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Preparation and in Vitro Evaluation for Different Types of Ondansetron Hydrochloride Transdermal Patches

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Abstract

This research aims to develop transdermal patches of Ondansetron hydrochloride (OSH) with different types of polymers as ethyl cellulose and polyvinyl pyrrolidone k30 in a ratio (3:0.5,3:1,3:2,2:1,1:1) with propylene glycol 20%w/w as a plasticizer by the solvent evaporation technique. Prepared transdermal patches were evaluated for physical properties. The compatibility between the drug and excipients was studied by differential scanning calorimetry (DSC), where there is no interaction between the drug and polymers. From the statistical study, there is a statistical difference between all the prepared formulations $p<0.05$. In-vitro release study of transdermal patches was performed by using a paddle over the disc. The release profile of OSH followed Korsmeyer - Peppas model in P2 (EC:PVP 3:1, P4 EC:PVP 3:2) formulations and, Higuchi model in P1, P3, P5 formulations. The best formulation P6 carrying EC:PVP in ratio1:1 released 96.47% of ondansetron hydrochloride during 12 hr. The release profile of P6 followed the Higuchi model and correlation coefficient (r^2 = 0.9815)

Keywords: Ondansetron hydrochloride, Transdermal patches, Ethyl cellulose, Propylene glycol, Polyvinyl pyrrolidone.

تحضير وتقييم في الزجاج لأنماط مختلفة من اللصاقات الجلدية من مادة الأوندانسيترون هيدروكلورايد

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الخلاصة

يهدف هذا البحث لتحضير لاصقات جلدية من نمط الماتريكس تحوي مادة الأوندانسيترون هيدروكلورايد باستخدام نسب مختلفة من مزيج البوليميرات إيتيل سيللوز المحب لغير الماء والبولي فينيل بيروليدون المحب للماء باستخدام البروبلين غليكول كملدن بنسبة 20%w/w. تم تقييم لاصقات الأوندانسيترون هيدروكلورايد من ناحية الخواص الفيزيائية. تمت دراسة التوافق بين السواغات والدواء من خلال المسح الحراري التفاضلي حيث لا يوجد تداخل بين البوليميرات المستخدمة والدواء. أظهرت الدراسة الإحصائية وجود فارق إحصائي بين جميع الصيغ المحضرة حيث كانت $P<0.05$. تم اجراء اختبار التحرر في الزجاج باستخدام جهاز المجداف فوق القرص paddle over the disk لمدة ١٢ ساعة حيث حررت الصيغتان P2, P4 الدواء من نمط كورس ماير بيباس , وحررت الصيغ P1, P3, P5 الدواء من نمط هيغوتشي. كانت الصيغة P6 المكونة من EC: PVP بنسبة ١:١ قد حررت ٩٦،٤٧٪من الدواء خلال ١٢ ساعة بنمط تحرر هيغوشي وكانت قيمة r^2=0.9815.

الكلمات المفتاحية : الأوندانسيترون هيدروكلورايد, اللصاقات الجلدية, ايتيل سيللوز, بروبيلين غليكول ,بولي فينيل بيروليدون

Introduction

Chemotherapy-induced nausea and vomiting (CINV) cause unpleasant side effects that affect the quality of life in patients and their compliance to chemotherapy[(1)]. Serotonin receptor blockers are used in the treatment of nausea and vomiting caused by chemotherapy in the acute phase, which extends from 0 to 24 hr[(1)]. Ondansetron hydrochloride (OSH) is a first-generation competitive serotonin receptor blocker used in the treatment of postoperative or chemotherapy-induced nausea and vomiting[(2)]. Orally administered of ondansetron hydrochloride (OSH) undergoes extensive metabolism in the liver by cytochrome enzymes P450, which explains a short biological half-life and reduced bioavailability[(3)]. The bioavailability of ondansetron hydrochloride is 60% after oral administration, and the half-life is 3-4 hr. Ondansetron hydrochloride has a low molecular weight(293.36 Da) and good transdermal penetration, so it has ideal properties to be introduced into the transdermal drug delivery system[(4)]. Transdermal therapeutic systems are defined as discrete dosage forms applied to intact skin where the drugs are delivered through the skin to the systemic circulation[(5)]. There are three types of transdermal patches: Single-layer Drug-in-Adhesive, the adhesive layer contains the drug and is responsible for releasing the drug. Reservoir, the drug layer is a liquid in a separate compartment in the form of a solution or suspension. The Matrix system is a semi-solid matrix that contains the drug in the form of a solution or suspension, where the adhesive layer surrounds the drug layer[(6)].

