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FORMULATION DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCH OF ONDENSETRON HYDROCHLORIDE

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ABSTRACT

The purpose of this research was to develop a matrix-type Transdermal therapeutic system containing drug Ondansetron hydrochloride with different ratio of hydrophilic and hydrophobic polymeric systems by using the film casting techniques on glass petridish of polyethylene glycol to the polymers such as Hydroxypropyl Methyl Cellulose incorporated as plasticizer and β-Cyclodextrine was used to enhance the Transdermal permeation of Ondensetron Hydrochloride. Formulated transdermal patches were physically evaluated with regard to thickness, moisture content, moisture uptake, tensile strength, folding endurance, flatness, drug content drug diffusion, and Surface Morphology. All of them F3 prepared formulations indicated good physical stability & better drug diffusion. The in vitro permeation studies of formulations were performed by using Franz diffusion cells. It was observed that the formulation F3 shows better extended release up to 8 hrs. The release rate found to follow first order rate kinetic. It's having majority of importance in Chemotherapy-induced nausea and vomiting is a common side effect by cancer patients during chemotherapy treatment. Ondansetron is a serotonin subtype 3 (5-HT3) receptor antagonist used in Chemotherapy-induced nausea and vomiting management. Orally administered Ondensetron Hydrochloride undergoes extensive hepatic first-pass metabolism, which accounts for its low bioavailability and short half-life. It tends to be vomited before being absorbed and has limited use in

patients with difficulty swallowing after chemotherapy. In this situation Transdermal delivery is a potential route for the administration of Ondansetron hydrochloride.

KEYWORDS: Ondensetron Hydrochloride, Penetration Enhancer. Sustained Released, Transdermal Patches.

INTRODUCTION[1,2]

In the advent of modern of pharmaceutical dosage forms, transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery system. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Ondansetron is a potent antagonist of Serotonin (5-HT3) receptor which has been proved effective in prevention of chemotherapy and radiotherapy-induced nausea and vomiting. Ondansetron hydrochloride has been used by oral and injectable administration. Ondansetron hydrochloride is rapidly absorbed orally, but extensively metabolized by the liver. It should be administered 30 min before chemotherapy, and the orally administered antiemetic drug tends to be discharged by vomiting. On the contrary, intravenous administration renders rapid effect to a patient, but the onset of effect is too rapid to cause undesirable effects. In addition, it gives a local pain, and may cause an unexpected accident when it is not perfectly prepared. In this work an attempt was made to formulate and evaluate TDDS for sustained release Ondensetron Hydrochloride by solvent casting method. Low molecular weight, good permeability, poor bioavailability (60%) and shorter half-life (3-4 hrs) of Ondensetron Hydrochloride made it a suitable drug candidate for the development of Transdermal patches. by using specific Concentration of a β-Cyclodextrine as a penetration enhancer. and which helps to improve the rate of drug diffusion through the skin and achieve the desired plasma drug concentration. The main objective of formulating the Transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance.

MATERIAL AND METHODS

Ondansetron Hydrochloride was obtained as a gift sample from Research Fine Chem Lab Mumbai (Maharastra, India. PVA, HPMC and PEG-4000 Was obtained as a gift sample from Modern industries Nashik, β-Cyclodextrine and Polyvenyl Alcohol was obtained Research Lab Fine Chem Industries Mumbai. (Maharastra, India).

FT-IR Spectroscopy: In order to investigate the possible interaction between drug and selected polymers, FT-IR spectroscopy studies was carried out. IR spectrum for pure drug and physical mixture of drug-polymers (1:1) were compared. Then it was characterized for any change in the region of drug spectrum in presence of drug spectrum.

Calibration curve of Drug Ondensetron Hydrochloride in Methanol

The calibration curve of Drug Ondensetron Hydrochloride was performed in methanol. The calibration curve was found to be linear in the concentration range of 5-25 µg/ml having a coefficient of regression value $R^2 = 0.9996$.

Table No. 1: Concentration and Absorbance value for Drug Ondensetron Hydrochloride in Methanol.

