Archives of Pharmaceutical Sciences and Research E-ISSN 0975-2633 | PRINT ISSN 0975-5284
Vol 14 Issue 4 0032 – 045 December 2024 Research Article

DEVELOPMENT AND OPTIMIZATION OF ONDANSETRON TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Ondansetron delivery through oral route suffers low bioavailability due to first-pass metabolism. Several disadvantages with oral, intravenous and rectal administration include extensive liver metabolism, low bioavailability, vomiting before drug absorption, rapid onset that may result in undesirable side effects, and high clearance. Therefore, the objective of the present study was to optimize ondansetron transdermal patch formulation. Ondansetron transdermal patches is prepared by solvent casting method. The DOE was to optimize the critical process parameters to achieve desired Folding endurance, Thickness, drug release at 12 hours. Box Behnken quadratic design was selected to carry out with 13 experimental runs for the formulation of transdermal patch. The analysis was performed actual v/s predicted and optimization were conducted in quadratic model.

Key Words: Ondansetron, Transdermal Drug Delivery System, Box Behnken Design

INTRODUCTION

During the past few years, interest in the development of novel drug delivery systems for existing drug molecules has been renewed. The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent. Currently transdermal delivery is one of the most promising methods for drug application[1].

TDD is a painless way of systemically administering medications by putting a drug formulation on unbroken and healthy skin. The drug goes through the stratum corneum first, then into the deeper epidermis and dermis, without accumulating in the dermal layer. The medication is available for systemic absorption once it reaches the dermal layer. It can be used as a non-invasive alternative to parenteral methods, avoiding injection fear[2].

Some of the advantages associated with TDD are as follows:

(a) Avoidance of hepatic first-pass metabolism and other gastrointestinal tract issues such as presence of food and pH changes

(b) Sustained and controlled release over a long period of time

(c) Reduction of adverse effects or therapeutic failures associated with intermittent dosing

(d) Improved patient compliance because it is a convenient and painless administration route[3].

TDDS has become one of the most widely investigated routes of non-invasive drug delivery into the body through the skin, unlike conventionally used direct ad- ministration routes that make use of needle-based injections. TDDS has significantly influenced the delivery of various therapeutic agents, especially in pain management , hormonal therapy, and treatment of diseases of the cardiovascular and central nervous systems[4].

Skin is the most accessible and largest organ of the body with a surface area of 1.7 m^2, compromising 16% of the total body mass of an average person. The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the permeation of ultraviolet (UV) radiation, chemicals, allergens and the loss of water. Skin can be divided into three main regions: the outermost layer, the epidermis, which contains the stratum corneum; the middle layer, the dermis and the inner most layer, the hypodermis[5].

When a transdermal patch is applied to the human skin, it may retain the drug or active substance on the surface of the skin, without any absorption, e.g., in the case of cosmetics and antiseptics or it may allow the drug permeation through the skin into the deeper regions i.e., dermis and the epidermis. These formulations are also called dia dermal or endodermal formulations. The third enviable function is to have the drug absorbed systemically[6].

The skin covers a surface area of approximately 2 sq.m of the human body. It serves as a permeability barrier against the absorption of various chemical and biological agents by transdermal.

Drugs have been applied to the skin to treat superficial disorders, for the transdermal

administration of therapeutics to manage systemic ailments and as cosmetics, dating back to the oldest existing medical records of man. For instance, the use of salves, ointments, potions and even patches, consisting of plant, animal or mineral extracts, was already popular in ancient Egypt and in Babylonian medicine (around 3000 BC). However, the routine use of transdermal delivery systems only became a common practice in the latter third of the 20th century when delivery technology was developed to enable precise and reproducible administration through the skin for systemic effects[7].

Various non-invasive administrations have recently emerged as an alternative to conventional needle injections. A transdermal drug delivery system (TDDS) represents the most attractive method among these because of its low rejection rate, excellent ease of administration, and superb convenience and persistence among patients. TDDS could be applicable in not only pharmaceuticals but also in the skin care industry, including cosmetics. Because this method mainly involves local administration, it can prevent local build up in drug concentration and nonspecific delivery to tissues not targeted by the drug. However, the physicochemical properties of the skin translate to multiple obstacles and restrictions in transdermal delivery, with numerous investigations conducted to overcome these bottlenecks[8].

The skin forms an attractive and accessible route of delivery for systemic drugs because of the problems associated with other methods of administration, such as oral and parenteral. However, few drugs are able to passively diffuse across the uppermost layer of the skin, the stratum corneum, as a result of its effective barrier properties. The stratum corneum, or horny layer, consists of flat, roughly hexagonally shaped, partly overlapping cells, with a thickness of approximately 0.3 µm and a diameter of approximately 30 µm. Exposure to moisture predominantly results in the swelling of the corneocytes in the vertical direction. The cells are composed mainly of insoluble bundled-keratins, surrounded by a cell envelope stabilized through covalently bound lipid and cross-linked proteins[9].

Directly below the stratum corneum is the viable epidermis, which consists of three layers: the stratum granulosum, spinosum and Basale. The viable epidermis contains keratinocytes at varying stages of differentiation, as well as melanocytes, Langerhans cells (important for antigen presentation and immune response), and Merkel cells (involved in sensory perception). The dermal–epidermal junction is not flat, and distinct papillae or rete pegs can be observed using light microscopy. This layer facilitates the diffusion of, for example, xenobiotics and decreases in surface area with age. The dermal–epidermal junction is also thought to play a role in the permeation of large molecular weight proteins and peptides[10].