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The first generation is designed for drug delivery at low doses, the second generation has enhanced transdermal drug penetration with chemical permeability enhancers. The skin is the most common organ that receives one-third of the blood supply to all parts of the body. The skin was not known to be a systemic drug delivery route until the late twentieth century[7]. Transdermal drug delivery systems deliver the drug into systemic circulation at a controlled rate to maintain constant drug concentrations in the plasma for long periods[8]. Transdermal drug delivery systems avoid the first hepatic passage of drugs, reduce gastrointestinal side effects, and increase patient compliance[8]. The first transdermal system containing scopolamine was approved in the United States in 1979; the US Food and Drug Administration (FDA) approved nicotine patches in 1984. A decade later, transdermal patches for pain relief, analgesic activity, contraception, and hormone replacement therapy were FDA approved and marketed [9].

Materials and Methods

Materials

Ondansetron hydrochloride supplied from mahrshee laboratories pvt ltd panoli, India. Ethyl cellulose and polyvinyl pyrrolidone were obtained from SIGMA-ALDRICH. Chloroform and propylene glycol were obtained from warehouse chemicals of the College of the Pharmacy/ University of Damascus.

Methods

Solubility study

The solubility of ondansetron hydrochloride was determined using different pH grades from a phosphate buffer pH 5.8, 6.8, 7.4 at 37° C. A saturated solution was prepared from Ondansetron hydrochloride by taking 1 g in 10 ml of each solution and placing it in a 50 ml plastic tube in a mechanical shaker for 24 hours. The solution was filtered, 1 ml was taken, and the absorbance was measured with a spectrophotometer at a wavelength of 310 nm[10,11].

Spectrophotometric analysis

Determination of λ max of ondansetron hydrochloride:

The λ max was determined in phosphate buffer pH 5.8 by spectrophotometric scanning of OSH solution with a spectrophotometer in the range 200-400 nm.

Preparation of standard solution:

A stock solution of 1000 mcg/ml was prepared by taking 100 mg of the drug in a calibrated 100 mL volumetric flask and dilute it with a phosphate buffer with pH = 5.8. 1 ml was taken from the first stock solution and extended to 10 ml with a 10 ml calibrated volumetric flask to obtain a solution with a concentration of 100 mcg /ml(10), from this solution standard series with concentrations ranging from 5-30 mcg/ml was prepared and the absorption was measured with a spectrophotometer at a wavelength of 310 nm.The graph was drawn between the concentrations and the absorbance in phosphate buffer solution at pH 5.8.

Preparation of backing film for the transdermal patch

An aqueous solution of 4% polyvinyl alcohol was prepared by taking 4g of polyvinyl alcohol and add it to 100 ml of distilled water. It was placed in a water bath at 80 C° with stirring for two hr until a clear solution was obtained. After cooling the solution, 4 ml of the solution was poured into an Aluminum foil mold and dried at room temperature for 24 hr [12].

Figure 1. Aluminum foil mold

Preparation of transdermal patches

The polymers were weighed as in table 1, added to 10 ml of chloroform, and kept aside until the polymers were completely dissolved for 12 hr. Then propylene glycol was added with stirring for 30 min, then 16 mg of OSH was added with stirring for another 30 min. The polymer solution was poured over the supporting layer and dried at room temperature for 24 hr. The molds were covered with inverted glass funnels to control the evaporation of the solvent[13].

Table 1. Formulations of OSH Transdermal Patches

	P1	**P2**	**P3**	**P4**	**P5**	**P6**
EC	0.3g	0.3g	0.3g	0.3g	0.3g	0.3g
PVP	0.05g	0.1g	0.15g	0.2g	0.25g	0.3g
PG	0.067ml	0.076ml	0.086ml	0.096ml	0.10ml	0.11ml
OSH	16mg	16mg	16mg	16mg	16mg	16mg
solvent	Chloroform	Chloroform	Chloroform	Chloroform	Chloroform	Chloroform
	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml	Up to 10ml

***EC-Ethyl cellulose; PVP-Polyvinyl pyrrolidone; OSH-Ondansetron hydrochloride; PG-Propylene glycol.**

Evaluation of Transdermal Patches

Physical appearance

The prepared transdermal patches were evaluated for morphology, transparency and, flexibility of the film[14].

