ISSN: 2349-2678

Contents lists available at www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

NLM (National Library of Medicine ID: 101738825)

Index Copernicus Value 2019: 71.05

Volume 10 Issue 2; March-April; 2022; Page No. 15-30

RESEARCH ARTICLE

Formulation and Evaluation of Transdermal Patches of Granisetron Hydrochloride

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Conflicts of Interest: Nil

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ABSTRACT

The present study aims at development of a transdermal drug delivery system (TDDS) which can deliver the medication via skin portal to systemic circulation at a pre-determined rate and maintain a clinically effective concentration over a prolonged period of time. Transdermally delivered antiemetic agents provide the patient with a unique and convenient dosing schedule while providing nearly constant serum levels of medication over a prolonged period of time. Transdermal Drug Delivery Systems are defined as self-contained discrete dosage forms when applied to the intact skin that deliver the drug through the skin at a controlled rate to systemic circulation. Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and most dreaded side effects reported by cancer patients. Other common adverse effects (AEs) of chemotherapeutic agents include hair loss, malaise, fatigue, diarrhea, dehydration, neutropenia, fever, systemic infections, and thrombocytopenia. Although some of these AEs cannot be prevented, those that can, such as CINV, should be aggressively prevented and managed. Transdermal delivery of an antiemetic agent through intact skin would have better patient compliance and plasma level. The transdermal route is an alternative method for the administration of drugs. Some drugs have pre-systemic metabolism or instability in acidic environments or GI fluid that results in low therapeutic availability in systemic circulation or low oral bioavailability. To avoid that problem, transdermal patches are formulated.

KEYWORDS: Transdermal drug delivery system, antiemetic, Chemotherapy-induced nausea and vomiting.

Introduction

Conventional system of medication which required multi-dose therapy has numerous problems and complications. Conventional doses form whither tablet or an injection has to deliver right amount of medication at the right targeted site become complicated. To address these problems, a novel drug delivery system approaches known as controlled drug delivery system which facilitates drug release to systemic circulation at pre-determine rate. A class of novel drug delivery system is Transdermal drug delivery system (TDDS) which can deliver the medication via skin portal to systemic circulation at pre-determine rate and maintain clinically effective concentration over prolong period of time[(1,2).] Transdermally delivered antiemetic agent provide the patient a unique and convenient dosing schedule while providing nearly constant serum levels of medication over prolong period of time[(3,4,5)] . Transdermal Drug Delivery Systems are defined as self-contained discrete dosage forms

when applied to the intact skin deliver the drug through the skin at a controlled rate to systemic circulation[6]. Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and most dreaded side effects reported by cancer patients. Other common adverse effects (AEs) of chemotherapeutic agents include hair loss, malaise, fatigue, diarrhea, dehydration, neutropenia, fever, systemic infections, and thrombocytopenia. Although some of these AEs cannot be prevented, those that can, such as CINV, should be aggressively prevented and managed [7, 8]. CINV can be divided into three types: acute, delayed, and anticipatory Acute nausea or vomiting is defined as occurring within 24 hours after chemotherapy administration.

Delayed nausea or vomiting occurs at least 24 hours after the administration of chemotherapy, and it may last for more than 120 hours.

Anticipatory vomiting is a learned or conditional response that typically occurs when nausea and vomiting have been poorly controlled with previous chemotherapy. It affects patients before acute chemotherapy-related symptoms are expected to occur, either before, during, or after chemotherapy administration. Anticipatory nausea or vomiting is best treated with behavioural interventions and other non pharmacological approaches rather than with pharmacological therapy [9].

Granisetron Hydrochloride is a novel anti-emetic and anti-nauseant drug. It is a selective serotonin (5-HT_3) receptor antagonist with little or no affinity for other serotonin, beta-adrenergic, dopamine or histamine receptors. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT receptors. The stimulation of 5-HT_3 receptors by serotonin causes vagal discharge resulting in vomiting. Granisetron Hydrochloride blocks serotonin stimulation and subsequent vomiting. It is well absorbed from the gastrointestinal tract, having short biological half life and low oral bioavailability (60%) due to extensive first-pass metabolism. Therefore, it requires multiple dosing to maintain therapeutic drug blood level. These factors make granisetron, a suitable candidate for transdermal delivery, which avoids first pass metabolism, improves the bioavailability of drug, reduces the frequency of dosing and if toxic symptoms appear, the drug can be withdrawn immediately by removal of patches [10]. Hence, the proposed work involves the development and evaluation of transdermal drug delivery systems containing Granisetron Hydrochloride for the treatment of patients during chemotherapy-induced vomiting.

Transdermal patch was prepared with one or more objective.

1) To avoid pre-systemic metabolism.
2) To maintain constant and prolong drug level in plasma.
3) To improve patient compliance by reducing dosing frequency.

EXPERIMENTAL WORK:

Preformulation study:

Selection of λ max and Calibration curve of Granisetron Hydrochloride [29 30]

Preparation of standard stock solution of Granisetron Hydrochloride:

25mg of Granisetron Hydrochloride was dissolved in 25ml of distilled water by slight shaking to form the solution of 1000ug/ml. 1ml of this solution was taken and made up to 25ml with distilled water which give 40ug/ml concentration .

1) Preparation of working standard Solution:

From the standard stock solution 1, 2,3,4,5, and 6ml were withdrawn and volume was made up to 10 ml with distilled water to give a concentration of 4, 8, 12, 16, 20, 24 ug/ml. Absorbance of these solutions was measured against a blank of distilled water at 305nm.

Determination of pH [14]

The pH of the Granisetron Hydrochloride was determined using pH-meter for freshly prepared 1% aqueous solution of Granisetron Hydrochloride.

Determination of melting point [13,14]

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube was placed

in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and average value was noted.

Determination of partition coefficient [14]:

The partition coefficient (log D) is a measurement of lipophilicity of molecule which can be used to predict its capability to cross biological membrane. The partition coefficient study was performed using n-octanol and water as aqueous phase. The two phases were mixed with each other in a separating funnel. After mixing the system remain undistributed for half an hour. About 10 mg of drug added to this solution and was shaken occasionally in separating funnel. After shaken the resulting solution was kept a site for 24 h. After 24 h two phases were separated in a separating funnel. The aqueous phase was filtered through filter paper suitably diluted and amount of drug in aqueous phase and oil phase was determined by measuring absorbance at 305 nm. The partition coefficient of granisetron hydrochloride was calculated from the ratio between the concentration of granisetron hydrochloride in aqueous phase and oil phase.

