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FORMULATION DEVELOPMENT AND COMPARATIVE EVALUATION OF TRANSDERMAL DELIVERY SYSTEM FOR EFFECTIVE ANTI-EMETIC THERAPY

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Dolasetron, Eudragit RL-100, Eudragit RS-100, Ethylcellulose, Polyvinyl pyrrolidine, *In-vitro* drug release

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ABSTRACT: Transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Transdermal patches of dolasetron have prepared by the solvent evaporation method using eudragit RL-100: eudragit RS-100 and ethylcellulose: PVP, using different ratios (8:2, 6:4, 5:5), in solvents like ethanol and methanol (1.25:1.25). The dry films of the prepared patches evaluated for physicochemical parameters such as flexibility, thickness, smoothness, weight variation; moisture content, hardness and tensile strength. The formulation exhibited flexibility, uniform thickness and weight, smoothness, good drug content (92 to 96%) and little moisture content. The *in-vitro* diffusion studies carried out for the formulated TDD patches followed by the Higuchi diffusion mechanism. The fabricated formulation has identified as ideal formulations depending on their drug release properties on the comparison, at the end of 48 h of the formulations. The formulation is containing eudragit RL-100: eudragit RS-100 (hydrophobic polymers) or a combination of hydrophilic and hydrophobic polymers (ethylcellulose and PVP). The stability studies indicated that all the patches maintained the good physicochemical properties and drug content after storing the patches in different storage conditions. However, the compatibility studies indicated that there has no interaction between the drug and polymers. The higher percentage of drug released in formulations E1, P3 that follows zero-order kinetics (0.940) and Higuchi diffusion equation (0.875). Further, the E1 and P3 formulations have identified as ideal formulations depending on their comparison of the drug release properties.

INTRODUCTION: A medicated transdermal patch system is one of the novel drug delivery in which it is placed on the skin surface to deliver the specific dose of medicament *via* skin to the blood circulation through the skin and into the bloodstream [1].

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The main focus to make this TDDS is to enhance the skin instability and to diminish the retention and metabolism of the drug in the skin [2, 3].

The transdermal route of administration is recognized as one of the potential routes for the local and systemic delivery of the drugs and offers the several advantages over the conventional mode of drug administration including avoidance of the first-pass metabolism by the liver, minimization of pain, reduction of side effects, extended duration of the activity, reduction in the fluctuations of drug concentrations in the blood and of course a possible sustained drug release drug delivery [4, 5].

Moreover, this system is a viable alternative to deliver drugs with improved bioavailability [6]. Nausea and vomiting are quite often found in many therapeutic drugs' side effects, which cannot be avoided, which need urgent medication to stop. Dolasetron is an antinauseant and antiemetic agent indicated for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting. Dolasetron is a highly specific and selective serotonin 5-HT3 receptor antagonist, the serotonin 5-HT3 receptors located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema [7]. However, the oral and the parental route could not meet patient compliance as they produce unwanted shortcoming thus, an emerging need arises to explore the possible alternative route *via* the skin, *i.e.,* TDDS [8].

The present study demonstrates the significant amount of Dolasetron delivery across the skin through mucoadhesive patches formulations by matrix dispersion type transdermal therapeutic system. The various formulations containing Dolasetron have prepared by using two different types of rate-controlling polymer matrices *viz*. eudragit-RL-100 and eutragit-RS-100 incorporated with plasticizer diethyl phthalate [9]. Then these formulations were subjected to the evaluation of physicochemical parameters and *in-vitro* permeability of Dolasetron from adhesive film [10].

EXPERIMENTAL SECTION:

Materials: Dolasetron was a gift sample from M/s Sanofi-Aventis (U. S. LLC). Eudragit RL 100 (ERL 100), eudragit RS 100 (ERS 100) was obtained from Rohm Pharma, Germany, polyvinyl pyrrolidine (PVP) was procured from Ozone International, Mumbai and ethylcellulose was procured from Sulab Reagent, Mumbai. The other chemicals used in the study were of AR grade.