Folding endurance

Three transdermal patches were evaluated, so the patch was folded into a specific piece several times until it broke. Foldability is determined by the number of times the patch is folded without breaking[15].

Uniformity of weight

Ten transdermal patches were weighed from each formulation individually on a sensitive scale and the standard deviation from the mean was calculated[16].

The thickness of the patch

The thickness of the film was determined by using a micrometer screw gauge device at several points of the film, then the average readings and standard deviation were calculated[17].

Moisture uptake[14]

Three transdermal patches were selected from each formulation. Each patch was weighed before starting the test and then placed in a desiccator containing a saturated solution of potassium chloride, which gives relative humidity of 84% w/w. The weight of the patches was then taken for 3 days, then the uptake percentage was calculated from the following relationship:

M%= [Final weight – Initial weight / Initial weight] × 100.

Moisture content[18]

Three transdermal patches were selected from each formulation, where each patch was weighed before the start of the test, then it was placed in a desiccator containing Activated Calcium Chloride. The weight of the patches was taken for 3 days and moisture content was calculated from the relationship:

M%= [Initial weight – Final weight / Final weight] × 100.

Drug content determination:

One cm^2 of the film was weighed and dissolved in 10 mL of mixture of methanol and ethanol, then filled up with phosphate buffer solution to 100 mL. It was stirred for 24 hr, then the solution was filtered and the absorbance was measured at wavelength 310 nm maximum absorbance. The drug concentration was determined by the absorption equation from the standard graph[19].

In vitro release study:

The test was performed using a USP apparatus V (paddle over the disc). 500 ml of phosphate buffer solution was used at pH = 5.8, the device was set at a temperature of 32 + 0.5 ° C and a paddle speed of 50 rpm. The film was fixed on a circular glass disc by a stainless steel mesh and stainless steel clips then placed into the dissolution medium, so that it was 2.5 cm away from the paddle according to the requirements of the American Pharmacopeia. 5 ml were withdrawn after the following intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 hr and replaced with phosphate buffer pH=5.8. The absorbance of samples was then measured using a spectrophotometer at wavelength 310 nm[20].

Figure 2. Fixed transdermal patch

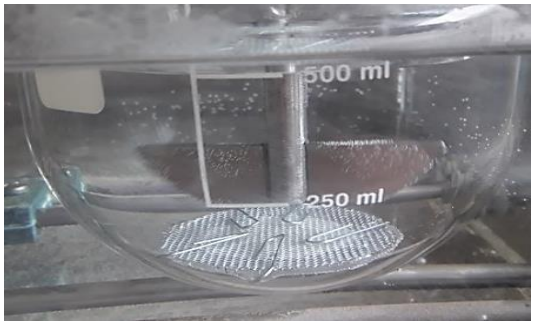

Figure 3. Paddle over the disc

Statistical analysis

The statistical study was performed using a one-way ANOVA analysis through the statistical analysis program Graph Pad Prism 9 to study the effect of polymer and its percentage on the release of the drug. After applying the test, the p-value was calculated and the results were interpreted.

Post-hoc Tukey-HSD (Honestly Significant Difference) test was performed where $p< 0.05$.

Differential scanning calorimetry (DSC) study

Thermal differential scanning of ondansetron hydrochloride, ethyl cellulose, polyvinyl pyrrolidone and, the physical mixture of the drug with the excipients was performed to determine any incompatibility between them. A device (DSC131, SITARAM, France) was used, and the samples taken with a quantity of 5 mg were placed in an open aluminum chamber against

another aluminum chamber used as a reference, then the temperature was raised from (25 to350) C° at a rate of 10 degrees per min[21].

Results and Discussions

Solubility study

Ondansetron was soluble within the PBS buffer pH 5.6. The solubility results are shown in Table 2.