C o/w = Concentration of drug in non-aqueous phase/Concentration of drug in aqueous phase.

Permeability parameter [15]:

Permeability Coefficient (P): Permeability coefficient is the velocity of drug passage through the membrane/skin in µg/cm^2/h. The permeability coefficient was calculated from the slope of the graph of percentage of drug transported vs. time as:

P = slope x Vd/S---------- (1)

Where, Vd = volume of donor solution,

S = surface area of tissue.

Flux (J)

Flux is defined as the amount of material flowing through a unit cross-sectional barrier in unit time. It is calculated by:

Flux (J) = P x CD..... (2)

Where, CD = concentration of drug in donor solution,

P = permeability coefficient.

Compatibility studies:

The compatibility of Granisetron hydrochloride and polymers (HPMC E15and Eudragit RLPO) under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and not affecting the shelf life of product or any other unwanted effects on the formulation. The physical mixture of drug & polymers were used for determination of Infrared spectrums [16].

Permeation study of pure drug

The *in-vitro* drug permeation studies were carried out by using Franz diffusion cell. The rat skin of abdominal part was cut and hair was removed and clamped between the receptor and donor compartments. The receptor compartment was filled with 15 ml of diffusion medium (Phosphate buffer pH 7.4) through sampling port taking care to remove all the air bubbles. The contents were stirred at 500 rpm. by externally driven, teflon coated small magnetic bead to keep them well mixed. The temperature of the system was maintained at 37.0±20^{0}C. Accurately weighed 5 mg of Granisetron Hydrochloride was dissolved in phosphate buffer pH 7.4 and placed in receptor compartment. At suitable time intervals, aliquots (1ml) were collected and suitable diluting the aliquot with phosphate buffer and absorbance was measuring at 305 nm using a double beam UV spectrophotometer. The diffusion medium of the same volume (3ml), which was pre warmed at 370^{0}C, was then replaced into the receptor compartment. Duration of the experiment was 12 h. The amount of drug permeated through skin was calculated from absorbance of aliquots [17].

Preparation of Transdermal patches:

Method

Matrix type transdermal patches were prepared using solvent evaporation method with HPMC E15 and Eudragit RL-100 and polyethylene glycol 400 as plasticizer. HPMC E15 was added to 20 ml of the solvent mixture (dichloromethane and methanol, 1:1) and

allowed to stand for 6 h to swell. Granisetron Hydrochloride was dissolved in 10 ml of solvent mixture and added to the polymeric solution. Measured quantity of Dimethyl Sulphoxide (5%v/w) was added as penetration enhancer and PEG 400 added as a plasticizer. This was set aside for 2 h to remove entrapped air, and then dissolve weighed Eudragit RL100 and of PEG 400 in 15 ml of solvent mixture and both polymeric solution mixed homogeneously then transferred to a petri plate and allowed to dry at room temperature Controlled solvent evaporation was achieved by inverting a funnel over the petridish for 24 h. The developed patches were removed carefully, cut to size 2.2 cm^2 and stored in a desiccator. The composition of the patches is shown in table no: 3 [18].

Table No: 3 Formulation compositions of transdermal patches:

BATCHES	GRA HCL	EUDRAGIT	HPMC E15	PEG-400	DMSO
F1	10mg	50mg	100mg	100ul	5%
F2	10mg	100mg	100mg	100ul	5%
F3	10mg	100mg	200mg	100ul	5%
F4	10mg	100mg	300mg	100ul	5%
F5	10mg	100mg	400mg	100ul	5%
F6	10mg	100mg	500mg	100ul	5%
F7	10mg	100mg	600mg	100ul	5%
F8	10mg	100mg	700mg	100ul	5%
F9	10mg	125mg	700mg	100ul	5%
F10	10mg	150mg	700mg	100ul	5%

Evaluation of Prepared Transdermal patches:

Thickness [31].

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

Flatness [32].

Longitudinal strips were cut out from the prepared medicated film the lengths of each strip were measured. Then variation in the length due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction (\%)} = \frac{L1\text{-}L2}{L2} \times 100$$

Where,

L1- initial length of strip, L2 - final length of strip

Weight uniformity [33].

For each formulation, three randomly selected patches were used. For weight variation test, three films from each batch were weighed individually and the average weight was calculated.

Folding endurance [34].

The folding endurance was measured manually for the prepared films. A strip of film 2.2cm^2 was cut 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/cracking gave the value of folding endurance.

Percentage moisture absorption [35].

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the

following manner. The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80- 90% RH. After 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

% moisture absorption = (Final weight – Initial weight) / Initial weight x100

Percentage moisture loss [36].

Percentage moisture loss was carried out to check the (physical stability) moisture sensitiveness during storage of patch. The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula:

% moisture loss = (Initial weight - Final weight) / Final weight x 100.

Drug content determination [37].

The patch of area 2.2×2.2 cm^2 was cut and dissolved in distilled water. Then solvent methanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with distilled water to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 305 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

***In Vitro* drug permeation study** [38]**:**

Preparation of skin

A full thickness of skin was excised from dorsal site of dead rat and skin was washed with water. The fatty tissue layer was removed by using nails of fingers. The outer portion with hairs was applied with depilatory and allowed to dry. With the help of wet cotton the hairs were scrubbed and washed with normal saline solution. The skin was kept in normal saline solution in refrigerator until skin was used for drug permeation study. Prior to use, the skin was allowed to equilibrate with room temperature. Then skin was mounted between donor and receptor compartment of cell. The skin was clamped in such a way that the dermal side will be in contact with receptor medium.

Diffusion cell [39]

The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. *In Vitro* studies are also done for TDDS development. In this work, K-C type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active Compartment (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. rat abdominal skin. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin was used to stir the receptor solution using magnetic stirrer. The rat abdominal skin was placed on receptor compartment and both compartments held tight by clamps. Phosphate buffer pH 7.4 was used as receptor solution. The volume of diffusion cell was 20 ml and stirred with magnetic bead. The temperature was maintained at 37 ± 1°C with the help of hot plate. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 305 nm.