Preparation of Transdermal Patches: The matrix-type transdermal patches Dolasetron (100 mg) composed of the polymers like eudragit-RL-100 and eutragit-RS100 in the ratio of 8:2, 6:4 and 5:5 were dissolved in the solvent mixture methanol and ethanol (1:1) in a magnetic stirrer [11]. The diethyl phthalate [12] was incorporated as a plasticizer at a concentration of 10% w/w of the dry weight of the polymer; the polymeric drug solution was poured over the surface of the mercury in a petri dish [13]. The rate of evaporation was controlled by inverting the funnel. After 24 h the dried films were then taken out and stored in desiccators for further evaluation.

Physicochemical Characterization of Patches:

Thickness and Weight Variation: The thickness was measured at five different points of the film through Baker Digital Caliper; the average of five readings was calculated [14]. The weight variation was studied by taking the individual weight of the 10 randomly selected patches from each formulation [15].

Drug Content: A 5 cm^2 film was cut into small pieces; 100 ml of the buffer (pH 7.4) was added and shaken continuously for 24 h then ultra-sonicated for 15 min [16]. After filtration, the drug was estimated spectrophotometrically at 240 and 340 nm. The preliminary studies indicated that there was no interference of polymers in the excitation and emission wavelengths of the drug.

Flatness: Three longitudinal strips were cut out from each film *viz*. 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured, and the variation in the length because of non-uniformity in flatness was measured by determining the percent constriction, with 0% constriction equivalent to 100% flatness [17].

Folding Endurance: Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking was measured [18].

Percentage of Moisture Content and Moisture Uptake: The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 h. The individual films were weighed repeatedly until they showed a constant weight [19]. However, a moisture uptake was measured by a weighed film that was kept in a desiccator at room temperature for 24 h and after exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained [20].

The percentage of moisture content was calculated as the difference between the initial and final weight concerning the final and initial weight correspondingly.

FTIR Analysis of Dolasetron TDD Patch: The FTIR spectra of the Dolasetron TDD patch were recorded with an equnox 55 Fourier transform infrared spectrometer (Bruker, Germany) by a direct transmission method scanning from 4000 to 400 cm^{-1} at a resolution of 2 cm^{-1} [21, 22].

X-ray Diffraction: The diffraction pattern of pure drug, polymers and formulated patches were scanned over 2θ range of 0° and 80° at a rate of 2° per min on 0.02º 2θ step size *via* X-ray diffract meter (Reguku Miniflex, Japan) consisted of a 30 kV, 15 mA generator with Cu-Kα radiation anode tube.

Scanning Electron Microscopy (SEM) Analysis of TDD Patch: The external morphology of the Dolasetron TDD patch was analyzed before and after the permeation experiment using sirion 200 scanning electron microscope philips, Netherlands. For SEM analysis, the surfaces of the corresponding patch were sputtered with gold in a vacuum before viewing under the microscope. The patches after the permeation experiment were washed several times by distilled water [23].

***In-vitro* Skin Permeation Studies:** *In-vitro* skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 20 ml, the excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH of 7.4 [24].

The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for the drug content spectrophotometrically at 284 nm [25]. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

The cumulative amounts of drug permeated per square centimeter of patches were plotted against time [26].

Stability Studies: To any rational design and evaluation of dosage forms, the stability of the active component must be a major criterion in determining the acceptance or rejection. The stability studies of the formulated transdermal patches were carried out on prepared films at different temperatures and humidity 25-30 °C (60% RH) and 45-50 °C (75% RH) over a period of 60 days. The patches were wrapped in aluminum foil and stored in the stability chamber and characterized for drug content and other parameters at regular intervals (0, 15, 30, 45 and 60 days) [27].