Table 2. Solubility of Ondansetron Hydrochloride. n=3

Solubility medium	Time duration(hr)	Solubility(µg/ml)
Phosphate buffer Ph=5.8	24	515±0.01 µg/ml
Phosphate buffer Ph=6.8	24	23±0.12 µg/ml
Phosphate buffer Ph=7.4	24	insoluble

The solubility of ondansetron hydrochloride exhibits high solubility at low pH (pH 5.8, this degree is considered close to the skin's pH so that the patch does not cause irritation to the skin) at 37°C because of Ondansetron HCl is a weakly basic drug belongs to BCS Class-II and it is showing distinct pH-dependent solubility ; however, it exhibits poor solubility at higher pH (6.8 pH phosphate buffer) at 37°C. These results were parallel with the findings of Anilkumar et al where the solubility
in phosphate buffer pH=6.8 was found to 36 µg/ml [22] .

Spectrophotometric analysis

Standard graph of OSH in PBS pH 5.8

The estimated λ max is 310nm that's agreed with the reported values figure. 4. Figure 5 showed the calibration curve within the involved media.The standard graph showed good linearity with R^2 =0.999 which indicates that it obeys "Beer-Lambert's" law.

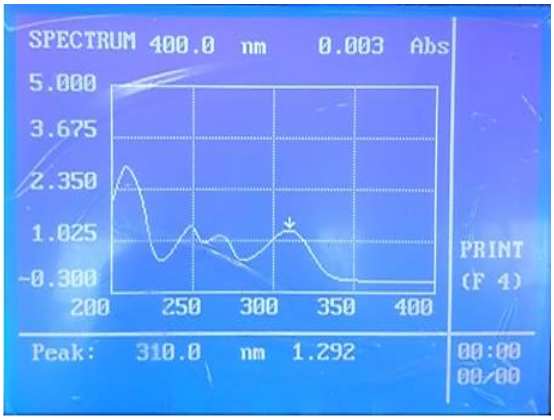

Figure 4. λ max of OSH in phosphate buffer pH=5.8

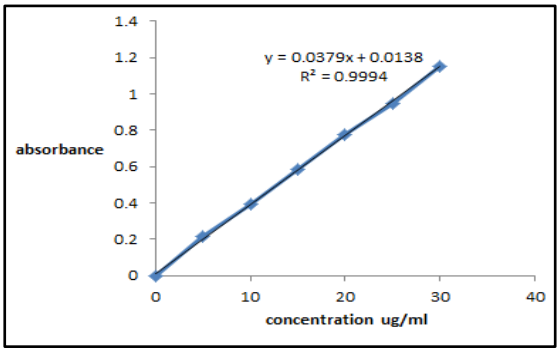

Figure 5. Standard curve of OSH in phosphate buffer pH=5.8

Evaluation prepared transdermal patches

A smooth, non-broken and, thin matrix was obtained. Table 4 shows the results of physical tests for the prepared formulations, where the results of the foldability test ranged between (22-100) times[4], which indicates that the use of propylene glycol as a plasticizer gave the unbroken film. For the weight test, there is no specific constitutional value for weights of transdermal patches. The weights of the patches ranged between (0.32-0.54) g, and we notice a small difference in the standard deviation values ranging between (0.003-0.01), which indicates uniformity of weight. For drug content uniformity test, results were found in the range (92-99) %, which indicates a homogeneous distribution of the drug within the patch.

Table 3. Physical evaluation of ondansetron hydrochloride films

Patch code	Weight variation (g) ±SD	Drug content (%)±SD	Thickness (mm) ±SD	Folding endurance ±SD
P1	0.32±0.004	98.49±0.7	0.1mm	22±2.16
P2	0.433±0.004	94.55±0.95	0.2mm	26±1.24
P3	0.443±0.012	97.89±0.24	0.2mm	46±1.24
P4	0.495±0.005	92.88±1.02	0.3mm	71±1.35
P5	0.545±0.003	96.67±0.56	0.3mm	97±2.05
P6	0.565±0.007	99.21±1.78	0.3mm	106±1

n=3, SD= Standard Deviation.

Moisture uptake and moisture content

Table 5 shows the results of the moisture uptake test for all prepared formulations. The formula P1 is the lowest among all formulations due to the decrease in the amount of PVP in the formula, which amounted to 3.29±0.05, while the moisture uptake percentage increases with the increase in the amount of PVP in the formula, and this is explained by its hygroscopic nature. In addition, the plasticizer works to separate the polymer chains from each other, which facilitates the absorption of water into the matrix, These results are in agreement with sheba et al where PG containing patches have higher percentage of moisture content and water absorption (> 1)[3]. The moisture content test showed an increase in moisture content with the increase in the amount of PVP in the formula. P6 gave the largest value of 6.82±0.18 after72 hours because it contained the largest amount of PVP unlike formula P1, which has the lowest value.