Sr. No.	Concentration µg/ml	Absorbance (λ_{max} 310 nm)
1.	0	0
2.	5	0.1
3.	10	0.209
4.	15	0.315
5.	20	0.408
6.	25	0.511

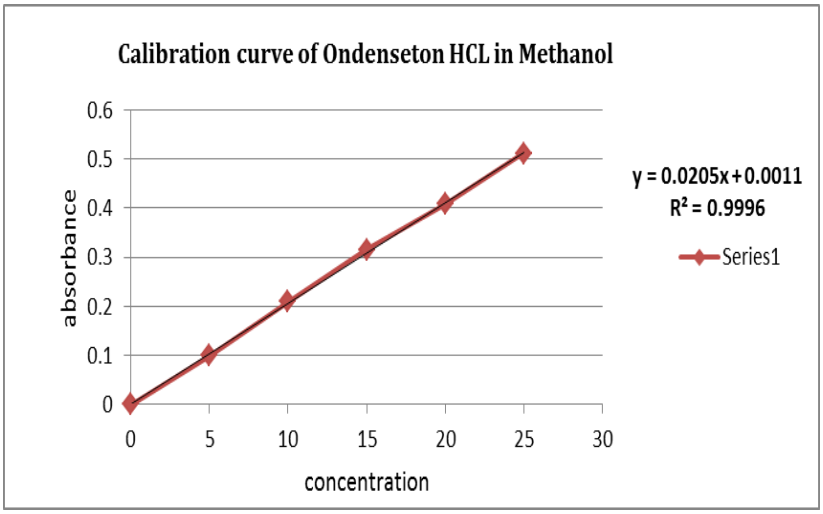


Figure No. 1: Beers-Lambert's plot for Drug Ondensetron Hydrochloride in Methanol.

FORMULATION OF TRANSDERMAL PATCHES

The transdermal patches were prepared by film casting techniques on glass petridish over alluminium foil. A 3^2 fractional factorial design were applied to formulate the matrix type transdermal film of Ondansetron Hydrochloride. Hydrophilic materials i.e. HPMC and PVA were dissolved in known volume of distilled water and hydrophobic materials i.e. β-Cyclodextrine and Ondansetron Hydrochloride were dissolved in 10 ml Methanol. Then both the solutions were mixed and stirred on magnetic stirrer to accomplish a homogeneous mixture. Known volume of PEG-4000 was mixed thoroughly in the solution and stirred for 30 min. The resulting whole solution was poured in a petridish containing alluminium foil paper. Alluminium foil paper is used to avoid the adherence of film to dish. The solvent was allowed to evaporate for 24 hr. at room temperature. The prepared transdermal Ondansetron Hydrochloride patches were store in a dessicator until further use. In formulation the concentration of drug Ondensetron Hydrochloride 60 mg HPMC 40 mg Methanol 10 ml kept as constant.

Table No. 2: Composition of Formulation Batch.

Sr. No	Ingredients / Patch	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Drug (mg)	60	60	60	60	60	60
2	Methanol (ml)	10	10	10	10	10	10
3	PEG-4000 %	5	-	5	5	5	5
4	PVA %	4	-	-	4	4	4
5	HPMC %	40	40	40	40	40	40
6	β-Cyclodextrine (mg)	-	2.5	2.5	-	-	2.5
7	Water (ml)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

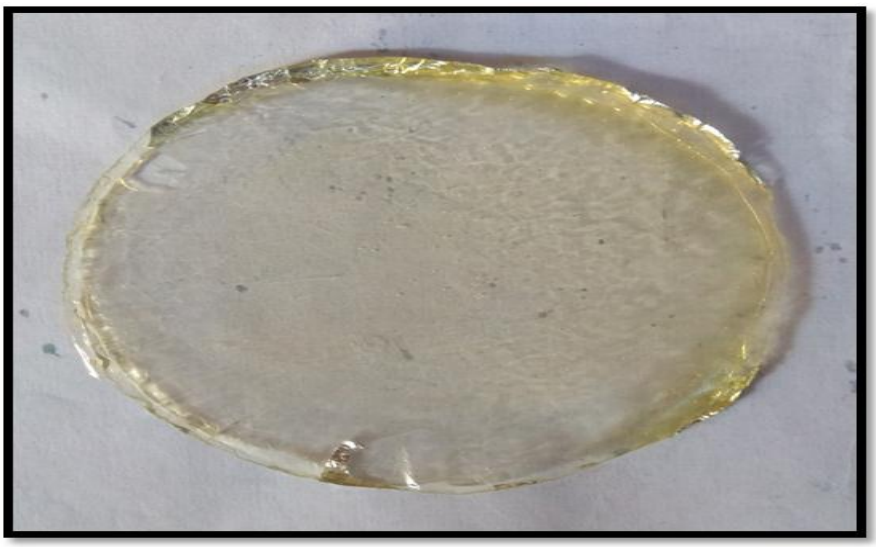


Figure No. 2: Prepared Transdermal patch of Ondensetron Hydrochloride.

