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In vitro evaluation of Transdermal Patch of Palonosetron for Antiemetic Therapy

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Abstract

Skin is one of the routes for systemic delivery of drugs through various drug delivery system. A transdermal Drug Delivery System (TDDS) is one of the most reliable and useful system to deliver drug systemically through skin. Generally medicated patch is placed on skin for delivery of medication through it into the blood stream. The aim of present study was to formulate and evaluate Palonosetron transdermal patch in vitro that could be used for antiemetic therapy. The incorporation ofPalonosetron a serotonin 5-HT_3 antagonist drug was envisaged. The TDDS was prepared by solvent evaporation technique and was evaluated for organoleptic characteristics and other physicochemical properties Thickness, Weight variation, Drug content uniformity, Tensile strength, % Elongation, Folding endurance & Moisture content. The in vitro permeation study of the patch was carried out through KesaryChein diffusion cell as barrier membrane. Phosphate buffer pH 7.4 was used as dissolution medium and the temperature was maintained at 37 ± 1^0C. The in vitro permeation study of the prepared patch indicated a time dependent increase in drug release throughout the study. The percentage of cumulative drug release was found to be 76.25% in 24 hours.The study shows a new approach to work in with Palonosetron.

Keywords. Palonosetron, Transdermal Drug Delivery System, Serotonin 5-HT_3 antagonist

Introduction

A transdermal drug delivery system useful for the controlled systemic delivery of drugs via. skin. It is not a new concept for drug delivery through the skin, because many topical preparations are available over the years for local and systemic delivery of drugs.[1] But due to the low bioavailability of those delivery systems it was found very difficult to achieve precise drug concentration. The TDDS can deliver certain medications to systemic circulation preferably at specific rate. It also offers significant advantages such as avoidance of the heptic-first-pass metabolism and avoidance of gastrointestinal drug absorption difficulty.[2] As it comprises with a face membrane, the backing sheet and membrane secured together to form an intermediate reservoir and an impervious backing sheet. [3-7]

Though the concept of TDDS is not much new but the use of this delivery system in the delivery of antiemetic drug is a new concept.[8] As vomiting/emesis is an abnormal indication of gastrointestinal tract, which needs an urgent medical attention. The oral route of medication is usually not suited and parenteral therapy has various limitations and drawbacks. Thus, a need arises to explore a possible alternate route through skin, that is, transdermal.[9] Although the conventional medicine, the antiemetic treatment has certain side effects. Hence, it needs to turn towards safe, effective and time tested system of delivery system. Thus, it is desirable to provide an effective and reliable transdermal drug delivery system for the treatment of vomiting and nausea.

Examples of marketed transdermal drug delivery system[3]

Sr. No.	Therapeutic agent	Marketed name (company)	References
1	Clonidine	Catapres TTS (BoehringerIngelheim)	[10, 11]
2	Estradiol	Vivelle (Novartis)	[6, 7, 12]
3	Fentanyl	Duragesic (Janssen)	[7, 13, 14]
4	Nicotine	Prosstep (Lederie)	[6, 7, 15]
5	Testosterone	Testoderm (Alza)	[6, 16, 17]
6	Nicotine	Habitrol (Novartis Consumer)	[15, 18]
7	Nicotine	Nicoderm CQ (Smithkline Beecham Consumer)	[7, 19, 20]
8	Nitroglycerine	Transderm-Nitro (Novartis)	[6, 14, 21]
9	Scopolamine	Transderm-Scop (Novartis Consumer)	[3, 8, 22]

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Objectives

The aim of the present study was to formulate and evaluate antiemetic transdermal drug delivery system to provide systemic release. In the present formulation, incorporation of Palonsteron an antiemetic drug was envisaged. At the same time in vitro evaluation also to be done.