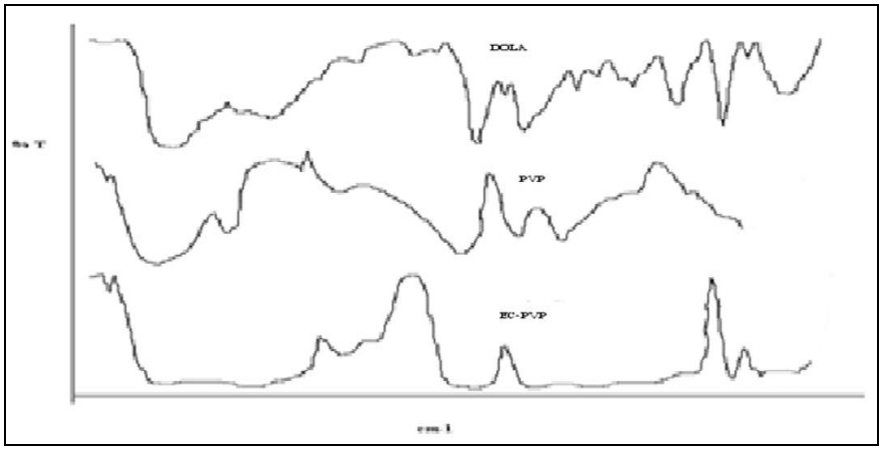
RESULTS: The matrix-type transdermal films of Dolasetron (100 mg) have prepared by the solvent evaporation technique using a combination of hydrophilic and lipophilic polymers. In the present study, a total of six formulations (E1, E2, E3, P1, P2, and P3) has prepared by varying polymer ratios, and by using different polymers. These patches have subjected to the evaluation of various physicochemical characteristics and drug release studies. All the patches prepared with different Polymer concentrations have found to be flexible, smooth, opaque, nonstick, and homogeneous. The PVP added to the insoluble film former ethyl cellulose that tends to increase its release rate. The resultant can be contributed to the leaching of the soluble component, which leads to the formation of pores and then decreases in the mean diffusion path length of the drug molecules. PVP acts as a nucleating agent that retards the crystallization of the drug and enhances the solubility of the drug in the matrix by sustaining it in an amorphous form. The results of the physicochemical evaluation of different polymeric films showed uniform drug content and minimum batch variation in **Table 1**.

The thickness of the patches varied from 0.12 to 0.16 nm. The results also showed the uniformity in weight of 0.2 g. The physical appearance of the patches and the effect on aging indicated that the patches need to be stored in properly sealed airtight packing to keep them protected from extremes of moisture that may alter their appearance; thus, the properties have found to be within limits and satisfactory.

TABLE 1: PHYSICOCHEMICAL CHARACTERIZATION

Formulation code	Thickness (nm)	Uniformity of weight (g)	Flatness and elongation break (%)	Folding endurance (no's)	Moisture content %	Moisture absorption (%)	Drug content mg
E1	0.16	0.228	99.6	124	3.6251	1.09	17.39
E2	0.14	0.219	102	119	2.9753	1.765	16.8
E3	0.15	0.223	96	127	2.4981	2.342	17.82
P1	0.12	0.238	104	102	5.0345	1.5321	18.29
P2	0.12	0.215	96	114	4.8715	2.4837	17.19
P3	0.13	0.209	96	105	4.0577	1.8652	18.46

Fourier Transform Infrared Spectroscopy (FT-IR): The FT-IR analyses of a physical mixture of drug-polymer have presented in **Fig. 1**, shows the major peak of dolasetron, eudragit RL 100 and eudragit RS 100, ethylcellulose and polyvinyl pyrrolidine (PVP). The spectrum of dolasetron displays a characteristic absorption at 2912.48 cm^{-1} (Methyl asymmetric stretch), 1463 cm^{-1} (Methyl asymmetric bend), 754.57 cm^{-1} (1, 2 disubstitution ortho), eudragit RL 100 displays peak at 1646.78 cm^{-1} (Ketone and alkyl CDC stretch), 2996.45 cm^{-1} (Methyl asymmetric stretch), 848.08 cm^{-1} (1, 4 distribution), eudragit RS 100 displays peaks at 1733.81 cm^{-1} (Ketone), 1636 cm^{-1} (Alkyl CDC stretch), 848.95 cm^{-1} (Disubstitution), PVP displays peaks at 3446.35 cm^{-1} (Ketone), 1647 cm^{-1} (Heterocyclic amine NH stretch) and 738.52 cm^{-1} (1, 2 disubstitution ortho). **Fig. 1** this confirms the dolasetron was not interacting with polymers during the preparation [21].