EVALUATION OF TRANSDERMAL FORMULATION[3,4,5]

Thickness: The thickness of the drug loaded patch is measured in different points by using a digital Varner Caliper and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Uniformity of weight: The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content determination: A film of required area (1 x1 cm / 2 x 2 cm etc.) is cut, put this small piece of film of suitable solvent (Methanol) in which drug is soluble and then the solution is shaken continuously for 24 h in Magnetic stirrer. Then the whole solution is ultrasonicated for 15 minute. After filtration, the drug is estimated spectrophotometrically and the drug content is determined.

Percentage of moisture content: The films are weight individually and left in a dessicator containing anhydrous calcium chloride or activated silica at room temperature for 24 hours. Individually films are weighed repeatedly until they showed a constant weight. Calculation of % of moisture content is done as the difference between initial and final weight with respect to the final weight.

$$\% \text{ moisture content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$$

Percentage of moisture uptake: A weight film kept in a dessicator at room temperature for 24 hours is taken out and exposed to 84% relative humidity (a saturated solution of potassium chloride) in a dessicator until a constant weight for the film is obtained. The percentage of moisture uptake is calculated as the difference between the final and initial weight with respect to initial weight.

$$\% \text{ Moisture Uptake} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

Folding endurance: folding endurance of patches can be determined by repeatedly folding a small strip of patch (2 x 2 cm) at the same place till it breaks. The number of time the film could be folded at the same place without breaking is the folding endurance value.

Tensile strength: One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Tensile strength= F/a. b (1+L/l)
Where,
F= is the force required to break
a= is width of film
b= is thickness of film
L= is length of film
l= is elongation of film at break point.

Flatness test: Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

Thumb tack test: It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

IN VITRO DRUG RELEASE STUDIES[6,7]

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms. There are various methods available for determination of drug release rate of TDDS.

In vitro permeation studies using dialysis membrane

In vitro permeation of Ondensetron hydrochloride from transdermal Patches was performed by using franz type of diffusion cell it consist of two part the upper part that is donor compartment and contain active ingredient and the carrier patch The lower part contains the

receptor solution, the water jacket for temperature control, and the sampling port. The permeability studies were carried out across egg membrane. The membrane was mounted over a Franz diffusion cell and was placed transdermal film. The receiver compartment of the diffusion cell was filled with 15ml of phosphate buffer (pH 7.4) and the setup was placed over a magnetic stirrer at 37 ^{0}C. Samples of 5ml were withdrawn and replenished immediately for same volume of phosphate buffer solution at 1, 2, 3, 4, 6 and 8 hr. They were stored separately till the analysis was performed. The content of Ondensetron Hydrochloride in the samples was analyzed by UV-Visible spectrophotometer at 310 nm.