Anatomy of skin

The human skin consists of mainly three layers: Epidermis, Dermis, Hypodermis and Epidermis:

The epidermis is a self-renewing, stratified squamous epithelium covering the entire outer surface of the body. Epidermis mainly composed of two parts: the living or viable cells of the Malpighian layer (viable epidermis) and the dead cells of the stratum corneum commonly known as the horny layer. The viable epidermis is divided into four distinct layers such as Stratum lucidum, Stratum granulosum, Stratum spinosum, and Stratum Basale. Stratum corneum is the outermost layer of skin also called a horny layer. Stratum corneum is a barrier that restricts the inward and outward movement of chemical substances[11].

Dermis:

The dermis is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of connective tissues, which contains blood vessels, lymph vessels, and nerves

Hypodermis:

The hypodermis or subcutaneous tissue supports the dermis and epidermis. It serves as a storage area for fat. Hypodermis layer helps to regulate temperature, provides nutritional support and mechanical protection [12].

Permeation enhancers in Transdermal drug delivery

The permeation pathways into the stratum corneum:

The drug molecules in the formulation that are in contact with skin will partition into the stratum corneum, while other drug molecules in the formulation will redistribute to take their place. The partitioning will be favourable for a lipophilic molecule from a hydrophilic

formulation. The drug redistribution in the formulation will depend, for example, on its viscosity. In formulations containing drug particles, drug dissolution will also affect these initial stages of the drug delivery process [13].

Through the stratum corneum

For most molecules, traversing the stratum corneum is the most difficult step that limits the rate of the permeation process.

There are three possible pathways to get past the stratum corneum: The intercellular (paracellular) pathway, Transcellular (intracellular) pathway, Trans appendageal (shunt) pathway

The intercellular pathway leads around corneocytes through the lipid matrix. Although the extracellular lipid phase is far from being homogenous, it is the only continuous phase in the stratum corneum. Thus, the lipid route is the principal pathway through the stratum corneum for most small-molecular drugs despite the pathlength is considerably greater than the stratum corneum thickness[14].

Another possibility to cross the stratum corneum is to take the transcellular route. Although shorter than the lipid route, this pathway involves several various environments, including the hydrated keratin-filled cell interior, the highly cross-linked protein cell envelope, covalent lipid monolayer at the corneocyte surface (the lipid envelope), and the free intercellular lipids. Most molecules do not prefer to cross the stratum corneum by this process that involves multiple partitioning- diffusion steps through hydrophilic and lipophilic domains[15].

Mechanism of drug permeation and permeation enhancer.

Skin is the outermost covering of the body, primarily functions as protective layer which protects the individual from the harmful ex-ternal stimuli like light, temperature, radiation, etc. and restrict the entry of pathogen or any other foreign material inside. The attribute of skin makes the topical or transdermal drug delivery very difficult. Hence, to improve the drug permeation across the skin and enhance the percutaneous absorption various novel strategies have been adapted including the vehicle system, permeation enhancer, novel drug carrier system, transdermal patches, etc. All these strategies enhance the drug permeation by temporary destructing the stratum corneum layer[16 17].

As per this theory, the drug permeation across skin, mainly depends on

1) drug interaction with intercellular lipid bilayer. 2) interaction with the keratinized cells 3) the interaction of excess of co-solvent or penetration enhancer with the lipid bilayer of the stratum corneum[18].

Drug Penetration Routes

There are two possible routes of drug penetration across the intact skin, namely the trans epidermal and trans appendageal pathways[19].

The trans epidermal pathway involves the passage of molecules through the stratum corneum, an architecturally diverse, multi-layered and multi-cellular barrier. Trans epidermal penetration can be termed intra- or intercellular. The intra-cellular route through corneocytes, terminally differentiated keratinocytes, allows the transport of hydrophilic or polar solutes. Transport via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continuous lipid matrix. The transappendegeal route involves the passage of molecules through sweat glands and across the hair follicles [20].

Preformulation: Preformulation is a group of studies that focus on the physicochemical properties of a drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drugs combination with pharmaceutical ingredients in the fabrication of dosage form[21].

Melting point determination: Melting point of drug was determined by taking a small amount of drug in a capillary tube closed at one end and was placed in melting point apparatus and temperature at which the drug melts was noted[22].

Determination of solubility: The solubility of ondansetron was determined using pH 7.4 phosphate buffer. The solubility of the active pharmaceutical ingredients (API) was resolute by the equilibrium solubility method. Which employ up to the saturation of a solution to obtain by stirring an excessive of API need to add in the medium until equilibrium is achieved. After equilibrating, the solution was kept in shaker

water bath (37 ± 1°C) up to 24 h for maximum solubility of the drug. After that, the samples were removed from shaker bath and filtered with 0.22 µm nylon non-pyrogenic disposable syringe filter. Finally, the filtered solution was diluted and estimated using ultraviolet (UV)- visible spectrophotometer[23].

FTIR: Excipients are integral components of almost all pharmaceutical dosage forms. To investigate any possible interaction between the drug and utilized excipient (Ethyl cellulose, poly vinyl pyrrolidine and methanol etc.) IR spectrum of pure drug (Ondansetron) and its physical mixture were carried by using FTIR.