X-Ray Diffractometry: The XRD study of pure crystalline drugs, polymers, and formulated patches have shown in **Fig. 2.1** and **2. 2**. The numerous distinctive peaks occurred on the crystalline drug of dolasetron diffract gram at approximately 2θ angles of 12.06, 12.46, 23.32, 30.12, and 30.24. However, the XRD profiles of pure crystalline drugs illustrate the similar peaks have observed for the formulated patches also. Based on these result, the formulated dolasetron showed that the drug has molecularly and evenly dispersed in the polymeric films [28].

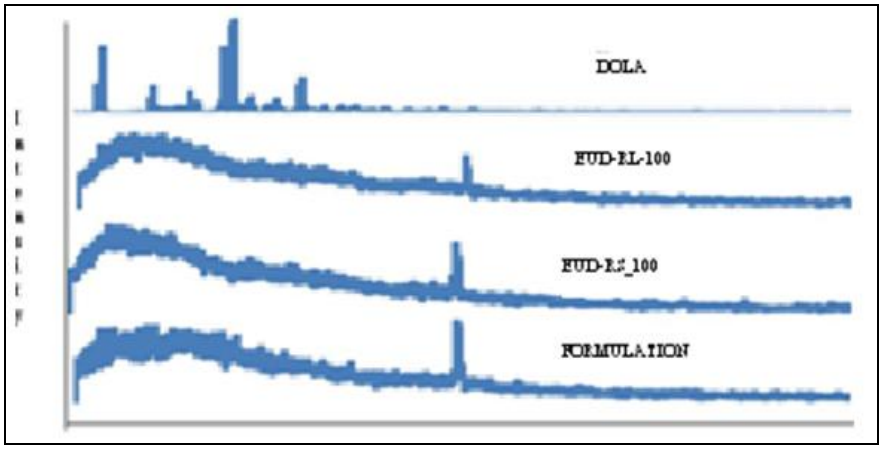


FIG. 2.1: POLYMERS (EUDRAGIT RL-100 AND RS 100) AND FORMULATED PATCH

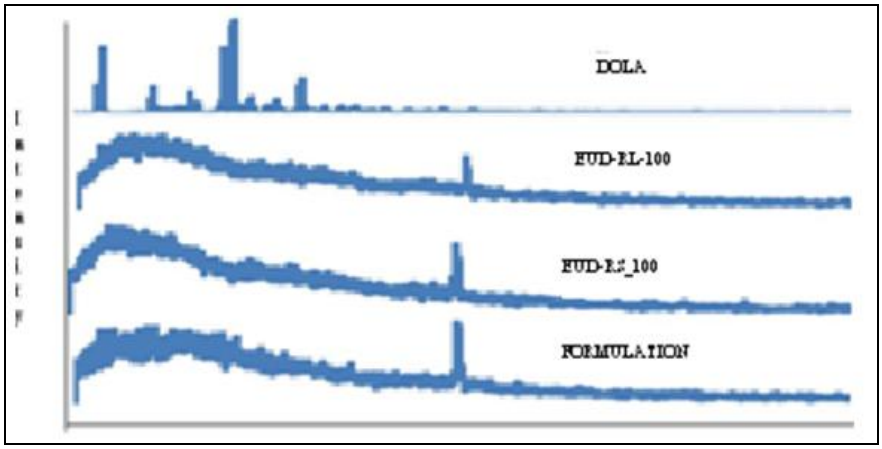


FIG. 2.2: POLYMERS (ETHYL CELLULOSE AND PVP) AND FORMULATED PATCH

Scanning Electron Microscope: The SEM **Fig. 2**, **3** analysis was performed to investigate the surface morphologies and pore size before and after diffusion of patches [29,] and the result was shown in **Fig. 3 (1-4)**.