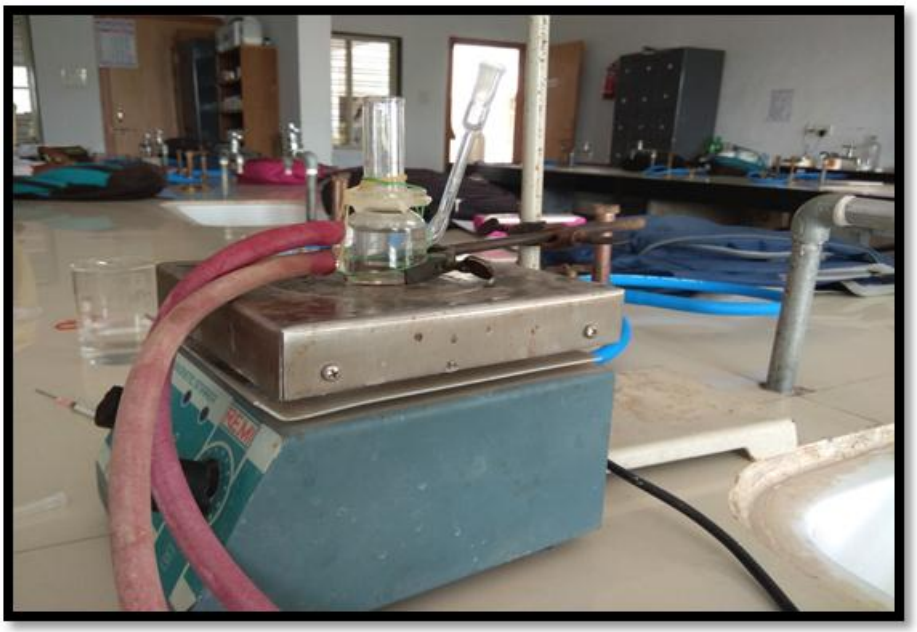


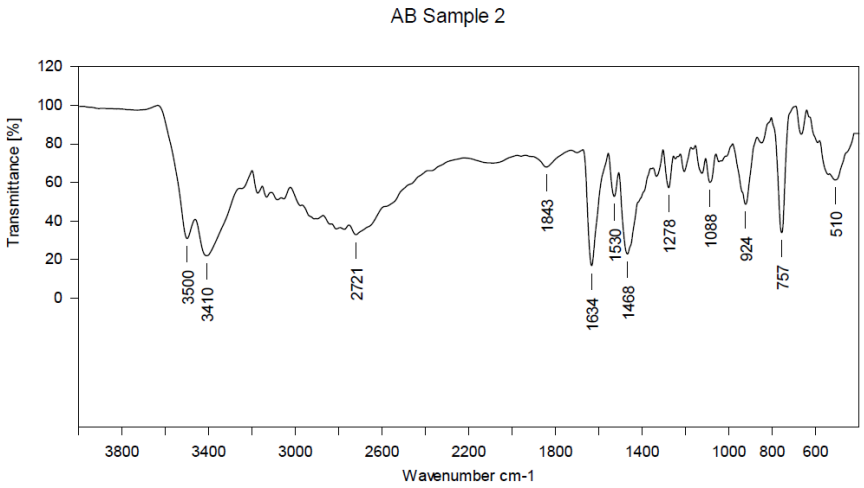
Figure No. 3: Drug Diffusion Study of Transdermal Patch.

RESULT AND DISCUSSION

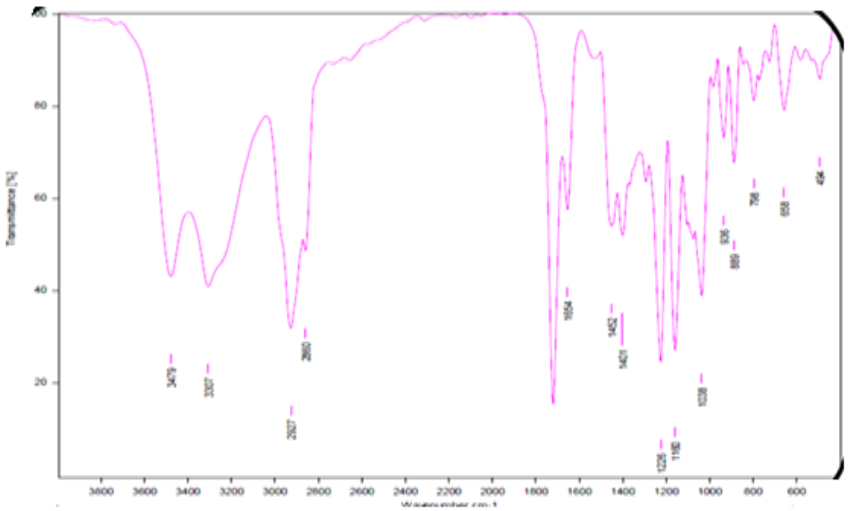
Table No: 3 Characteristic picks of Group.

Cm^{-1}	**Group**
3245	-NH (stretching)
3200-3180	-NH-CH_3
1635-1612	-C = O (ketonic group)
2720-2662	-CH_3
750-760	Aromatic Stretching

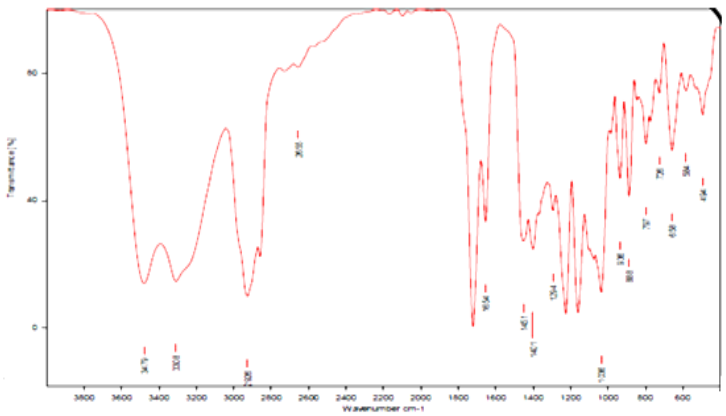
A)