Standard Calibration Curve

Stock solution: For the determination of absorption maxima stock solution was prepared by dissolving 100mg of accurately weighed Ondansetron in 100ml of methanol to get 1mg/ml solution. Further 10ml of this solution was pipetted into 100ml of volumetric flask and diluted to 100ml with phosphate buffer 7.4 to get 100µg/ml solution. This stock solution was subjected for UV scanning in the range of 200-800 using Double beam UV-VIS spectrophotometer, the absorption maxima obtained at 216 with a characteristic peak.

From the above stock solution pipette out 2,4,6,8,10 into a series of 10ml volumetric flask and was made up to 10ml with phosphate buffer pH 7.4 to get 20,40,60,80,100µg/ml of Ondansetron respectively. The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 216 nm. A calibration curve was plotted by taking concentration of the solution in µg/ml on X-axis and absorbance on Y-axis and correlation co-efficient "r2" was calculated[24].

Preparation of ondansetron transdermal patches using solvent casting method:

The ondansetron transdermal patches are prepared using solvent casting method whereby the water-soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and finally casted in to the Petri plate and dried, which is then cut into pieces of the desired size.

For the preparation of the patches, 300 -400 mg of Ethyl Cellulose dissolved in 5 ml methanol followed by the addition of 100-120 mg PVP with uniform but slow magnetic stirring. Then the plasticizer (PG, DBP in acetone, 30% of the total polymer weight) and 80-100mg of the drug were added to the solution and stirred for 15-20 min. Next the total mass was slowly poured into the centre of SS rings having a backing layer of aluminium foil. The total mass was dried at room temperature for 48 hrs. The dried patches were kept in scaled and stored in desiccators until use. The final step, drying the film, removes the solvent and helps to obtain the finished product. Usually, glass, plastic, or Teflon plates are used as an inert base for film casting. When the manufacturing technology is transferred from laboratory scale to production scale, several problems can be encountered. These problems can include the casting of the film, obtaining uniform thickness of the film, and proper drying of the sample. The selection of the proper type of dryer is needed in the final step of drying. Once the films are dried, cutting, stripping, and packaging is done. Suitable size and shapes of films can be cut. The commonly available sizes of films are 3 x 2 cm2 and 2 x 2 cm^2 [25].

EVALUATION

Weight Variation: All the transdermal patches were visually inspected for colour, clarity, flexibility & smoothness.

Thickness: Thickness of the patches was assessed at 3 different points using digital micrometer. For each formulation, three randomly selected patches were used[26].

Physical Appearance: Three disks of 2x2 cm were 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.

Folding Endurance: The folding endurance of the prepared patch was measured manually. A strip of the film (4x3 cm) was cut evenly and repeatedly folded at the same place till it was broken. The thinner the patch more flexible it is[27].

In-vitro diffusion drug release: In vitro release studies were carried out using Franz diffusion cell whereby a piece of the circular patches was mounted over the donor compartment. The backing membrane side of the patch was exposed to the atmosphere while the receptor compartment was filled with freshly prepared phosphate buffered saline (pH 7.4). Temperature was maintained at 32°C by circulating water through the water jacket and stirring at 40 – 50

rpm. The patch was in contact with the receptor liquid surface. Samples (0.5 mL) were withdrawn at 1 h interval for 12 hours and immediately replaced with the same volume of medium. Each sample was filtered, diluted suitably and analysed spectrophotometrically at 216 nm. [28, 29]

Release kinetics: The results of in vitro release profiles obtained for formulations were fitted into models of data treatment as follows**.**

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer Peppa's equation).

1.Zero Order Kinetics: A zero-order releases would be predicted by the following equation[67].

At = A0 – K0t

Where: At = Drug release at time 't'

A0 = Initial drug concentration

K0 = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K0.

2.First Order Kinetics: A first-order release would be predicted by the following equation

Log C = Log C0 – 303.2Kt

Where: C = Amount of drug remained at time 't'

C0= Initial amount of drug.

K = First-order rate constant (hr).

When the data are plotted as a log of percent cumulative drug release remaining versus time yields a straight line, indicating that the release follows First-order kinetics.

The constant 'K' can be obtained by multiplying 2.303 with slope values.

3.Higuchi's Model: Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

Q = A [D (2C - Cs) Cs t] 1/2

Where, Q = Amount of drug released at time 't'

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

CS = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which 'Q' amount of drug is released

simplified equation if one assumes that D, CS and A are constant. Then equation becomes:

Q = Kt½

4.Korsmeyer and Peppas Model: The release rates from controlled release polymeric matrices can be described by the equation

n Q = K1t

Q is the percentage of drug released at time 't'

K is a kinetic constant incorporating structural and geometric characteristics

'n' is the diffusional exponent indicative of the release mechanism[29].

Stability studies: A stability study was performed as per ICH guidelines to observe the stability of optimized formulation F13 ondansetron transdermal patch[30].

RESULTS

Melting point determination: Melting point allows identification of unknown sample by comparing known compound. The obtained average melting point was 231.40°C.

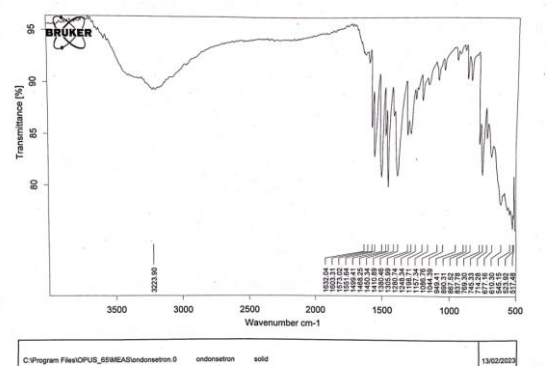
Solubility studies

Solubility studies of Ondansetron was carried on Distilled water found to be 62.03 ± 3.35 and ondansetron with buffer pH 7.4 is 82.14±1.49.