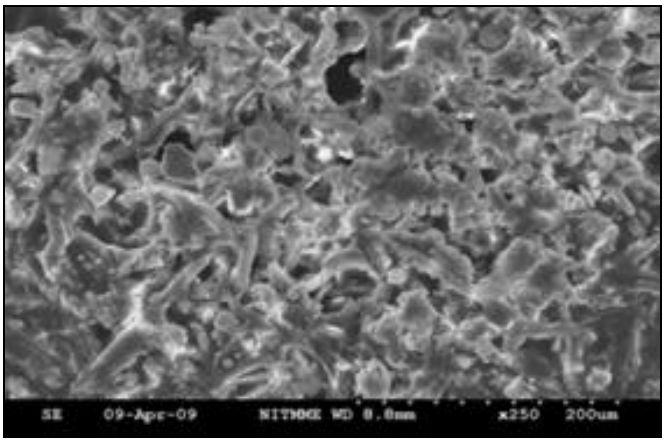


FIG. 3.1: ETHYL CELLULOSE-PVP PATCH BEFORE DIFFUSION

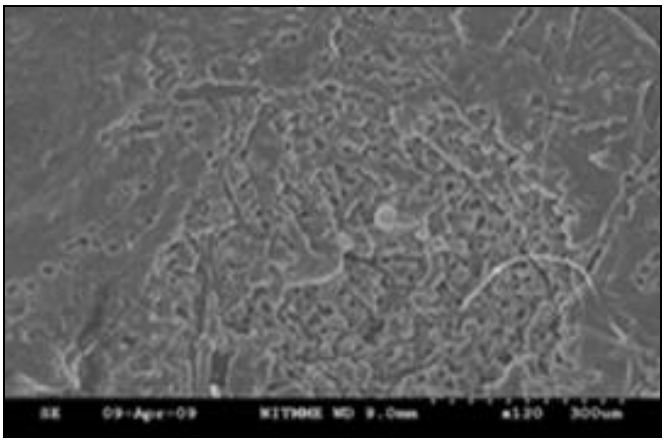


FIG. 3.2: ETHYL CELLULOSE-PVP PATCH AFTER DIFFUSION

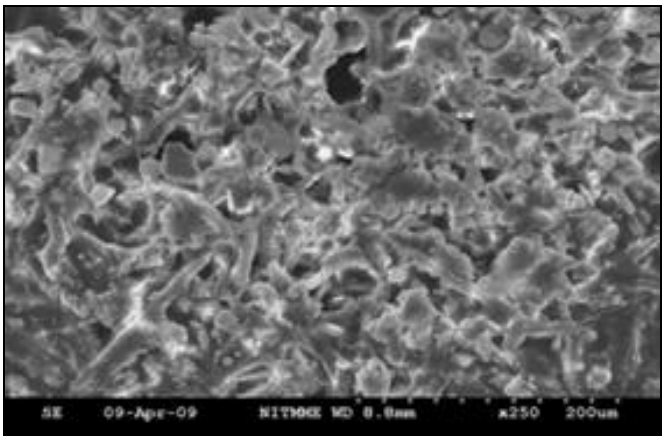


FIG. 3.3: EUDRAGIT RL-100 AND RS-100 PATCH BEFORE DIFFUSION

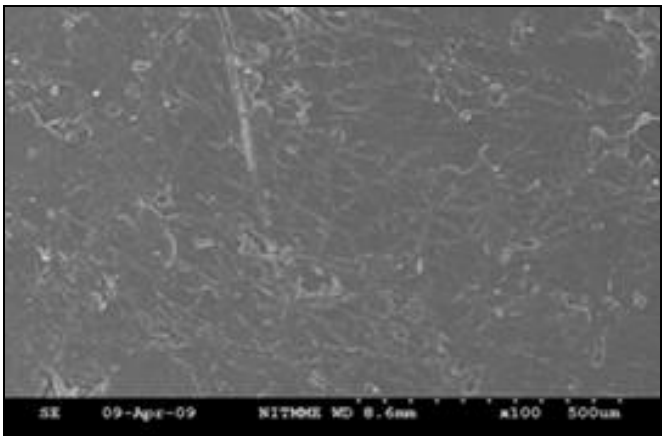
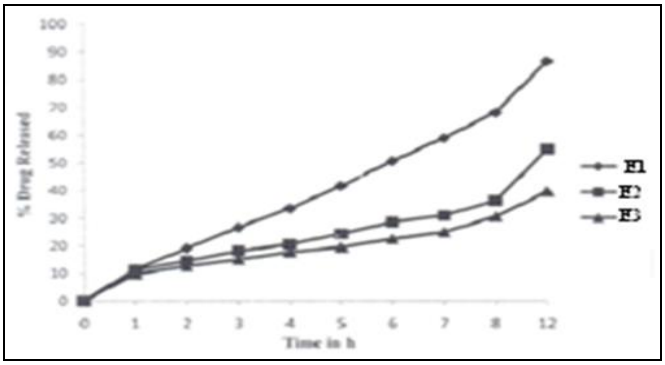
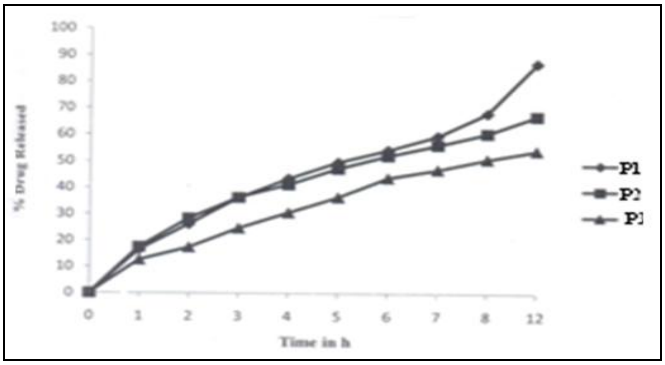


FIG. 3.4: EUDRAGIT RL-100 AND RS-100 PATCH AFTER DIFFUSION

In-vitro **Diffusion Studies:** The release of dolasetron from formulated patches was studied was modified by Franz diffusion cell [26, 30, 31] in pH 7.4 buffer solution using the exercised rat skin. The drug release from the patches was calculated at the end of 12 h. The formulation E1-83.244, E2-72.097, E3-66.246, P1-70.269, P2-79.548, and P3-81.682% of drug released at 12 h **Table 2-7** and **Fig. 4**.