RESULT AND DISCUSSION:

Preformulation study

Selection of λ max and Calibration curve of Granisetron Hydrochloride [29, 30]

a) Wavelength selection.

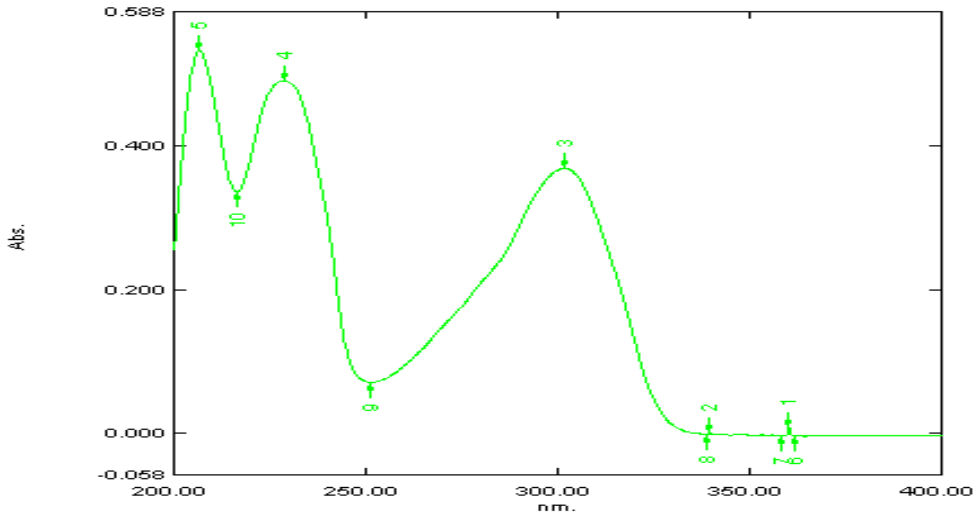

Fig No: 8 UV Spectra of Granisetron Hydrochloride

b) Calibration curve: Result of UV analysis was shown in table no: 4

Table No: 4 Result of UV analysis

Absorbance of various standard concentrations of Granisetron Hydrochloride solutions were read at 305nm λ max. and calibration curve was plotted to check the linearity.

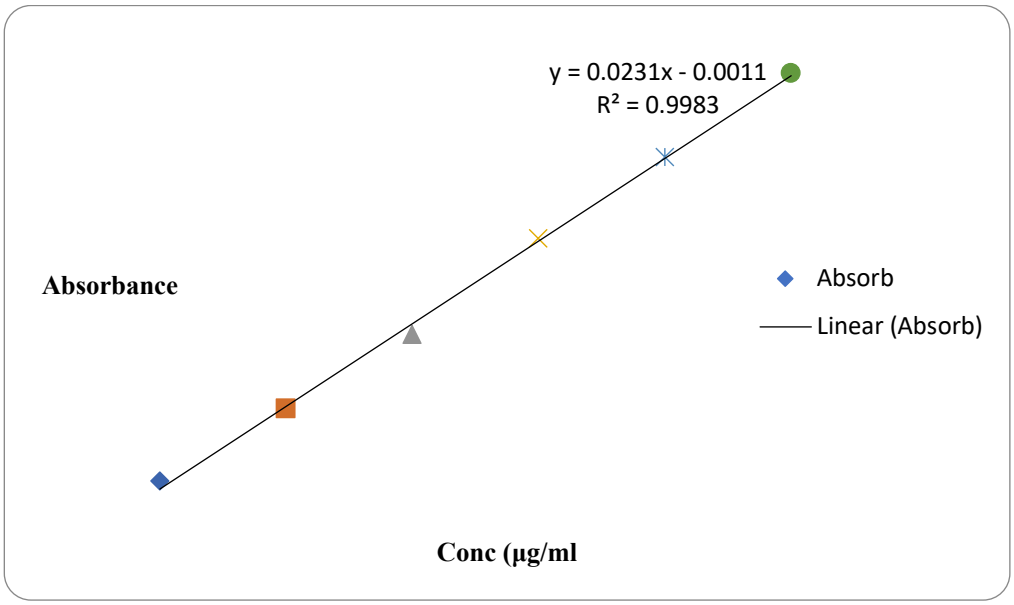

Fig No: 9 Calibration curve of Granisetron Hydrochloride

Table No: 5 Parameters found in calibration curve.

Sr. No	Parameters	Drug (Granisetron Hydrochloride)
1.	Detection Wavelength (λ max)	305nm
2.	Regression Equation	y=0.0231x-0.0011
3.	Correlation Coefficient	0.9983

Concentration (ug/ml)	Absorbance
4	0.100
8	0.181
12	0.264
16	0.372
20	0.463
24	0.557

8.2 Result of determination of pH and melting point:
pH and melting point of Granisetron hydrochloride were shown in table no: 6.

Table No: 6 Melting Point and pH.

SN	Drug	Melting Point	pH
1	Granisetron Hydrochloride	219^0c	4.6

Result of determination of partition coefficient:
Partition coefficient of Granisetron Hydrochloride were shown in the table no: 7

Table No: 7 Partition coefficient.

Sr.no	Partition coefficient of drug	Solvent system	Log D values
1	Granisetron Hydrochloride	Octanol : water	2.6

Result of Permeability parameter:
Permeability parameter includes determination of Flux and Permeability coefficient which is shown in table no: 8

Table No: 8 Result of Permeability parameter.

Formulation	Flux µg/cm²/h	Permeability coefficient µg/cm²/h
F1	142.02	96.83
F2	103.97	70.88
F3	105.17	71.70
F4	106.70	72.75
F5	109	74.31
F6	97.02	66.15
F7	75	51.13
F8	72.68	49.55
F9	59.38	40.48
F10	48.06	32.76

Permeation study of Granisetron Hydrochloride in phosphate buffer pH 7.4

Table No: 9 Permeation study of Granisetron Hydrochloride in phosphate buffer pH 7.4

Sr. No.	Time(min)	% permeated
1	0	0
2	30	3.25
3	60	5.5
4	90	11
5	120	12.36
6	150	16.25
7	180	18.02
8	210	20.14
9	240	24.31
10	270	25.15
11	300	30.03
12	330	34.98
13	360	35.22
14	390	37.52
15	420	37.98
16	450	38.16
17	480	38.4
18	510	38.76
19	540	39
20	570	39.29
21	600	39.35

Result of Compatibility studies:

The possible interaction between the drug and polymers was studied by IR spectroscopy. Physical mixture of drug and polymer were used to study interaction between drug and different polymers.