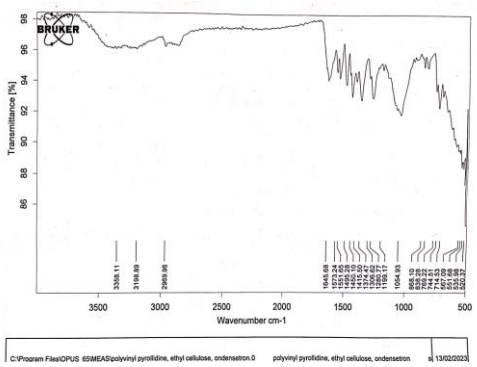
Compatibility studies:

FT-IR analysis:

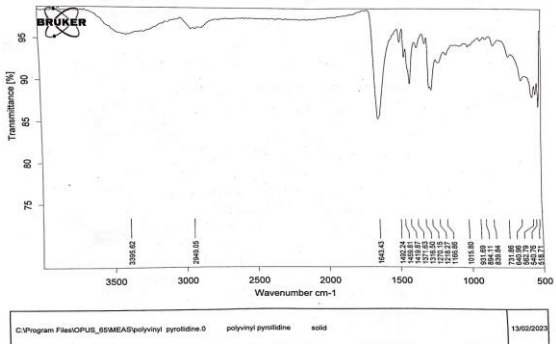
Drug polymer and crosslinking agent compatibility studies were carried out using IR (FTIR) to check the possible interaction of the drug and excipients in the Ondansetron having Characteristics peaks in the region of which were found to be observed in combination of drug and excipients which were identical to that of pure drug.



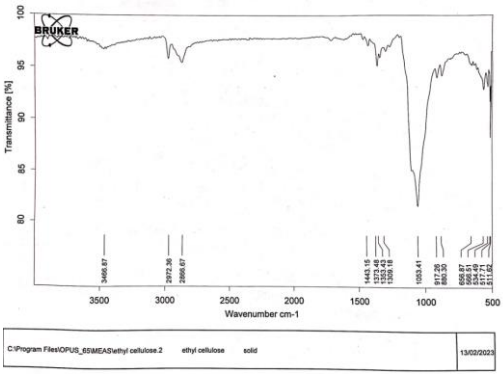
FTIR Pure drug ondansetron



FTIR Spectrum of pure drug ondansetron with ethyl cellulose and PVP



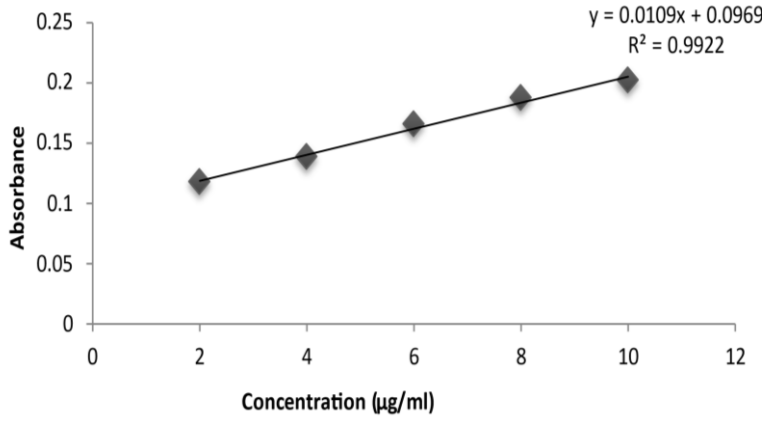
FTIR spectrum of pure drug with polyvinyl pyrrolidine



FTIR Spectrum of pure drug ethyl cellulose

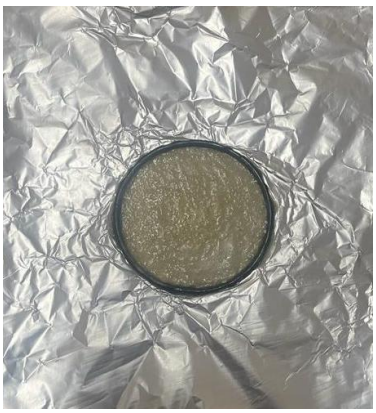
Concentration (µg/mL)	Absorbance
20	0.118
40	0.138
60	0.165
80	0.187
100	0.202

Standard calibration of Pure Drug Ondansetron with pH 7.4



Standard calibration graph of Ondansetron with pH 7.4

The standard curve for ondansetron was obtained by measuring absorbance at 216 nm by plotting graph of absorbance versus concentration for 20, 40, 60, 80, 100 µg/mL ranges. The regression equation generated y = 0.0109+ 0.0969 and R^2 = 0.9922.