Materials and methods

The Reagent and materials of Pharma/ best possible grade were used as supplied by the manufacturer. PalonosetronHCl (Pharma Grade) Sun rise Pharma, Polyvinyl Pyrrolidone (LR) Hi-media pharma, Ethyl Cellulose (Pharma Grade) Colorcon Goa, Eudragit (LR) EvonikPharma Germany Chloroform (LR) Merck Ltd., Mumbai Oleic acid (LR) Ranbaxy fine chemicals Ltd., New Delhi, Dibutyl Phthalate (LR) Ranbaxy Fine Chemicals Ltd., New Delhi, Methanol (LR) Rankem, fine chemicals Limited, Mumbai, Poly Vinyl Alcohol (LR) Hi-media pharma. No foreign matter or impurities were found during inspection.

Formulation of an Antiemetic Transdermal Patch

The matrix-type transdermal patches containing PalonosetronHCl were prepared using different ratios of ethyl cellulose, polyvinylpryrrolidone, Eudragit and polyvinyl alcohol. The polymers in different ratios were dissolved in the respective solvents.[4] Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Di-n-butyl phthalate and propylene glycol were used as plasticizers. Oleic acid was used as the penetration enhancer. Then the solution was poured on the Petri dish having surface area of 78.5 cm^2 and dried at the room temperature. Then the patches were cut into 5x5 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 14.5 mg the formulation.[23]

Evaluation of Prepared Patches

Organoleptic Characteristics. Appearance, color, clarity, flexibility, and smoothness of prepared patch was physically inspected.
Thickness. The thickness of patch was measured by Vernier calipers. The thickness uniformity was measured at different sites and average was calculated.[24]
Weight Uniformity. Sixpatches of equal size were taken and weighed on electronic balance to check for weight variation.[24]
Folding Endurance. The patch was taken and folded repeatedly at same point till it breaks. The number of times patch could be folded without breaking was noted.[25]
Moisture Content. Theprepared patch was weighed and kept in the desiccator containing fused calcium chloride for about 24 hours. After that it was taken out and weighed again.[25]The percentage of moisture content was calculated on the basis of the following formula:

$$\text{Percentage of moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Drug Content. The patch was dissolved in methanol and the remaining volume was made up with distilled water to 100mL.Then the solution was filtered and the absorbance of the solution was taken at 304 nm and concentration was calculated.
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In Vitro Permeation Study of Patch.

Egg shell membrane was used for the in vitro permeation study of the prepared transdermal patch because the egg shell membrane resembles stratum corneum of human which consists of keratin mainly in it.[26] The membrane was prepared accordingly reported by Shah etal before use.[27]During the whole experiment37 ± 1^0C was maintained to provide a skin surface temperature on the outer jacket of water of the cell, and the pH 7.4 was maintained used as dissolution medium. After that the patch was cut in 5 5mm^2 piece which was taken and applied over the mounted membrane in diffusion cell and the samples were withdrawn from different compartment at regulated intervals. The sampling schedule was at 0, 0.5, and 1 hr for the first hour of release and then it was at every hour interval till 6^{th}hour of release.After that the whole system was kept in its normal position overnight and then next day reading was taken at 24^{th}hour.One mL of the receptor solution was collected as sample each time and simultaneously one mL of phosphate buffer solution was added back to the receptor cell for maintaining the same initial volume of the receptor cell solution. The collected samples were analysed using UV-Vis spectrophotometer.[24]

Results and Discussion

Vomiting/emesis is an emergent situation for which oral route of medication is usually not suited, especially in motion sickness condition where oral or parenteral route of administration is not admissible. However various antiemetic formulations are available through oral route but becomes useless during continuous vomiting. So, a pharmaceutical strategy was envisaged to generate significant scientific data by designing and developing a novel, safe,

noninvasive, and patient-friendly dosage form, that is, transdermal drug delivery dosage form.For the design and development of antiemetic drug into novel dosage form. The rationale behind formulation is to provide better patient compliance with reduced dose.