Table 4. Moisture uptake and moisture content of OSH films.

Patch code	Moisture uptake 72hr±SD	Moisture content 72hr±SD
P1	3.29±0.05	4.45±0.16
P2	5.21±0.48	4.83±0.05
P3	5.6±0.19	5.14±1
P4	6.17±0.15	5.52±1.82
P5	7.01±0.13	6.7±1.82
P6	7.21±0.48	6.82±0.18

***72 h: test after 72 hr, SD= Standard Deviation.**

In vitro release study

The cumulative % of ondansetron hydrochloride release were shown in Table 5, and release curves of ondansetron hydrochloride were shown in Figure 6.

There is an initial release from all formulations after 30 min and it lasted for 12 hr.

The release of the drug from formulations P1-P6 gradually increases with the increase in the amount of PVP while the amount of EC remains constant, this is explained by the hydrophilic nature of PVP which facilitates absorption of water to the matrix enhances the release of the drug, in addition, the PVP works to form pores in the matrix structure that facilitates drug particles leave to the dissolving medium[3]. Furthermore, the presence of PVP in patches with chloroform as casting solvent reduce the crystalline state of the drug, which leads to an increase in drug release. These results are in agreement with mutalic et al where the formulation with EC:PVP (3:2) exhibited the greatest percentage of drug release value (71.25 %±8.55) compared to the lowest value observed with the formulation containing EC:PVP (4.5:0.5) (47.65%±9.55)[23]. .

Formulation P6 gave the highest release rate when using EC and PVP with a ratio of 1:1. One- way ANOVA analysis produced statistically significant differences among all formulations where p=0.001, ($p<0.05$).

Table 5. *In vitro* drug release from P1 to P6.

Time hr	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	٠
0.5	16.2±0.75	24.25±0.68	35.9±0.75	33.46±0.12	34.31±0.14	32.92±0.39
1	20.23±1.97	28.8±0.21	41.73±1.09	41.4±0.02	42.53±0.47	37.40±0.02
2	29.34±0.96	34.71±1.72	56.44±0.16	46.84±0.23	52.09±0.66	47.30±0.19
3	34.33±0.11	37.46±1.28	57.11±0.35	48.53±0.67	59.85±0.09	54.55±0.96
4	37.01±0.18	41.77±0.18	59.63±0.82	52.86±0.82	63.24±0.31	60.77±0.1
5	40.01±0.42	44.1±0.48	60.01±0.55	55.36±0.77	66.06±0.45	66.23±0.56
6	41.47±1.29	45.17±1.31	60.61±0.35	56.93±0.43	67.56±0.37	69.79±0.54
7	41.96±0.91	47.39±0.68	60.97±0.55	58.51±0.14	68.65±0.96	74.03±0.03
8	45.94±0.27	51.77±0.79	63.31±0.67	63.79±0.37	73.25±0.85	79.02±0.35
10	50.15±0.76	59.4±0.68	64.94±0.79	73.45±0.36	80.1±0,45	88.81±0.39
12	53.93±0.47	65.82±0.77	68.72±0.63	83.21±0.10	87.18±0.83	96.47±0.23

n=3, Mean ±SD= Standard deviation.

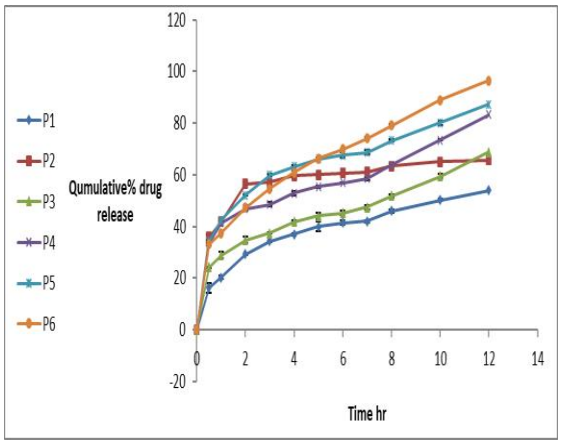

Figure 6. Release curves of ondansetron hydrochloride films.