The Ondansetron transdermal patches are prepared using solvent casting method

Formulation Code	Ondansetron	Drug-Polymer	PVP	Ethyl Cellulose	Solvent
	mg	mg	mg	mg	ml
1	20	30	15	30	10
2	20	50	20	40	10
3	20	40	10	30	10
4	20	30	10	40	10
5	20	30	20	40	10
6	20	40	15	40	10
7	20	40	20	50	10
8	20	50	15	50	10
9	20	40	10	50	10
10	20	50	15	30	10
11	20	30	15	50	10
12	20	50	10	40	10
13	20	40	20	30	10

Preparation of ondansetron transdermal patch

Response	Source	Sum of Squares	df	Mean Square	F-value	p-value	
1: Folding endurance	**Model**	57.58	3	19.19	35.47	< 0.0001	significant
2: Thickness	**Model**	0.0004	3	0.0001	8.97	0.0046	significant
3: Drug release	**Model**	114.55	3	38.18	20.31	0.0002	significant

Optimization of Ondansetron transdermal patch

Factor Coding: Actual

Folding Edurance (%)

Design Points:

Above Surface

Below Surface

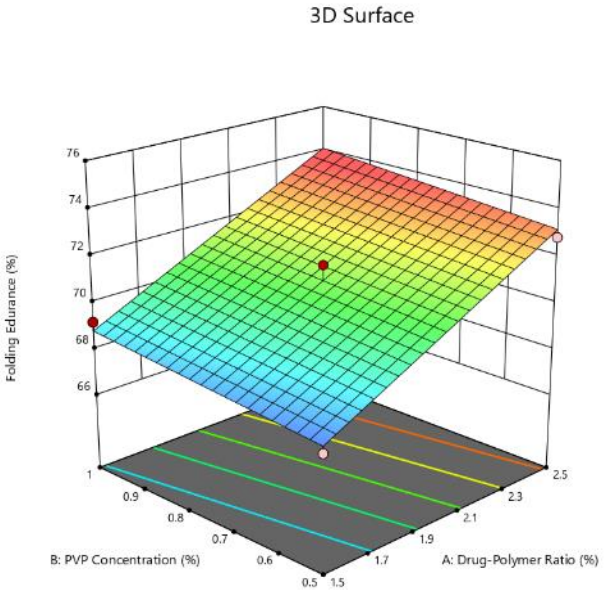
67.42 73.68

X1 = A

X2 = B

Actual Factor

C = 2



Factor Coding: Actual

Thickness (Micrometer)

Design Points:

Above Surface

Below Surface

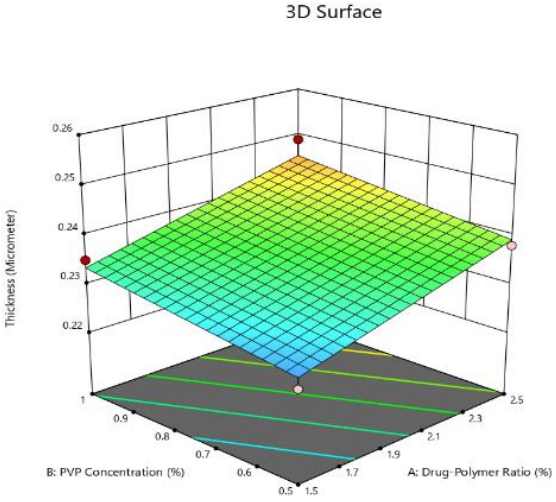
0.224 0.249

X1 = A

X2 = B

Actual Factor

C = 2



Factor Coding: Actual

Drug Release

Design Points:

Above Surface

Below Surface

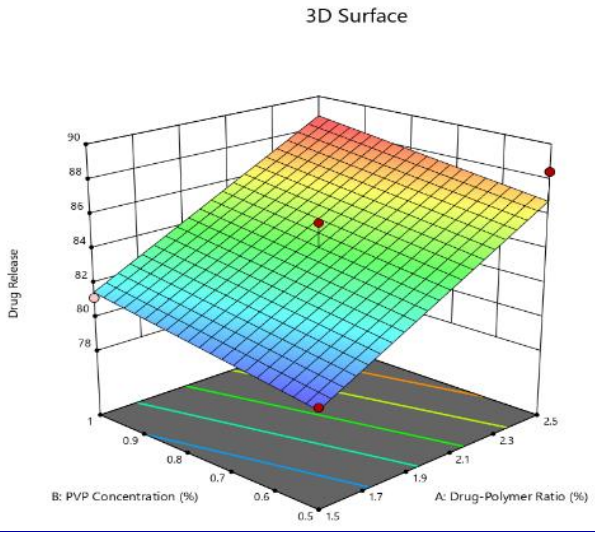
79.64 88.45

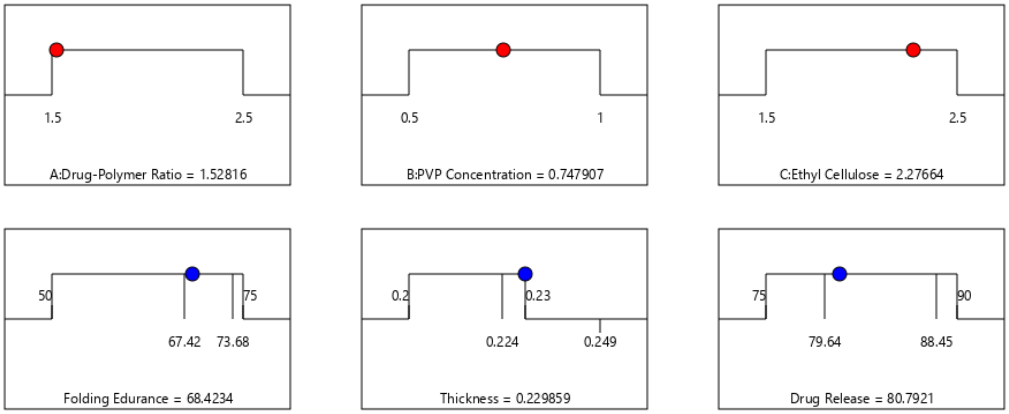
X1 = A

X2 = B

Actual Factor

C = 2





Numerical optimized ramp profile graph of Transdermal patch containing Drug polymer ratio, PVP concentration, Ethyl cellulose