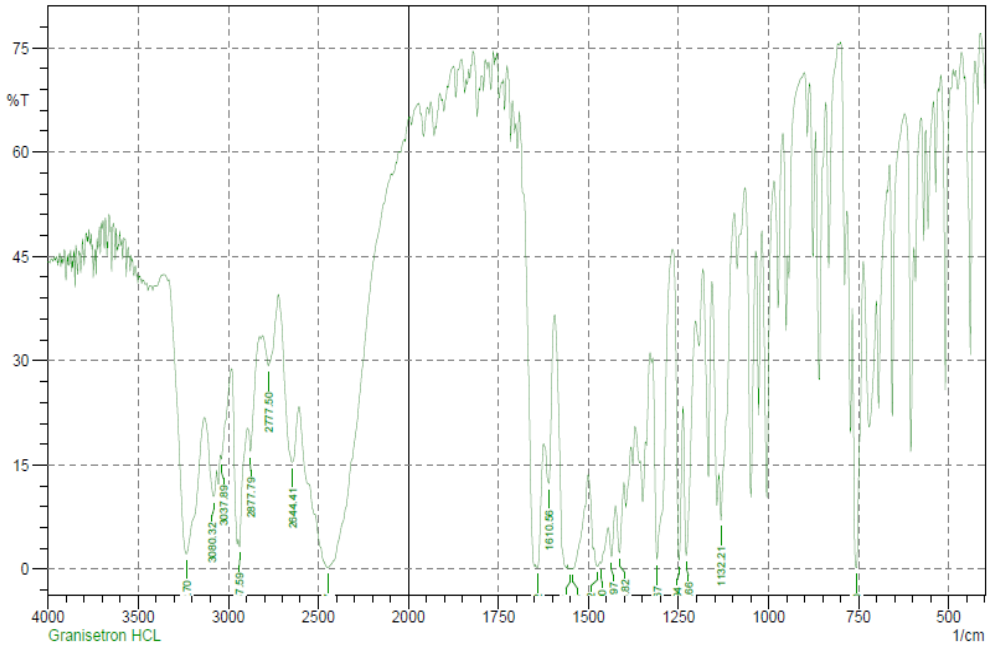

Fig No: 9 IR Spectra of Granisetron Hydrochloride

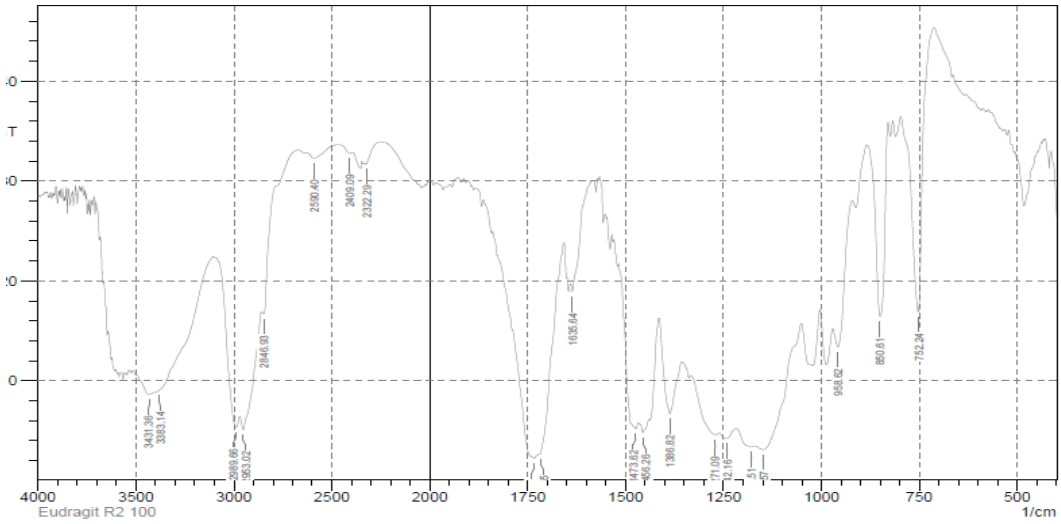

Fig No: 10 IR spectra of Eudragit RL100

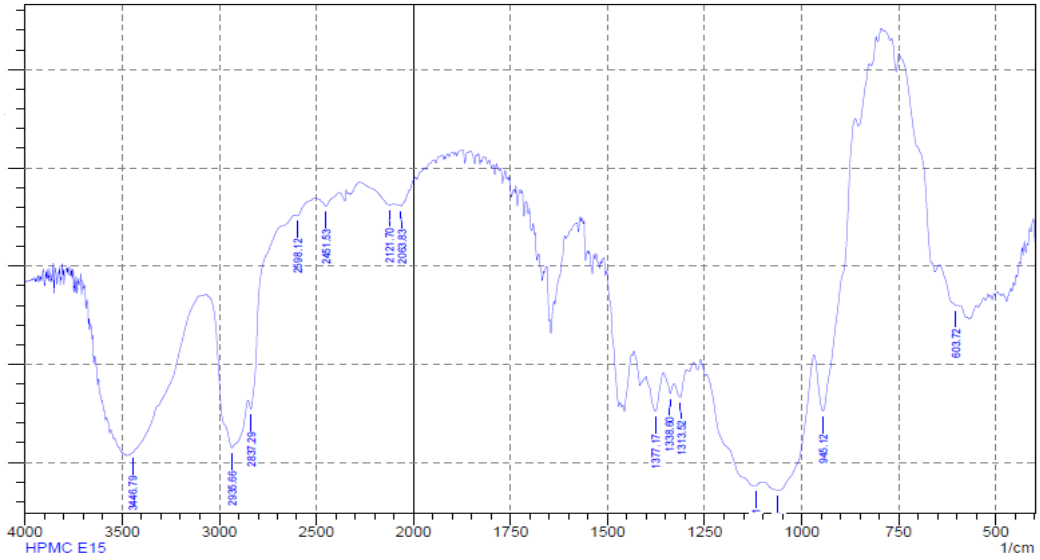

Fig No:11 IR Spectra of HPMC E15.