EUDRAGIT RL-100 AND EUDRAGIT RS-100 **ETHYL CELLULOSE AND PVP FORMULATION**

FIG. 4: *IN-VITRO* DIFFUSION PROFILEOF FORMULATED TDD PATCHES

TABEL 2: KINETIC DATA OF EUDRAGIT RS 100 AND RL 100 (8:2) FORMULATION

Time	SQRT	LOG -T	DR	DTR	LOG - DR	LOG - DTR	CR - DTR
0	0	0	0	100	0	2	4.641589
1	1	0	13.568	86.432	1.132576	1.936675	4.421385
2	1.414214	0.30103	22.082	77.198	1.344038	1.898638	4.271161
3	1.732051	0.477121	25.572	74.428	1.407765	1.871736	4.206415
4	2	2.60206	27.341	72.659	1.46814	1.868289	4.172821
5	2.236068	0.69897	33.783	66.217	1.528698	1.82097	4.045664
6	2.44949	0.778151	37.146	62.854	1.569912	1.798333	3.975981
7	2.645751	0.8455098	63.48	36.52	1.802637	1.562531	3.317749
8	2.82427	0.90309	66.888	33.112	1.835348	1.519985	3.299951
12	3.464102	1.07181	83.244	18.056	1.913517	1.256622	2.623456