OPTIMIZED FORMULATION: Optimization formulation of ondansetron transdermal patch

The optimization of Ondansetron transdermal patches was done by Boxbehnken design Quadratic model, 12.0.1.0 version of optimization was used. Drug polymer ratio%, PVP concentration %, Ethyl cellulose% were considered as variable, Folding endurance, thickness, Drug release at 12 hr were used as Responses for formulation design. From the optimization, the desirability of different variables was produced, and thus optimized formula was obtained. The optimized formula shows a particular percent combination of formulation design F14.

INGREDIANTS	AMOUNT
Drug polymer ratio	**1.52 %**
PVP concentration	**0.747 %**
Ethyl cellulose	**2.27 %**

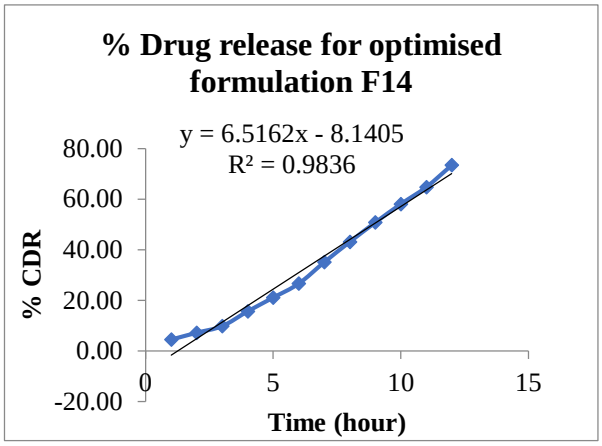
Optimised Formulation F14

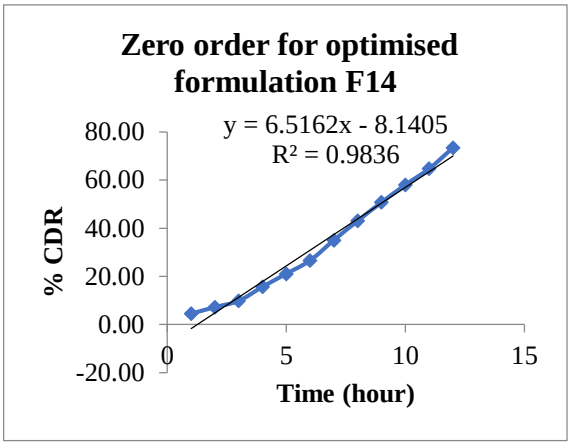
Formulation code	Folding endurance	Thickness	Drug release
F14	**68.42**	**0.22mm**	**77.49%**

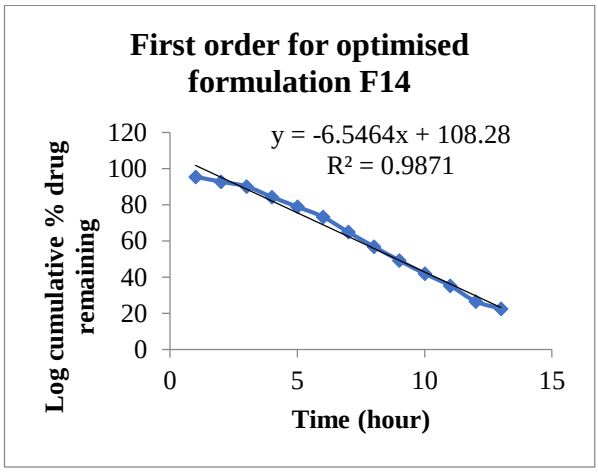
Physicochemical evaluation of optimized formulation F14 of ondansetron transdermal patch

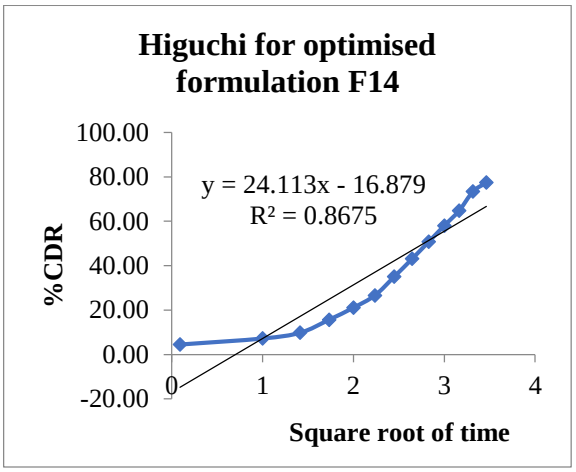
Time (hours)	Drug release	Time (hours)	Drug release
30 min	4.55	7	43.13
1	7.26	8	50.82
2	9.86	9	58.08
3	15.71	10	64.80
4	21.13	11	73.47
5	26.65	12	77.49
6	35.11		