Kinetic modeling of drug release

Several models describe the kinetics of drug release from the pharmaceutical form, such as Korsmeyer- Peppas, Higuchi, zero order and first order. Table 7 shows the value of correlation coefficient R^2 for the release models of zero order, first order, Higuchi and Korsmeyer- Peppas. The formulations (P2, P4) gave a release from the Korsmeyer- Peppas model, where the value of the correlation coefficient R^2 was maximum and the value of the exponential coefficient n was calculated, it was less than 0.5, this indicates that the mechanism of drug release is diffusion from a non swellable matrix. The formulations (P1, P3, P5, P6) also gave release from the Higuchi model, where the value of the correlation coefficient was greater compared to the rest of the types, that is, the release of the drug from the matrix is proportional to the square root of the time. It also indicates that the process of diffusion through the matrix is the main mechanism to release the drug.

Table 6. Kinetics study of prepared transdermal patches

Patch code	Zero order		First order		Higuchi		Korsmeyer - Peppas	
	slope	R^2	slope	R2	slope	R^2	n	R^2
P_1	3.6506	0.8205	0.0454	0.861	14.689	0.972	0.1772	0.9167
P_2	4.0967	0.8315	0.0336	0.9301	16.222	0.954	0.0381	0.9576
P_3	3.5891	0.5299	0.0217	0.7154	16.069	0.7772	0.0217	0.7154
P_4	4.8155	0.7808	0.0325	0.9447	19.264	0.9142	0.0325	0.9447
P_5	5.2648	0.7443	0.0338	0.8835	21.72	0.9269	0.0338	0.8835
P_6	6.4571	0.8636	0.0439	0.9555	25.449	0.9815	0.0439	0.9555

Table 7.Value of n and drug release mechanism[24].

Release exponent (n)	Drug transport Mechanism	Rate as a function of time	Drug release mechanism
n< 0.5	Quasi – Fickian diffusion	t^n	Non swellable matrix diffusion
0.5	Fickian diffusion	$t^{0.5}$	
0.5 < n < 1.0	Anomalous (Non -fickian transport)	t^{n-1}	For both diffusion and relaxation (erosion)
1	Case II transport	(time – independent)	Zero order release
Higher than 1	Super case II transport	T^{n-1}	(relaxation / erosion)

Differential scanning calorimetry (DSC) study

The DSC thermogram of ondansetron HCl showed a sharp endothermic peak at 187.47C with a starting point of 180.97C and an endpoint of 240.06C as shown in Figure7a which corresponds to the melting point of the substance and indicates that the substance is pure and has a crystalline shape.

The DSC thermograms of ethyl cellulose and PVP K30 showed endothermic peaks at 348.66°C as shown in figure 7b and 87.04°C as shown in figure 7c, respectively.

The DSC thermograms of physical mixture OSH +PVPK30 as shown in figure 7d and physical mixture of OSH+ EC as shown in figure 7e, showed endothermic peaks separately, not overlapping with each other and without changing the melting point of the active substance, which indicates that there is no interaction between Ondansetron and used excipients.

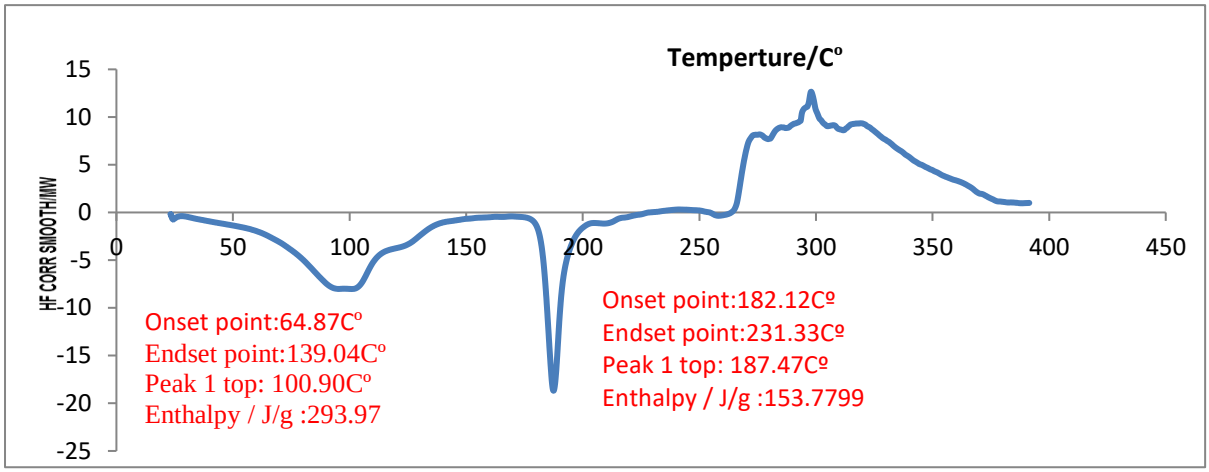

Figure 7a. DSC of ondansetron hydrochloride.