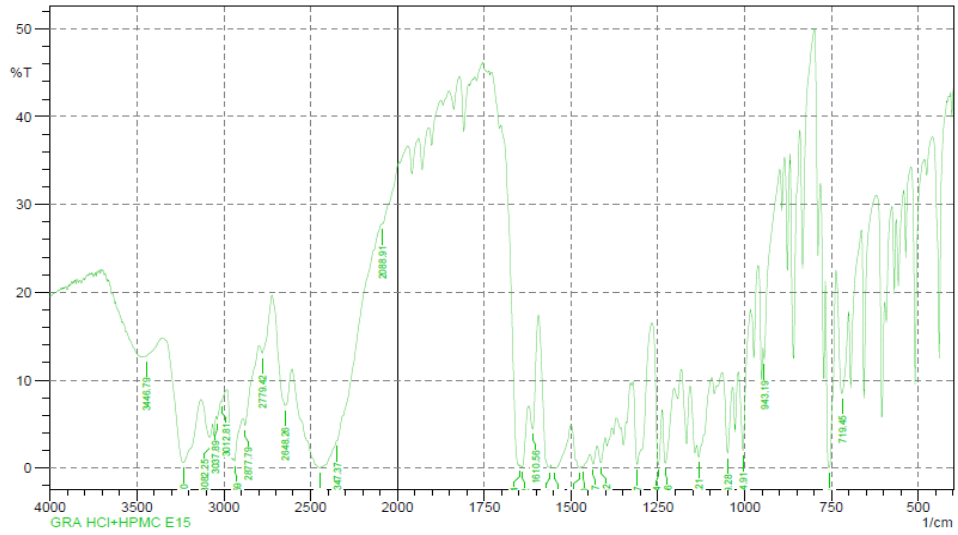

Fig No:12 IR Spectra of Granisetron Hydrochloride with HPMC E15

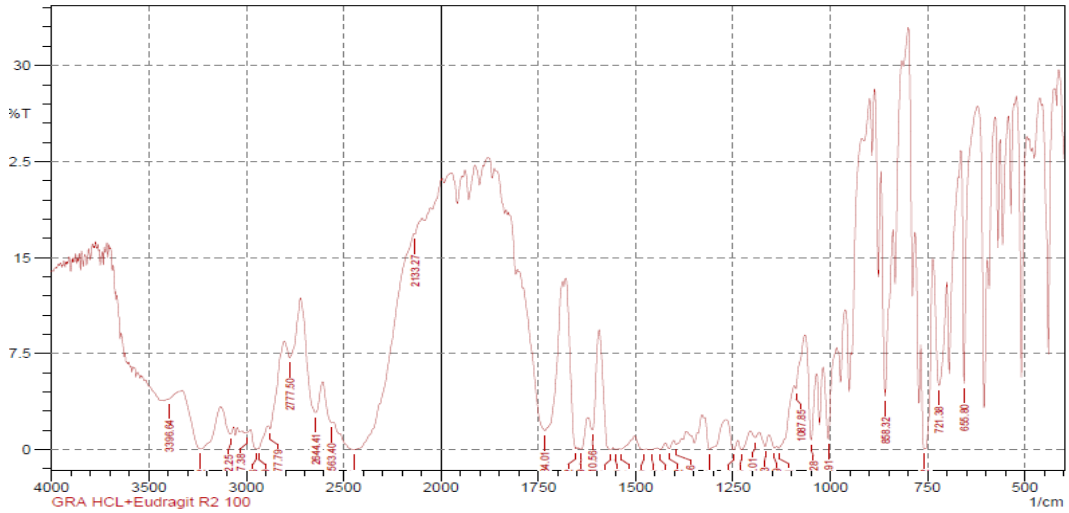

Fig No:13 IR Spectra of Granisetron Hydrochloride with Eudragit RL-100

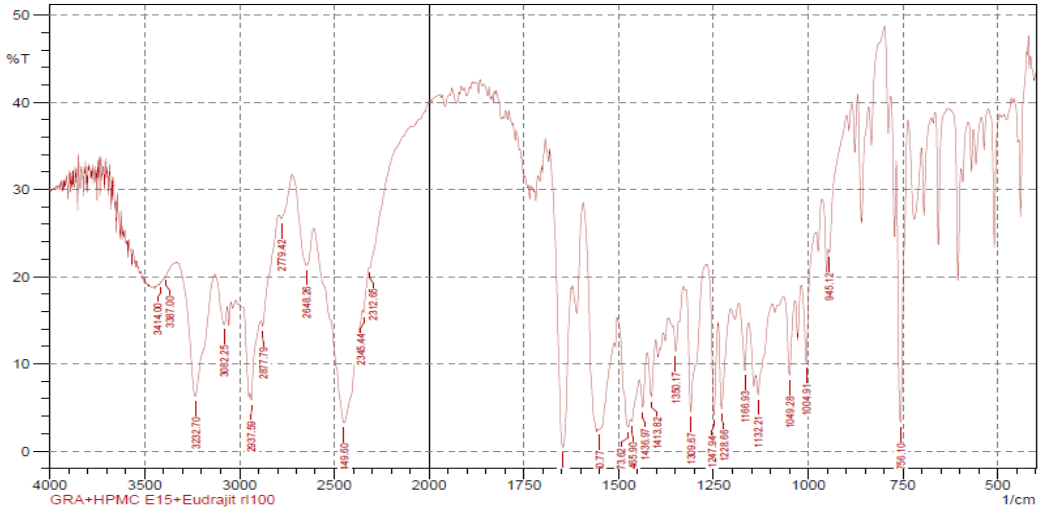

Fig No:14 IR Spectra of Granisetron Hydrochloride with HPMC E15 and Eudragit RL-100

Results of IR study.