AB Sample 2
Transmittance [%]
120
100
80
60
40
20
0
3500
3410
2721
1843
1634
1530
1468
1278
1088
924
757
510
3800
3400
3000
2600
2200
1800
1400
1000
800
600
Wavenumber cm-1

B)



C)



D)

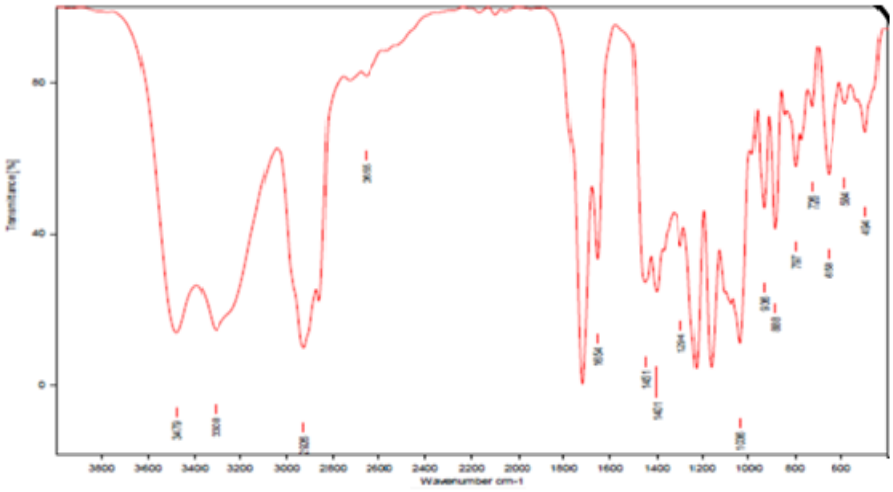


Figure No. 4: (A) IR Spectrum of Ondansetron HCl (B) IR Spectrum of Ondansetron HCl + β-Cyclodextrine (C) IR Spectrum of Ondansetron HCl + Polyvenyl Alcohol (D) IR Spectrum of Ondansetron HCl + HPMC.

The IR spectrum of Original drug was found to be similar to be standard spectrum of Ondensetron Hydrochloride. The spectrum of Ondensetron Hydrochloride shown following functional group in their frequency.

Table No. 4: Evaluation Data of Ondensetron Transdermal Patch.

Formulation Code	Thickness	%Drug Content	% Moisture Content	% Moisture Absorption	Folding endurance
F1	0.66 ±0.02	77.875 ± 2.14	0.5±0.01	2.5±0.02	221±2
F2	0.36±0.01	84.125 ± 0.225	1.2±0.03	2.9±0.03	186±1
F3	0.76±0.02	97.875 ± 5.32	2.1±0.01	3.2±0.15	215±3
F4	1.16±0.01	60.375 ± 0.41	1.9±0.02	3.4±0.03	174±2
F5	0.91±0.01	72.875 ± 2.22	1.5±0.02	4.2±0.02	187±2
F6	1.08±002	76.625 ± 0.80	1.6±0.01	3.0±0.06	212±2

Scanning electron microscopic (SEM) studies

The surface morphology of the formulations was studied with SEM figure No-8.15 (A&B). EC is partially crystalline and ondansetron is crystalline in nature SEM studies indicated that EC, Cyclodextrine in the film, Micrograph of transdermal film prepared using Methanol as casting solvent at 500× magnification. A surface morphology of film was observed.