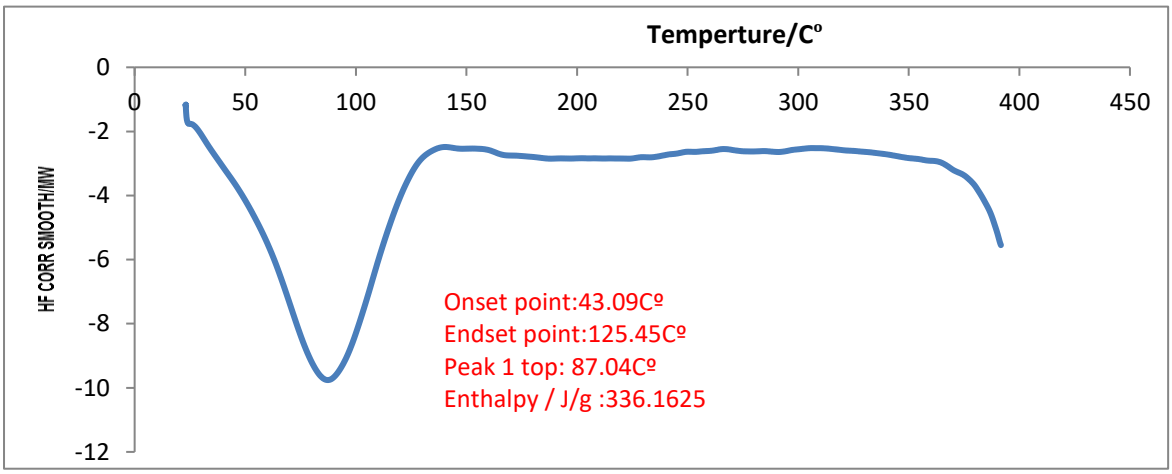

Figure 7b. DSC of PVP k30

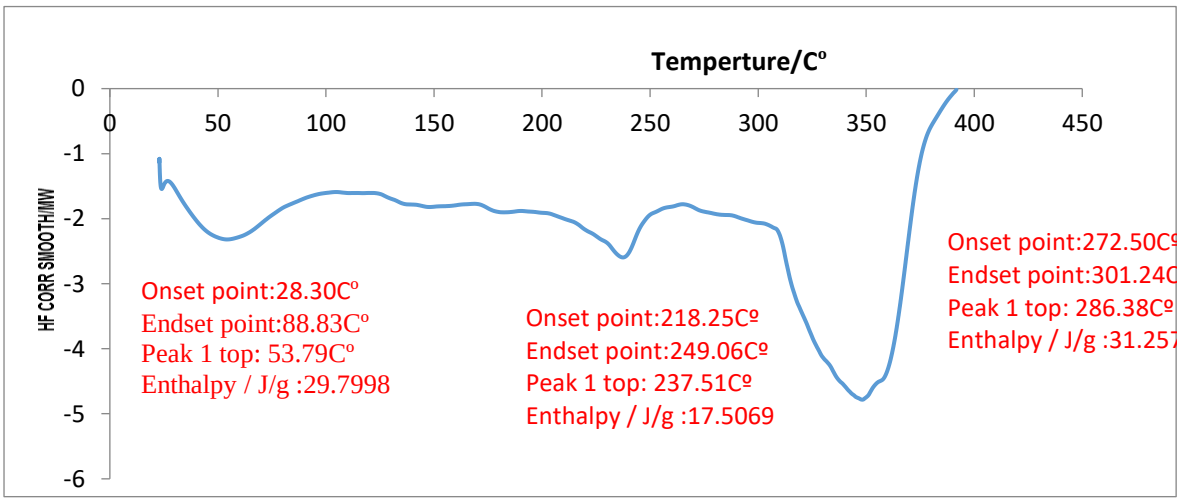

Figure 7c. DSC of EC

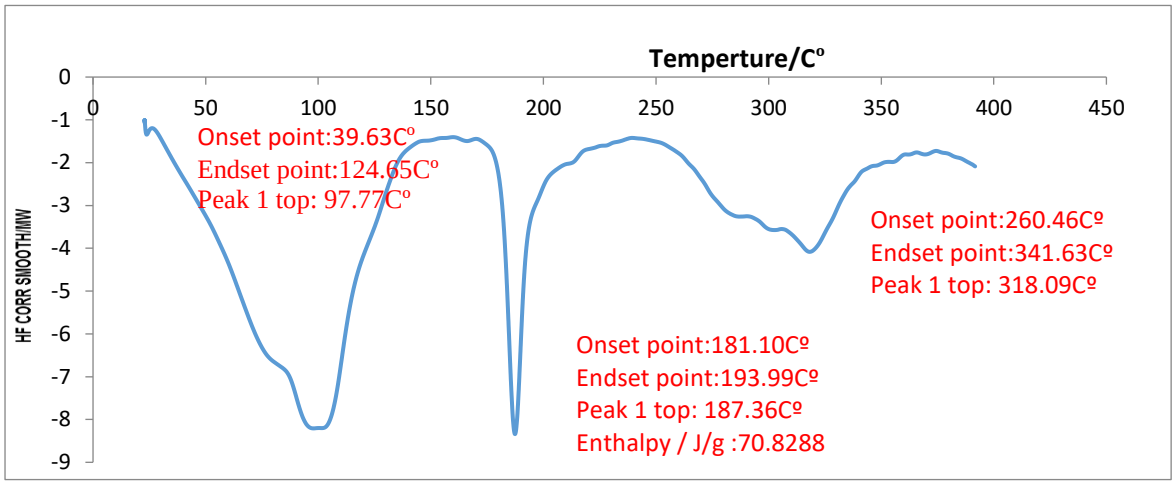

Figure 7d. DSC of OSH+PVP K30.

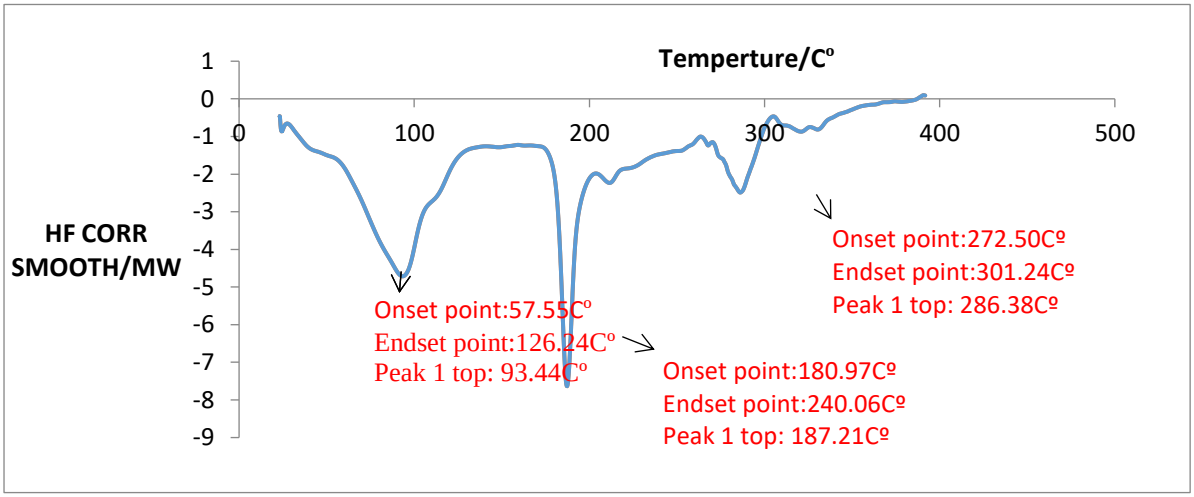

Figure 7e. DSC of OSH+EC

Conclusion

Ondansetron hydrochloride transdermal patches were prepared using two different types of polymers, polyvinyl pyrrolidone and, ethyl cellulose . Formula P6 gave the highest release rate among the prepared formulas, reaching to 96% w/v (cumulative drug release) after 12 hr. The release kinetics of all formulations were studied and the P6 formula followed the Higuchi model. Formula P6 can be nominated for further studies in animal models and pharmacokinetic studies.

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