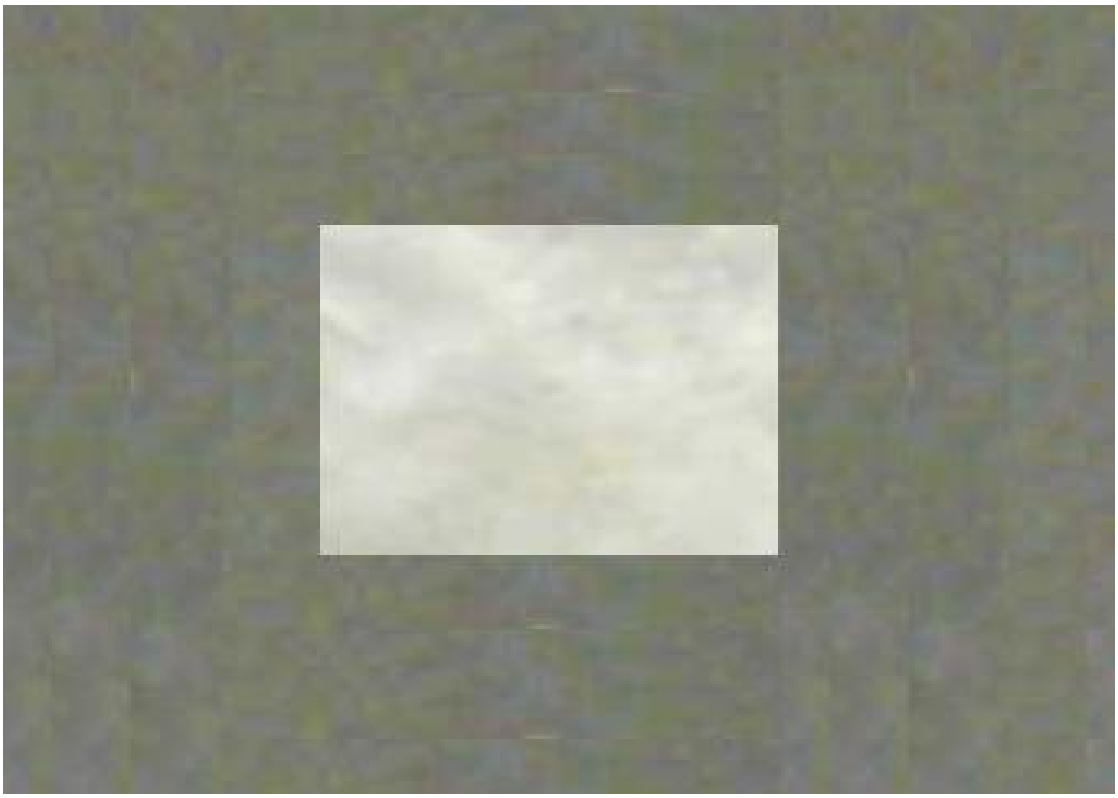
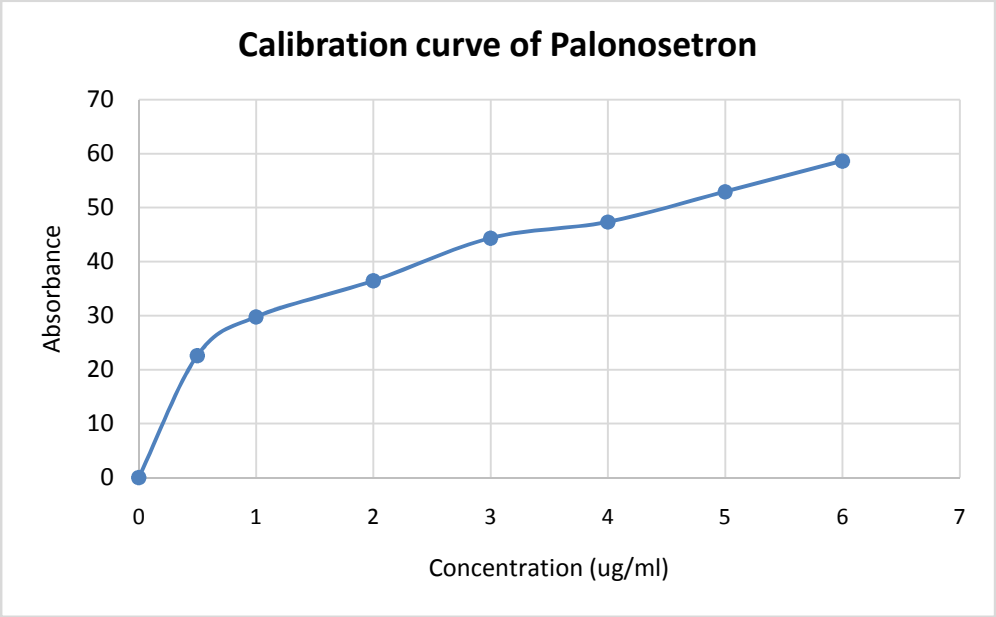