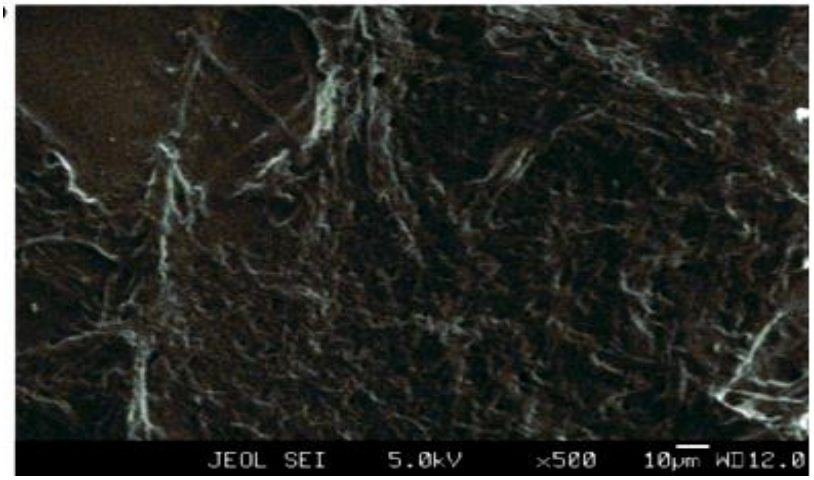


Figure No. 5: Scanning electron microscopic Study.

Six formulations of Ondansetron Hydrochloride Transdermal patches were prepared using different polymer concentrations and using a β-Cyclodextrine as penetration enhancer. These formulated transdermal patches were transparent, smooth, uniform and flexible. The addition of plasticizer was found to be essential to improve mechanical properties of patches & easily removed from alluminium foil surface without any rapture. These formulations are subjected to evaluation parameters like thickness, moisture content, moisture uptake, folding endurance, flatness, drug content, IR studies In-vitro drug release studies. From the IR spectra, it was clear that there was no change in peak positions of Ondansetron HCL, when mixed with the polymers. Thus, there was no interaction between Ondansetron Hydrochloride and polymers. The physical evaluation of Transdermal patches for all formulations was performed. Thickness of Transdermal patches varies from 0.36 to 1.16 mm. Moisture content of Transdermal patches varies from 0.5 % to 2.1 %. Moisture content studies indicate that the increase in the concentration of hydrophilic polymer i.e. HPMC was directly proportional to the increase in moisture content of the patches. The moisture content of the prepared transdermal film was low, which maintains suppleness, thus preventing drying and brittleness. Moisture uptake studies also indicate that the increase in the concentration of hydrophilic polymer i.e. HPMC was directly proportional to the increase and moisture uptake of the patches. The moisture uptake of the transdermal formulations was also low, which protects the film from microbial contamination as well as bulkiness of transdermal patch. The prepared transdermal films showed good surface Morphology and there was no sign of cracking in prepared transdermal film. Folding endurance test results indicates that all the patches will withstand to rupture and would maintain their integrity with general skin folding when used. All the patches were showed near to satisfactory flatness, which indicates

negligible amount of constriction of the prepared transdermal patches. Thus, a patch does not constrict, when it is applied on the skin. Drug content was found to be in the range of 97.87 % to 60.37 % indicating that the drug was uniformly distributed throughout the patches. The β-Cyclodextrine is act as a penetration enhancer to the skin and may improve the drug penetration from the skin to the blood.

In vitro Drug Diffusion

Diffusion studies for different formulations were performed in Franz diffusion cell using pH 6.8 Phosphate buffer as a diffusion medium at 37 ± 0.5 ^{O}C Experiments were perform. Cumulative amount of Ondensetron Hydrochloride released from the device into receptor fluid was plotted as a function of square root of time for each medicated disc subjected under diffusion study. The results of in vitro drug diffusion study for transdermal patches are depicted in Table No: 3.

Table No. 5: In vitro drug release of formulations.

Time in hr	Cumulative amount of Ondensetron Hydrochloride release (%)					
	F1	F2	F3	F4	F5	F6
1	4.667 ±0.53	5.585±0.61	6.044±1.22	6.962±0.45	12.012±1.50	6.962±0.06
2	6.656±0.61	7.115±0.79	8.493±1.41	14.614±1.50	6.182±0.45	33.896±0.38
3	11.859±0.08	27.00±0.79	23.643±0.91	34.81±0.79	38.793±2.12	42.006±0.57
4	21.959±0.97	33.896±0.53	42.465±1.40	36.191±1.50	42.006±0.89	50.423±0.79
5	35.120±0.17	40.629±0.89	64.808±0.17	40.935±0.79	58.840±1.14	56.238±0.49
6	40.935±0.79	42.312±0.79	72.918±1.67	42.312±0.17	60.829±1.14	73.071±0.5
7	49.199±0.70	64.502±0.17	83.325±1.59	55.779±1.76	75.82±1.14	77.815±1.1
8	57.615±0.70	72.000±0.53	95.720±0.07	59.146±0.97	79.346±0.70	80.570±0.70