Major peaks (wave number, cm-1)	Pure drug (Granisetron HCL)	Physical Mixture A	Physical mixture B	Physical mixture C
Aromatic ring	756	758	756	756
Amine(C-N)	1132,1228,1309,1247	1132,1228,1247	1132,1228,1247	1132,1228,1247
C=O-NH- **O=NH**	1610, 1614, 3232 doublet.	1610,1639	1610,1614	1610,1641
Aromatic-C=C-	1413,1436,1473,1543, 1550.	1413,1436	1413,1436,1473	1413,1436,1473
CH3-/Alkanes	2877,2937	2877,2937	2877,2937	2877,2937
C=C-H stretch	3080	3080	3082,3232.	3082

There was no considerable change in the positions of characteristic absorption bands and bonds of various functional groups present in the drug. This observation clearly suggests that the drug remains in its normal form with no prominent change in its characteristics even in its physical mixture and formulation. The results of IR spectra indicated the absence of any well defined interaction between drug, and polymers.

Result of Thickness, weight variation, folding endurance.

Table No: 10 Result of Thickness, weight variation, folding endurance.

Batches	Thickness(mm)	Weight variation	Folding endurance	Flatness
F1	1.1±0.012	14.10±0.11	90±0.014	100%
F2	1.13±0.152	15.08±0.076	91.66±1.52	100%
F3	2.03±0.0577	16.16±0.15	93±0.015	100%
F4	3.13±0.152	17.3±0.22	94±0.019	100%
F5	3.33±0.152	18.7±0.22	125.66±1.32	100%
F6	3.4±0.0577	19.5±0.231	122±0.016	100%
F7	3.7±0.100	20.73±0.208	122.33±1.52	100%
F8	3.8±0.100	21.56±0.305	125±1.52	100%
F9	3.89±0.111	22.2±0.221	124±1.37	100%
F10	3.97±0.152	23.09±0.231	125±0.149	100%

All the values represent mean ± S.D. (n=3)

The thickness of Granisetron Hydrochloride patches were between 1.1-3.97 mm. These show Uniformity in thickness of patches. The weight variation of Granisetron Hydrochloride patches were in between 14.10-23.09 mg. This showed uniformity in weight of patches. The variation of weight indicates that the polymeric solution of the drug is well dispersed on flat surface. However, little variation in weight observed in different formulation may attribute to the variation in polymeric content. The Folding endurance of patches were found to be satisfactory between 90-125 .This shows that patches would maintain their integrity and not break easily during handling. All films shows 100% flatness.

Result of % moisture absorption, % moisture loss and Drug Content

Table No: 11 Result of % moisture absorption, % moisture loss, Drug Content.

Batches	Moisture Loss (%)	Moisture absorption 80-90% RH	Drug Content (%)
F1	0.23±0.12	0.29±0.32	93.89
F2	0.25±0.21	0.3±0.42	93.85
F3	0.30±0.054	0.39±0.51	94.69
F4	0.38±0.046	0.4±0.81	98.71
F5	0.41±0.121	0.32±0.70	98.8
F6	0.50±0.213	0.41±0.42	97
F7	0.54±0.121	0.48±0.11	96.09
F8	0.69±0.49	0.51±0.32	97
F9	0.67±0.29	0.51±0.37	97.04
F10	0.61±0.125	0.51±0.70	96.06

All the values represent mean ± S.D. (n=3).

The % moisture absorption of Granisetron Hydrochloride patches were between 0.29 to 0.51% at 80-90% RH. The moisture uptake increases as concentration of hydrophilic polymer increases Also, as the moisture uptake was less, patches were not moisture sensitive during storage. The % moisture loss of Granisetron hydrochloride patches were between 0.23 to 0.61%.The moisture content increases as concentration of hydrophilic polymer increases and decrease as the concentration of hydrophobic polymer decreases and as the moisture content was less, patches were not moisture sensitive during storage. Drug contain of patches of all batches were in between 93-97%.

Result obtained of *In Vitro* permeation study of Transdermal patches of Granisetron Hydrochloride of batches F1 to F5.

Table No: 12 *In Vitro* permeation study of Transdermal patches of Granisetron Hydrochloride of batches F1 to F5.

Time(H)	**% Drug Diffuse**				
-	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	20.83	15.25	15.45	15.65	16.12
2	16.22	18.32	21.35	23.97	26.68
3	20.22	25.33	30.64	32.66	38.76
4	23.25	28.36	35.87	38.55	49.09
5	30.21	36.57	45.36	49.97	55.4
6	37.26	44.85	52.66	55.97	61.11
7	48.66	55.36	60.89	65.88	70.7
8	58.69	64.98	67.69	73.97	78.55
9	64.33	72.58	76.08	79.66	85.24
10	68.56	76.33	80.55	84.66	88.74
11	75.22	77.65	82.75	87.25	93.02
12	75.22	77.65	86.37	93.5	96.43

All the values represent mean ± S.D. (n=3)

In Vitro permeation studies of prepared transdermal patch were performed with diffusion cell. Batch F1 was designed containing 50 mg of Eudragit RL 100 and 100 mg HPMC E15 which show flux of 142µg/cm^2/h which is highest among all batches but flux get decreased with time. Batches F2 to F5 were designed by keeping constant amount of Eudragit RL100 and varying concentrations of hydrophilic polymer HPMC E15. Batch F2 showed flux 103.97µg/cm^2 but flux get decreased after 9 h. Batch F3 showed flux 105.17 µg/cm^2 but showed similar problem to that of batch F2 that flux is get decreased after 10 h. Batch F4 showed flux of 106.70µg/cm^2 but flux was not linear after 10 h. Batch F5 showed flux of 109 µg/cm^2.