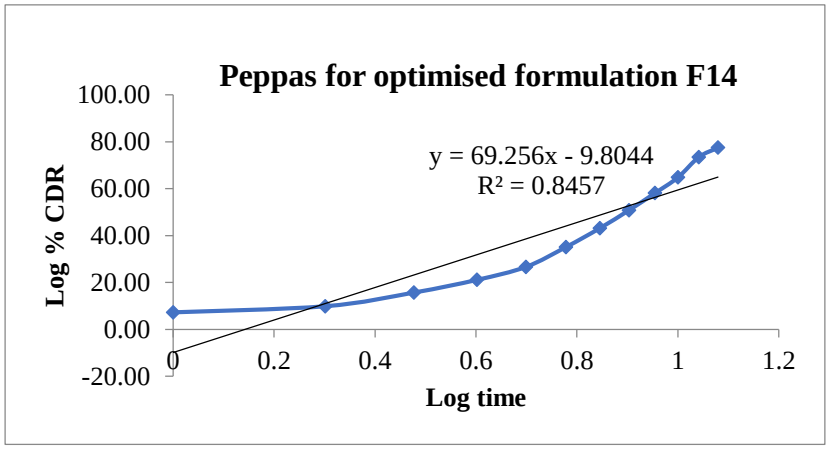
Invitro Drug release studies of optimized formulation F14 Ondansetron Transdermal patch











Optimized formula	Folding endurance(%)	Thickness(mm)	Drug release
Predicted	68.42	0.22	80.79%
Experimental	71.02	0.23	77.49%

Comparison between the experimental (E) and predicted (P) Values for the Optimized Formulation F14 ondansetron transdermal patch

Formulations	Weight	Weight variation	Percentage
F1	780mg	10.1	101.3%
F2	764mg	-5.9	99.2%
F3	765mg	-4.9	99.3%
F4	772mg	2.1	100.2%
F5	777mg	7.1	100.9%
F6	771mg	1.1	100%
F7	766mg	-3.9	99.4%
F8	762mg	-7.9	98.9%
F9	760mg	-9.9	98.7%
F10	774mg	4.1	100.5%
F11	779mg	9.1	101.1%
F12	770mg	0.1	100%
F13	769mg	-0.9	99.8%

Weight variation of ondansetron transdermal patch F1 -F13

The Transdermal patches of each formulation were weighed subjected to weight variation test, difference in weight of each patch were calculated. The average weight of Transdermal patch is approximately 780 mg.

Formulations	Thickness (mm)
F1	0.238
F2	0.249
F3	0.235
F4	0.225
F5	0.235
F6	0.236
F7	0.238
F8	0.242
F9	0.235
F10	0.241
F11	0.224
F12	0.238
F13	0.236

Thickness of ondansetron patches of F1-F13

The transdermal patches of each formulation are assessed using digital micrometer. The optimized formulation F14 shows maximum 0.22 mm. The maximum thickness showed by F2 0.24mm. This indicates that the patches were uniform and reproducible

Formulations	Physical appearance
F1	Dry, Brittle
F2	Dry, moist sticky
F3	Dry, moist sticky
F4	Translucent
F5	Dry, Brittle
F6	Transparent

F7	Dry, moist sticky
F8	Dry, moist sticky
F9	Dry, moist sticky
F10	Dry, moist sticky
F11	Dry, moist sticky
F12	Dry, moist sticky
F13	Dry, moist sticky