Figure 1: Sample of prepared transdermal antiemetic patch

Table 1: Standard calibration curve of PalonosetronHCl

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	4	0.277
3	6	0.361
4	8	0.482
5	10	0.58
6	12	0.60
7	14	0.823
8	16	0.928



Graph 1: Calibration curve of Palonosetron

Initially a standard calibration curve for Palonosetron was prepared. The absorbance values are given in Table 1. Using concentration and absorbance data, Beer and Lambert's plot was obtained. The plot is shown in Graph 1.

Organoleptic Characteristics

The prepared patches were slightly opaque, pale whitecolored, jellified preparations showing good flexibility and smoothness as given in Table 2. A sample of prepared patch is shown in Figure 2.

Thickness

The mean thickness of prepared patches was 0.61 ± 0.02608mm as given in Table 3.

Weight Uniformity. The mean weight of prepared patches was 0.26217±0.00248gm as given in Table3.

Folding Endurance. The mean folding endurance of prepared patches was 78.66667±1.21106as given in Table 3.

Moisture Content. The mean moisture content of prepared patches was 4.86833±0.0694% as given in Table 3.

Drug Content. The mean drug content of the prepared patches was 0.29267±0.0055mg in w/w ratio with the weight of patch as given in Table 3.

In Vitro Permeation Study of Patch. The in vitro permeation studies of the prepared transdermal patches indicated a time dependent increase throughout the study as shown in Figure 4. The drug release from patches was rapid during first hour and it slowed down thereafter. The percentage of drug release was 22.60% after30 minutes which further increased to 29.78% in one hour. The cumulative drug release increased gradually and reached 58.65% in 6 hours. Finally, at the end of study, the cumulative drug release reached a remarkable peak, that is, 76.25% in 24 hours, as given in Table 4.

Table 2: Oragnoleptic Characteristics of Transdermal Patch

S. No.	Physical Characteristics	Finding
1	Color	Pale white
2	Appearance	Jelly
3	Smoothness	Good
4	Clarity	Opaque
5	Flexibility	Excellent

Table 3: Physical characteristics of patch

S. No.	Thickness (mm)	Weight (gm)	Folding endurance	Moisture content (%)	Drug Content (mg)
1	0.64	0.261	80	4.98	0.298
2	0.57	0.265	78	4.78	0.285
3	0.61	0.263	77	4.82	0.291
4	0.62	0.258	79	4.85	0.296
5	0.59	0.262	78	4.90	0.298
6	0.63	0.264	80	4.88	0.288
Mean±SD	0.61±0.02608	0.26217±0.00248	78.66667±1.21106	4.86833±0.0694	0.29267±0.0055

Table 4: In vitro permeation study of patch

S. No.	Collection Time (in hrs)	Concentration (ug/ml)	%CDR
1	0	0	0
2	0.5	6.428	22.6
3	1	8.26	29.78
4	2	10.245	36.45
5	3	12.590	44.35
6	4	15.856	47.35
7	5	18.355	52.95
8	6	20.245	58.65
9	12	21.865	64.38
10	24	31.585	76.25

Conclusion

According to the current demand in pharmaceuticalscenario, it was felt that new drug delivery system is necessary to handle the vomiting condition especially in motion sickness where if a patient needs to travel for more than 24hrs. And the unavailability of dosage form which can provide relief for more than 24hrs, transdermal patch shall be a better option than oral dosage form. Because the patch was found to be stable, controlled release, with longer duration of action without any signs of skin irritation. The study shows a novel approach in pharmaceutics to use various antiemetic drugs with other dosage forms. Further, a clinical study is warranted to evaluate therapeutic efficacy of current dosage form.

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