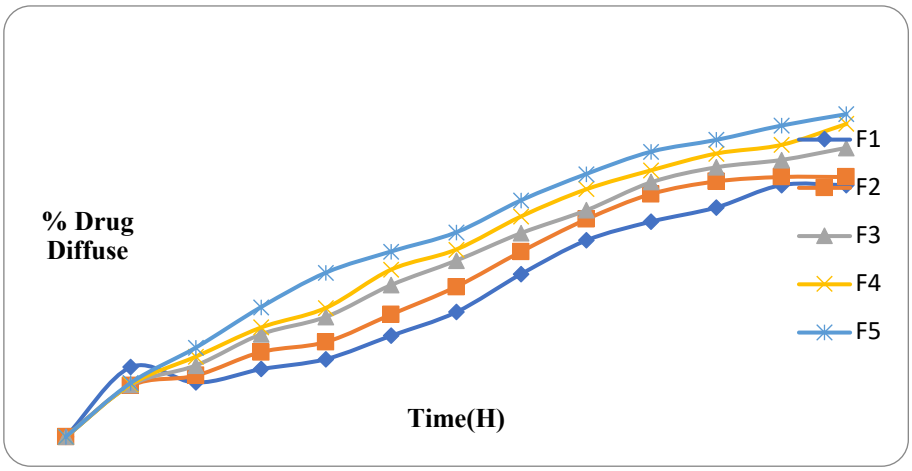

Fig. No: 15 Comparative Drug Diffusion studies of batches F1 to F5

Result obtained of *In Vitro* permeation study of Transdermal patches of Granisetron Hydrochloride of batches F6 to F10.

Table No: 13 *In Vitro* permeation study of Transdermal patches of Granisetron Hydrochloride of batches F6 to F10.

Time(H)	% Drug Diffuse				
-	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	14.23	10.66	10.56	8.71	7.05
2	22.74	18.33	15.26	12.33	7.92
3	30.52	25.33	21.28	15.98	10.01
4	37.13	30.64	26.22	20.21	11.27
5	45.2	39.28	30.69	25.66	15.9
6	54.97	48.39	40.27	30.54	20.69
7	65.7	58.69	47.54	35.39	25.97
8	72.97	67.95	54.67	45.69	35.59
9	78.99	75.22	60.83	53	48.66
10	88.35	80.23	70.88	64.94	59.66
11	91.44	82.27	77.85	73.41	70.23
12	92.71	87.24	84.78	79.76	76.22

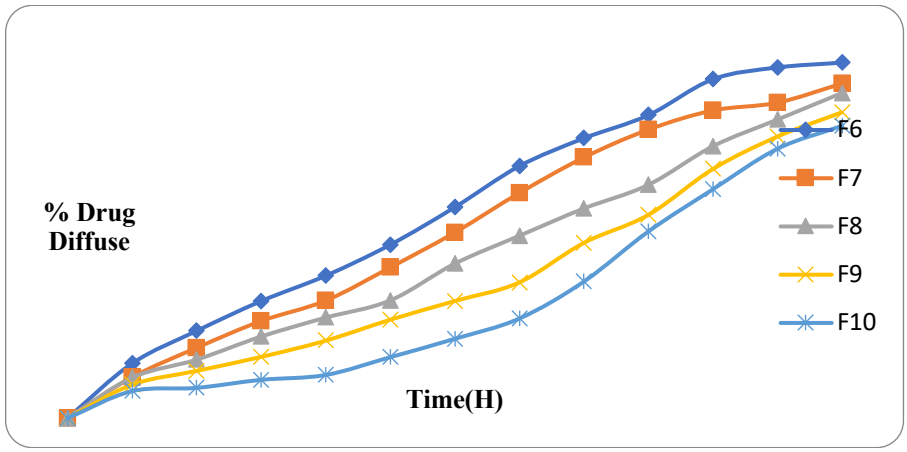

Fig. No: 16 Comparative Drug Diffusion studies of batches F6 to F10

After seeing permeation study of batches F6 and F8 it was observed that as concentration of hydrophilic polymer increases leads to decrease in flux is from 97.02 to 72.68µg/cm^2/h. Similarly Batch F9 and F10 were show decreased in flux from 59.38 to 48.06 with increasing concentration of hydrophobic polymer [(15)]. Batch F5 were shows linear permeation of Granisetron Hydrochloride with flux of 109 µg/cm^2/h. From above result it was seen that increasing the amount of the polymer HPMC E15 produced the water-swollen gel like state that could substantially reduce the penetration of the dissolution medium into the patches and so the drug release was delayed [(15)]. The Eudragit layer minimizes the permeation of the drug molecules from the patches. In addition, Eudragit layer could control the release of the drug from the patches [(15)]. The formulation that showed required maximum drug release was selected as the optimized formulation. The main objective of formulating the transdermal system was to prolong the drug release time reduces the frequency of administration and to improve patient compliance.

CONCLUSION :

In this work an attempt was made to develop and evaluate transdermal patches of Granisetron hydrochloride. Based on the results of the present study, it could be concluded that selected polymers were better suited for development of transdermal patches of Granisetron hydrochloride. Batch F5 was the optimised formulation showed uniform thickness, and drug content uniformity. It also showed good folding endurance. The formulation F5 showed Drug release up to 96.43%. In order to get therapeutically effective steady state concentration. The patch area needed to be increased to 5.29 cm^2 (2.3×2.3).

Bibliography

1. Panchagnula R, Sandhu P, Bilandi A, Kataria S, and Middha A. Transdermal delivery of drugs. Ind J Pharmacol 1997; 29:140-56.
2. Kshirsagar N A, Rajkapoor B, Vijayaraghavan C. Drug delivery systems. Ind J Pharmacol 2000; 32:54-61.
3. Gupta J R D, Tripathi P, Irchhiaya R, Garud N, Dubey P, Patel J R. Formulation and Evaluation of matrix type transdermal patches of Glibenclamide. Int J Pharm Sci Drug Res; 2009; 1:46-50.
4. Vyas S P, Roop K K. Controlled drug delivery concepts and advances. 1st Ed. New Delhi: Vallabh prakash publishers 2005; 411-47.
5. Sanap G S, Dama G Y, Hande A S, Karpe S P, Nalawade S V, Kakade R S. Preparation of transdermal monolithic systems of indapamide by solvent casting method and the use of vegetable oils as permeation enhancer. Int J Green Pharm 2008; 2:129-33.
6. Gupta D, Irchhiaya N, Garud N, Tripathi P, Dubey P, Patel J. R. Formulation and Evaluation of Matrix Type transdermal patches of Glibenclamide. Int J Pharm Sci Drug Res; 2009;1:46-50
7. Shih Y T, Elting L S. Costs of uncontrolled chemotherapy induced Nausea and vomiting among working-age cancer patients receiving highly or moderately emetogenic chemotherapy. J Clin Oncol 2007; 3:678-685.
8. Du X L, Osborne C, Goodwin J S. Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. J Clin Oncol 2002; 20:4636-4642.
9. Calpena A C, Lauroba J, Suriol M. American Society of Health-System Pharmacists (ASHP). Therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemo -therapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999; 56: 729-764.
10. Linda S, Crawford S.M, Taylor P.A. The comparative effectiveness of ondansetron and granisetron in once daily dosage in the prevention of nausea and vomiting caused by cisplatin: a double blind clinical trial". The Pharm J 2009; 265: 59-62.