Physical appearance of ondansetron patches of F1-F13

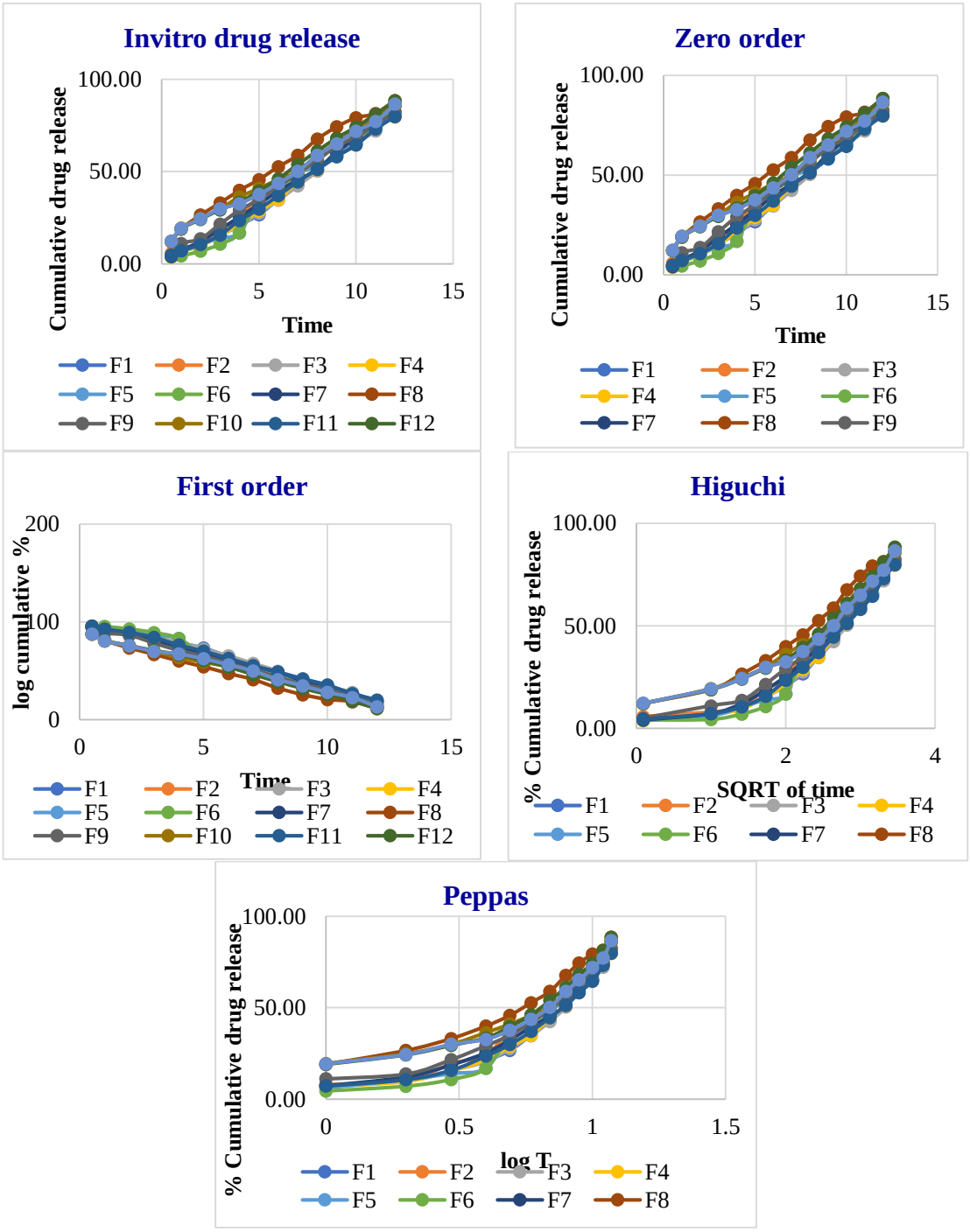
Formulations	Folding Endurance %
F1	67.42
F2	73.43
F3	71.27
F4	67.58
F5	69.19
F6	71.65
F7	71.88
F8	72.92
F9	71.25
F10	73.68
F11	67.54
F12	72.82
F13	72.13

Folding endurance of ondansetron patches of F1-F13

The recorded folding endurance of the films was maximum 72.82 % for F12 minimum for F1 67.42%. The folding endurance of optimized formulation F14 is 68.42 %. It means all formulations had good film properties.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0.5	4.55	5.85	4.44	3.68	4.12	4.12	4.11	12.13	4.98	12.13	4.55	12.24	12.35
1	7.26	8.02	7.15	6.72	6.18	4.44	7.25	18.96	11.05	19.39	7.26	18.96	19.28
2	9.86	10.18	10.40	9.53	10.62	7.04	12.13	26.54	13.65	24.70	10.62	24.16	24.3
3	15.71	19.29	15.60	15.39	13.98	10.73	18.74	33.05	21.56	29.90	15.71	29.36	29.90
4	21.13	24.27	20.48	21.45	16.90	16.79	25.35	39.87	29.15	36.30	23.51	33.37	32.61
5	26.65	37.1	27.63	28.82	35.10	35.32	32.2	45.73	34.89	40.96	29.80	39.55	37.60
6	35.11	42.15	34.57	34.89	42.15	41.93	39.54	52.66	41.93	45.73	37.06	46.05	43.66
7	43.13	50.71	42.37	44.64	49.30	48.22	45.40	58.84	48.98	50.17	44.53	53.86	50.17
8	50.82	57.11	50.39	51.15	52.77	56.78	51.25	67.62	56.13	58.84	51.36	61.12	58.84
9	58.08	64.8	61.01	59.38	58.73	63.83	60.35	74.34	63.61	65.56	58.30	68.16	65.12
10	64.80	70.66	66.21	65.56	65.56	68.70	68.81	79.22	68.71	72.39	64.48	74.13	71.95
11	73.47	77.49	72.07	74.56	73.48	74.02	79.00	81.50	75.32	78.90	73.15	81.06	77.14
12	80.16	86.75	82.37	79.64	81.16	85.55	86.31	88.42	82.38	86.25	79.75	88.45	86.62

Comparative data of percentage in vitro diffusion drug release of Transdermal patch formulation of F1 to F13



Stability studies: The stability studies of formulation of ondansetron transdermal patches was carried out for 3 months. During this period, the formulations were stable and showed no significant changes in visual appearance, colour, texture and drug content.

CONCLUSION: The optimization of Ondansetron transdermal patches was done by Box Behnken design Quadratic model, 12.0.1.0 version of optimization was used. Drug polymer ratio%, PVP concentration %, Ethyl cellulose % were considered as variable, Folding endurance, thickness, Drug release at 12 hr were used as Responses for formulation design. From the optimization, the desirability of different variables was produced, and thus optimized formula was obtained. The formulations conducted for physicochemical parameters such as drug content uniformity, folding endurance, weight uniformity, thickness uniformity, were found to be within the limit of pharmacopeial specifications. During and at the end of the stability study the optimized formulation showed the In vitro drug release and no colour changes

from that observed at the initial study. The results indicated that there was no influence on the chemical and physical stability of the prepared Ondansetron based transdermal patches.

FUTURE PROSPECTS: Studies have shown promising results, and there is a scope for further studies. Physiological pharmacokinetic model should be conducted for the further development of the formulation and clinical trials.

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