



Development and Evaluation of Granisetron Transdermal Patches for Supportive Therapy of Chemotherapy Induced Nausea and Vomiting.

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ABSTRACT:

The present aim 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 clinically effective concentration over a prolonged period of time. Transdermal Drug Delivery Systems 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) side effects reported by cancer patients. Other common adverse effects (AEs) of chemotherapeutic agents. 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. 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 Granisetron, antiemetic, Chemotherapy-induced nausea and vomiting.

1. Introduction:

Conventional system of medication has numerous problems and complications. Conventional doses form either 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 circulation⁶. 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, diarrhoea, 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 therapy⁹. Granisetron Hydrochloride is a novel antiemetic and anti-nauseant drug. It is a selective serotonin (5-HT₃) 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-HT₃ 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 patches¹⁰. 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.

2. Instrumental Work:

2.1 Preformulation study:

Selection of λ max and Calibration curve of Granisetron Hydrochloride¹¹¹².

2.2 Determination of pH¹³

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

2.3 Determination of melting point¹³¹⁴

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.

2.4 Determination of partition coefficient¹³

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. $C_{o/w} = \text{Concentration of drug in non-aqueous phase} / \text{Concentration of drug in aqueous phase}$.

2.5 Permeability parameter¹⁵

Permeability Coefficient (P): Permeability coefficient is the velocity of drug passage through the membrane/skin in $\mu\text{g}/\text{cm}^2/\text{h}$. The permeability coefficient was calculated from the slope of the graph of percentage of drug

transported vs. time as:

$$P = \text{slope} \times V_d / S \text{-----} (1)$$

Where, V_d = 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:

$$\text{Flux (J)} = P \times CD \text{.....} (2)$$

Where, CD = concentration of drug in donor solution, P = permeability coefficient.

2.6 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°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 37°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 aliquots¹⁶.

2.7 Compatibility studies:

The compatibility of Granisetron hydrochloride and polymers (HPMC E15 and 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 ¹⁷.

2.8 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 cm² and stored in a desiccator. The composition of the patches is shown in table¹⁸.

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

Table No: 1 Formulation & compositions of transdermal patches

2.9 Evaluation of Prepared Transdermal patches:

Thickness¹⁹

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.

Flatness²⁰

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.

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

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

Weight uniformity²¹

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 endurance²²

The folding endurance was measured manually for the prepared films. A strip of film 2.2cm² 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.

2.10 Diffusion cell ²³

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°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.

3. Result And Discussion:

3.1 Wavelength selection.

Selection of λ max and Calibration curve of Granisetron Hydrochloride.

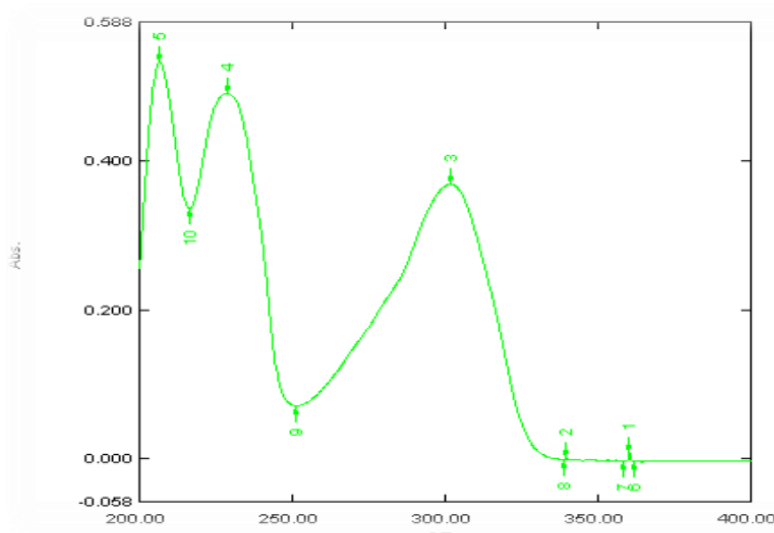


Fig No: 1 UV Spectra of Granisetron Hydrochloride

Sr. No	Parameters	Drug (Granisetron Hydrochloride)
1.	Detection Wavelength (λ max)	305nm