Cumulative Drug Released of Ondensetron Hydrochloride from Transdermal Patches

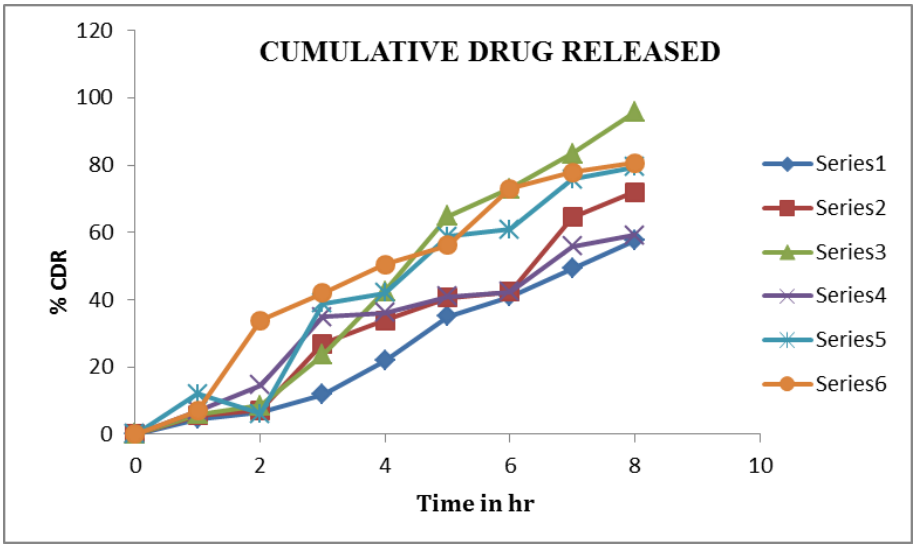


Figure No. 6: Cumulative Drug Released from prepared patch.

EFFECT OF β-CYCLODEXTRINE ON RELEASE PROFILE OF DRUG FROM TRANSDERMAL PATCHES.

In order to perform different release kinetics; depending upon different release mechanism involved, effect of β-Cyclodextrine on Drug release profile from Transdermal Patch (formulation F1- F6) were determined. Drug release data given in Table No: 8.13 the formulation containing required amount of β-Cyclodextrine (F 3) showed longer time release and fast release because It act as a Penetration enhancer β-Cyclodextrine is may one of the best penetration enhancer which increase the drug permeation through the skin. β-Cyclodextrine at specific Concentration may show the lag time up to 8 hrs, it may increase the drug permeation rate by acting as a penetration enhancer. Formulation F3 shows delayed release or Maximum drug release as compared to formulation F1, F4, F5, because of addition of β-Cyclodextrine. as a penetration enhancer.

The formulation F2 & F6 also contain the β-Cyclodextrine but it contain the Polyvenyl alcohol which is soluble in prepared polymer mixture but it appear as crystal on a surface of prepared transdermal patch due to these reason the smooth and even surface of prepared patches is not formed and which restrict the uniform contact to the surface where it releases the drug. For these reason the drug released from F2 & F6 are not satisfactory.

β-Cyclodextrine is may act as a penetration enhancer for drug Ondensetron Hydrochloride for maintaining the desired concentration of Drug in to the plasma which prevent the chemotherapy induced nausea and vomiting in cancer therapy patient it helps to reduced the repeated administration of drug. β-Cyclodextrine is a cyclic oligosaccharides and Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability of drug and helps to improve the drug penetration through the skin.

CONCLUSION

In conclusion, it may be concluded that formulation of Ondansetron Hydrochloride transdermal patches with suitable and optimum concentration of excipients in form of polymers, plasticizers, & permeation Enhancers β-Cyclodextrine. may be used to get the effective rate of release of drug from the patches. Among all the prepared films, F3 would be better formulation based on the in vitro permeation studies as it sustained the release of drug for longer duration without significantly releasing the drug in a burst manner in the initial

hours. The drug release kinetics of all fabricated patches follows first order kinetics except B5 &B7 showing zero order release kinetics, whereas, the mechanism of drug release of all formulations were non-Fickian. Further, in vivo studies have to be performed to correlate with in vitro release data for the development of suitable controlled released patches for Ondensetron Hydrochloride.

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