11. Sharma N, Agarwal G, Rana A C, Kumar D. A Review: Transdermal Drug Delivery System: A Tool For Novel Drug Delivery System Int J Drug Dev Res 2011; 3:60-70.
12. Jamakadi J S, mulla B L, shivkumar N H. Formulation characterization and evaluation of matrix type transdermal patch of model antihypertensive drug. Asian J Pharm 2010; 3:15 30.
13. Derwhekar G, Jain D, Patidar V. Formulation and Evaluation of transdermal drug delivery system of Clopidogrel bisulphate. Asian J Pharm Life Sci; 2011; 3:1-10.
14. Reymond C Rowe, Paul J Sheskey, and Marian E Quinn Text book of Pharmaceutical Excipient Sixth edition; 36-326.
15. Gudalwar B R, Borkar V. K, Sonkamble M. K, Khalkar S. G, Jadhav J. K. Development of Bilayered transdermal patches of ondansetron Hydrochloride: Physicochemical and Ex vivo characterization. Int J Pharm Res; 2012; 3:1-22.
16. Nanda S, Saroha K, Yadav B, Sharma B. Formulation and Characterization of Transdermal Patch of Amlodipine Besylate Int J Pharm Sci; 2012; 3:604-620.
17. Vinod K, Sravani P, David Banji, Teja B.B. Transdermal Drug Delivery System Overcoming Challenges Of Popular Drug Delivery Systems. Int J Pharm World Res 2010;1(3):1-14.
18. Das A, Ghosh S, Dey B, Das S. A Novel technique for treating the type-II diabetes by Transdermal patches prepared by using multiple polymer complexes. Int J Pharm Res Dev;2010;2:195-204.
19. Amjad M, Chand S, Sabreesh H, Kumar G. Formulation and Evaluation of transdermal patches of Atenolol. Int J Pharm Res; 2011; 1:109-119.
20. Christian C, Zhang K, Elizabeth G, Jalota L, Hornuss C, Katherine E. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. J Clin Therapeutics; 2010; 32:1-10.
21. Jeong S, Hwang J, Deog J, Sunhee S, Jang Y. The antiemetic effect of a novel tropisetron patch in anticancer agents-induced kaolin pica model using rats. J Sci Direct; 2005; 20:167-174.
22. Mukherjee B, Mahapatra S, Gupta R, Patra B. Tiwari A, Arora P. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation. J Sci Direct; 2005; 59:475-483.
23. Goodman & Gilman's text book of pharmacology the pharmacological basis of therapeutics - 11th ed. (2006)
24. Kumar K.P. Transdermal Drug Delivery System-A Novel Drug Delivery System And Its Market Scope And Opportunities Int J Pharma Bio Sciences 1(2)2010: 1-21
25. Chein Y.W. Novel Drug Delivery System 2nd edition.Informa Healthcare Reprinted 2011;50:301
26. Shingade GM, Aamer Quazi, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad DD. Review On: Recent Trend On Transdermal Drug Delivery System. J Drug Del Therapeutics 2012; 2(1):66-75.
27. Latha S, Selvamani P, Thirunavukkarasu C, Kadambavadani R. Formulation Development and Comparison in Evaluation of Transdermal Drugs Delivery System for Anti-Emetic Therapy. Int J Res Pharm Bio Sci; 2010:6:10-19.
28. Kumar J.K, Pullakandam N, Prabu S.L. Transdermal Drug Delivery System: An Overview. Int J Pharm Sci Rev Res 2010; 3(2): 49-54
29. Sharma N, Agarwal G, Rana A. C. A Review: Transdermal Drug Delivery System: A Tool For Novel Drug Delivery System. Int J Drug Dev & Res; 2011; 3 (3): 70-84.
30. Keleb E, Sharma R K, Esmaeil B M. Transdermal Drug Delivery System- Design and Evaluation. Int J Adv Pharm Sci 2010; (1):201-211
31. Latheeshjlal.L, Phanitejaswini P, Soujanya Y, Swapna U. Transdermal Drug Delivery Systems: An Overview. Int J PharmTech Res 2011;3(4): 2140-2148

32. Sowmya C, Reddy S C, Amrutha V, Anilkumar D, Lohitha M. Transdermal Therapeutic Systems - An Over View. Int J Pharm Industrial Res 2012;2(2):197-211.
33. Saroha K, Yadav B, Sharma B. Transdermal Patch: A Discrete Dosage Form. Int J Current Pharmaceutical Res 2011:3(3): 98-108.
34. Debjit B C, Margret C, Jayakar B, Sampath K P. Recent Advances In Transdermal Drug Delivery System Int J PharmTech Res 2010;2(1):68-77
35. Patel D S, Patel M V, Patel K N, Patel B A, Patel P A. Transdermal Patches: A Complete Review on Transdermal Drug Delivery System. International Journal for Pharmaceutical Research Scholars 2012; 1(1): 55-71.
36. Lende L K, Grampurohit N.D, Gaikwad .D.D, Gadhave M.V, Jadhav S.L. Transdermal Patches: A Review. Int J Pharma Res Dev 2011;4(03):096-103.
37. Guyot M, Fawaz F. Design and *In Vitro* Evaluation of Adhesive Matrix For Transdermal Delivery Of Propranolol. Int J Pharmaceutics 2000; 204:171-182.
38. Sinha V R, Pal K M. Permeation Enhancers for Transdermal Drug Delivery Drug Dev Industrial Pharmacy 2000; 26(11): 1131-1140.
39. Aqil M, Ali A. Monolithic Matrix Type Transdermal Drug Delivery Systems of Pinacidil Monohydrate: In Vitro Characterization. European J Pharm Biopharmaceutics 2002; 54:161-164.