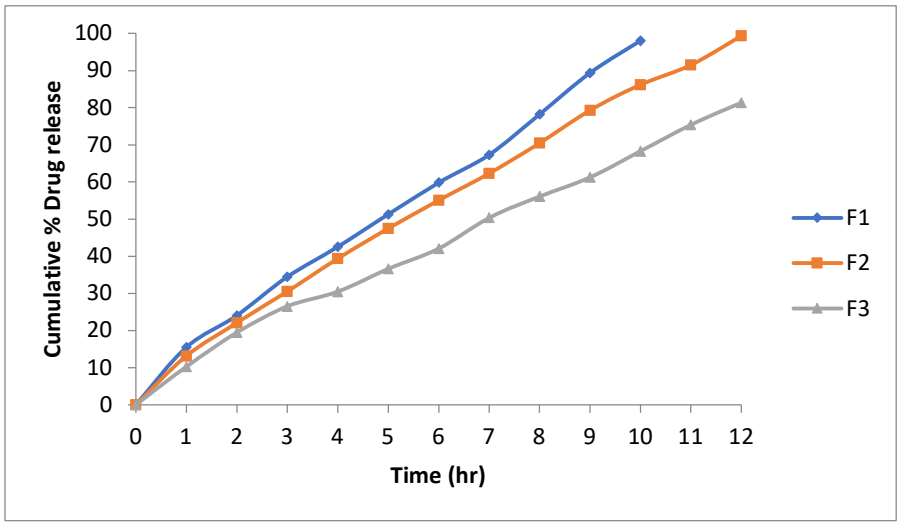

Fig 6: Cumulative % drug permeation of ondansetron hcl patch (F1, F2 and F3)

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 8: *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

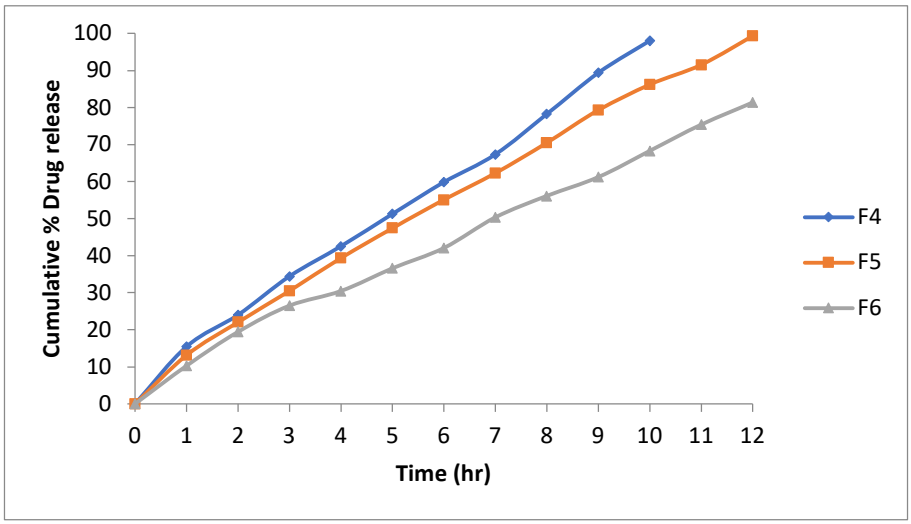

Fig 7: Cumulative % drug permeation of ondansetron HCL patch (F4, F5 and F6)

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 9: *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

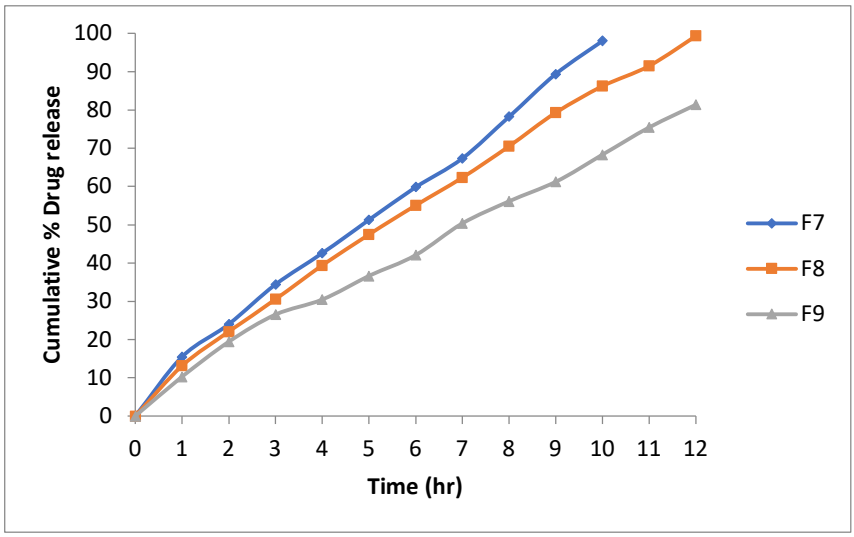

Fig 8: Cumulative % drug permeation of ondansetron hcl patch (F7, F8 and F9)

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.

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 10: 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

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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