TABLE 3: KINETIC DATA OF EUDRAGIT RS 100 AND RL 100 (6:4) FORMULATION

Time	SQRT	LOG -T	DR	DTR	LOG - DR	LOG - DTR	CR - DTR
0	0	0	0	100	0	2	4.641589
1	1	0	20.187	79.813	1.305074	1.902074	4.305509
2	1.414214	0.30103	27.29	72.71	1.4360004	1.861594	4.173798
3	1.732051	0.477121	33.257	66.743	1.521883	1.824406	4.056348
4	2	0.60206	38.663	61.337	1.587296	1.787723	3.943733
5	2.236068	0.69897	42.68	57.32	1.6304224	1.758306	3.85569
6	2.44949	0.778151	47.459	52.541	1.636919	1.720498	3.74541
7	2.645751	0.845098	53.011	46.989	1.724366	1.671996	3.608545
8	2.82427	0.90309	58.564	41.436	1.767631	1.617378	3.460397
12	3.464102	1.079181	72.097	28.913	1.85179	1.461093	3.069241

TABLE 4: KINETIC DATA OF EUDRAGIT RS 100 AND RL 100 (5:5) FORMULATION

Time	SQRT	LOG -T	DR	DTR	LOG - DR	LOG - DTR	CR - DTR
0	0	0	0	100	0	2	4.641589
1	1	0	1.45	98.55	0.161368	1.993657	4.619048
2	1.414214	0.30103	18	82	1.255273	1.913814	4.344481
3	1.732051	0.477121	22.12	76.87	1.364176	1.885757	4.251925
4	2	0.60206	31.605	67.191	1.515993	1.827311	4.065404
5	2.236068	0.69897	36.38	61.662	1.583629	1.7990018	3.950686
6	2.44949	0.778151	41.517	58.183	1.621353	1.764796	3.874943
7	2.645751	0.845098	44.786	55.128	1.651975	1.741372	3.8059
8	2.82427	0.90309	49.638	50.992	1.690267	1.707502	3.708236
12	3.464102	1.079181	66.246	33.823	1.820707	1.529212	3.233298

TABLE 5: KINETIC DATA OF ETHYL CELLULOSE AND PVP (8:2) FORMULATION

Time	SQRT	LOG -T	DR	DTR	LOG - DR	LOG - DTR	CR - DTR
0	0	0	0	100	0	2	4.641589
1	1	0	26.634	76.437	1.372231	1.883304	4.243927
2	1.414214	0.30103	35.248	69.735	1.480941	1.843451	4.116078
3	1.732051	0.477121	46.463	62.627	1.572558	1.796762	3.971189
4	2	0.60206	51.526	58.122	1.621986	1.764341	3.873539
5	2.236068	0.69897	44.623	55.277	1.650531	1.742544	3.809326
6	2.44949	0.778151	53.475	46.525	1.728151	1.667686	3.596628
7	2.645751	0.845098	46.389	43.211	1.754264	1.635594	3.509119
8	2.82427	0.90309	44.569	39.401	1.782465	1.595507	3.402795
12	3.464102	1.079181	70.269	25.782	1.870509	1.411317	2.954193

TABLE 6: KINETIC DATA OF ETHYL CELLULOSE AND PVP (6:4) FORMULATION

Time	SQRT	LOG -T	DR	DTR	LOG - DR	LOG - DTR	CR - DTR
0	0	0	0	100	0	2	4.641589
1	1	0	26.428	73.572	1.422064	1.866713	4.190227
2	1.414214	0.30103	32.358	67.642	1.509982	1.830216	4.07448
3	1.732051	0.477121	47.777	52.223	1.679219	1.717862	3.737839
4	2	0.60206	55.965	44.035	1.747917	1.643798	3.531284
5	2.236068	0.69897	58.812	41.188	1.769466	1.614771	3.45348
6	2.44949	0.778151	62.245	37.755	1.794104	1.57674	3.354735
7	2.645751	0.845098	65.872	34.128	1.818701	1.533111	3.243672
8	2.82427	0.90309	70.949	29.051	1.850946	1.464161	3.074117
12	3.464102	1.079181	79.548	19.095	1.903605	1.298962	2.710113

TABLE 7: KINETIC DATA OF ETHYL CELLULOSE AND PVP (5:5)