Table No: 2 UV Spectra of Granisetron Hydrochloride

3.2 pH and melting point:

pH and melting point of Granisetron hydrochloride were shown in table

Sr. No	Drug	Melting Point	pH
1	Granisetron Hydrochloride	219 ^o c	4.6

Table No: 3 pH and melting point

3.3 Partition coefficient of drug Granisetron Hydrochloride

Sr.No	Partition coefficient of drug	Solvent system	Log D values
1	Granisetron Hydrochloride	Octanol : water	2.4

Table No: 4 Partition coefficient of drug Granisetron Hydrochloride

3.4 Permeation study of Granisetron Hydrochloride in phosphate buffer pH 7.4

Sr. No.	Time(min)	% permeated
1	0	0
2	30	3.0
3	60	5.1
4	90	11.2
5	120	12.3
6	150	15.2
7	180	18.3
8	210	20.1
9	240	24.3
10	270	25.1
11	300	30.0
12	330	34.8
13	360	36.1
14	390	37.5
15	420	37.9
16	450	38.2
17	480	38.3
18	510	38.8
19	540	39.1
20	570	39.3
21	600	39.7

Table No: 5 Permeation study of Granisetron Hydrochloride in phosphate buffer pH 7.4

3.5 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. 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 define interaction between drug, and polymers.

3.6 Thickness, weight variation, folding endurance.

Batches	Thickness	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±0.07	91.66±1.52	100%
F3	2.03±0.0577	16.16±0.15	93±0.015	100%
F3	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	18.7±0.22	122±0.016	100%
F7	3.7±0.100	20.73±0.20	122.33±1.52	100%
F8	3.8±0.100	21.56±0.30	125±1.52	100%
F9	3.89±0.111	22.2±0.22	124±1.37	100%
F10	3.97±0.152	23.09±0.23	125±0.149	100%

Table No: 6 Thickness, weight variation, folding endurance.

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 in variation in weight observed in different formulation may attribute to the variation 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.

3.7 Result obtained of In Vitro permeation study of Transdermal patches of Granisetron Hydrochloride of batches F1 to F10.

Time (Hr)	Batches									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	16.22	15.22	15.45	15.65	16.12	14.23	10.66	10.56	8.71	7.05
2	20.22	18.32	21.35	23.97	26.68	22.74	18.33	15.26	12.33	7.92
3	20.83	25.33	30.64	32.66	38.76	30.52	25.33	21.28	15.98	10.01
4	23.25	28.36	35.87	38.55	49.09	37.13	30.64	26.22	20.21	11.27
5	30.21	36.57	45.36	49.97	55.41	45.2	39.28	30.69	25.66	15.91
6	37.26	44.85	52.66	55.97	61.11	54.97	48.39	40.27	30.54	20.69
7	48.66	55.36	60.89	65.88	70.71	65.7	58.69	47.54	35.39	25.97
8	58.69	64.98	67.69	73.97	78.55	72.97	67.95	54.67	45.69	35.59
9	64.33	72.58	76.08	79.66	85.24	78.99	75.22	60.83	53.11	48.66
10	68.56	76.33	80.55	84.66	88.74	88.35	80.23	70.88	64.94	59.66
11	75.22	77.65	82.75	87.25	93.02	91.44	82.27	77.85	73.41	70.23
12	75.22	77.65	86.37	93.51	96.43	92.71	87.24	84.78	79.76	76.22

Table No: 7 In Vitro permeation study of Transdermal patches of Granisetron Hydrochloride of batches F1 to F10.

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/cm²/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/cm² but flux get decreased after 9h. Batch F3 showed flux 105.17 µg/cm² but showed similar problem to that of batch F2 that flux is get decreased after 10 h. Batch F4 showed flux of 106.70µg/cm² but flux was not linear after 10 h. Batch F5 showed flux of 109 µg/cm². 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/cm²/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/cm²/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.

4. Conclusion:

In this work to development and Assesment of transdermal patches of Granisetron Hydrochloride For Supportive Therapy Of Chemotherapy Induced Nausea And Vomiting. Based on the results, it could be concluded that selected polymers were better suited for development of transdermal patch of Granisetron hydrochloride For Supportive Therapy of Chemotherapy Induced Nausea And Vomiting. 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 96.43%. Upto 12hrs maintain clinically effective concentration over prolong period of time.

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