Time	SQRT	LOG -T	DR	DTR	LOG - DR	LOG - DTR	CR - DTR
0	0	0	0	100	0	2	4.641589
1	1	0	1.45	98.1613	0.161368	1.993659	4.619045
2	1.414214	0.30103	26.79	73.21	1.427973	1.86457	4.183343
3	1.732051	0.477121	32.538	67.462	1.512391	1.829059	4.070862
4	2	0.60206	50.63	49.37	1.704408	1.693463	3.668493
5	2.236068	0.69897	57.683	42.317	1.761048	1.626515	3.48475
6	2.44949	0.778151	64.011	35.989	1.806255	1.55617	3.301591
7	2.645751	0.845098	70.554	29.446	1.848522	1.469026	3.087987
8	2.82427	0.90309	75.853	24.147	1.879973	1.382863	2.890376
12	3.464102	1.079181	81.682	19.322	1.906755	1.286052	2.683391

TABLE 8: STABILITY STUDIES

Storage condition and month	Formulation code	Thickness (nm)	Uniformity of weight (g)	Flatness and elongation break (%)	Folding endurance (no's)	Moisture content (%)	Moisture absorption (%)	Drug content (mg)
25 °C / 65% RH and 3rd Month	E1	0.16	0.228	99.6	124	3.6251	1.09	17.39
	E2	0.14	0.219	102	119	2.9753	1.765	16.8
	E3	0.15	0.223	96	127	2.4981	2.342	17.82
	P1	0.12	0.238	104	102	5.0345	1.5321	18.29
	P2	0.12	0.215	96	114	4.8715	2.4837	17.19
	P3	0.13	0.209	96	105	4.0577	1.8652	18.46

DISCUSSION: Dolasetron has formulated into matrix type patches in an attempt to solve the problems associated with oral administration. Transdermal delivery offers several advantages over oral routes for controlled drug delivery [31] *viz.* avoidance of hepatic first-pass metabolism, the ability to control drug delivery for a longer time than the gastrointestinal transit of oral dosage forms, the ability to avoid a changing physiological environment and chemical or metabolic degradation, the ability to discontinue administration by removal of the system. The dermally applied materials, absorbed in quantities large enough to elicit a pharmacological effect, have been known for years [32]. Matrix dispersion type transdermal patches of dolasetron prepared by using the varying the ratio of drug: polymer (Eudragit RL-100, eudragit RS-100, ethylcellulose and polyvinyl pyrrolidine) in the ratio of 8:2, 6:4 and 5:5 respectively. The establishment of steady-state levels *in-vitro* release for 12 h shows the clear advantage of the transdermal patch over current modes of administration to get the desired overall sustained prolonged drug release. The results of the physicochemical evaluation of different polymeric films showed uniform drug content and minimum batch variation in **Table 1;** the thickness of the patches varied [15]. The results also showed uniformity in weight per cm^2 of the area. The physical appearance of the patches and the effect on aging indicated that the patches need to be stored in properly sealed airtight packing to keep them protected from extreme moisture that may alter their appearance; thus, the properties have found within the limits and satisfactory. Here the polymers like eudragit RL and eudragit RS 100 formulated into matrix type patches in an attempt to solve the problems occurring in conventional dosage forms, namely poor bioavailability due to hepatic metabolism and the tendency to produce rapid blood level spikes, leading to frequent dosage.

The drug release has found as linear and follows the Higuchi diffusion equation [24]. The release kinetics of dolasetron formulation follows zero-order kinetics, hixon Crowell equation has also found as linear [30]. The transdermal patch formulation found efficacious, safe, stable, and nonirritant to the skin. The establishment of steady-state levels *in-vitro* for 12 h shows the clear advantage of transdermal patches over current modes of administration.

CONCLUSION: In the current situation, many drug treatment protocols could produce a side effect. Among them, vomiting and nausea are a familiar and unavoidable condition. Based on the emergence in the present pharmaceutical scenario, the novel drug delivery system is the most important one to hold this type of condition. However, the unavailability of the dosage form to give relief from this condition for a long period, a transdermal patch system has been formulated and assumed that this could be better than the oral dosage form. The study showed a novel approach in pharmaceutics to use the various antiemetic drugs with other dosage forms. Further, a complete clinical study performed to evaluate the therapeutic efficacy of the current dosage form of dolasetron.

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