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"FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF PREDNISOLONE"

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ABSTRACT:

The purpose of this research work was to develop and evaluate transdermal patch of Prednisolone, using Xanthan gum, Guar gum and Polyacrylamide in different ratios prepared by the Glass Substrate Technique. The physicochemical compatibility of the polymers and the drug was evaluated by FTIR. The results suggested that no physicochemical incompatibility between the polymer and the drug. Drug free films were formulated and evaluated characteristics like flexibility and smoothness. Further drug loaded films were formulated and evaluated for thickness, weight uniformity, drug content, folding endurance and drug release. The XRD analysis confirmed the amorphous dispersion of the drug in the formulation. SEM analysis showed surface morphology of prepared formulations. Drug diffusion through cellophane membrane was carried out using Franz diffusion cell by in-vitro study. The film prepared with formulation PDS 9 showed maximum diffusion release at the end of 24 hours. It is shown that drug release follows order and non Fikinian mechanism of release diffusion. The PDS 9 formulation was found to be stable with respect to drug content as well as physical changes at 40 ºC and 75 % RH.

Keywords: Transdermal drug delivery, Prednisolone, Xanthan gum, Guar gum, Polyacrylamide.

INTRODUCTION

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin into the bloodstream. This often, promotes healing to an injured area of the body. The main advantage of a transdermal drug delivery route over other types of medication delivery route such as oral, topical, intravenous, intramuscular, etc. is that they provide a controlled release of the medication into the patient, usually through a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. Transdermal drug delivery offer controlled release of the drug to the patient, and helps to maintain a steady blood level profile, resulting in reduced systemic side effects and, sometimes, improved efficacy over other dosage forms. The main objective of transdermal drug delivery system is to deliver drugs through skin into systemic circulation at predetermined rate with minimal inter and intra-patient variations.[1]

UIcerative colitis and Crohn's disease, collectively known as idiopathic inflammatory bowel disease (IBD), remain a diagnostic and therapeutic challenge. Whereas, other inflammatory diseases of the gut are distinguished either by a specific etiologic agent or by the nature of the inflammatory activity, ulcerative colitis and Crohn's disease are disorders with unknown etiologies, uncertain and unpredictable courses, and variable responses to medical and surgical management.[2]

Prednisolone is a potent, synthetic non-halogenated corticosteroid with high topical anti-inflammatory effect and little systemic effects. Because of low incidence of corticosteroids adverse effects and high topical effects, prednisolone is an important choice for treatment of IBD.[3]

Prednisolone exhibits affinity to the corticosteroid receptors with a high ratio of topical to systemic anti-inflammatory activity by decreasing the production of cytokines and interleukins. It has high first pass metabolism and a half life of 2 to 3 h with an oral bioavailability of only 20% thus, to increase the systemic effect of drug as well as bioavailability we selected drug as suitable candidate for transdermal drug delivery system.[4,5]

Materials and Methods:-

Prednisolone was obtained as a gift sample from Apotex pvt ltd., xanthan gum and guar gum were obtained from Yarrow chemicals, polyacrylamide and cellophane membrane were obtained from HiMedia laboratories pvt ltd., and glycerin was obtained from s.d.fine-chem ltd.

Method of preparation of Transdermal patches:-

Glass plate substrate method:-

The polymers were dissolved in 20ml of distilled water. The drug is dissolved in 4ml of Alcohol in a separate beaker and is transferred into the polymeric solution. The organic solvent is evaporated from the solution using magnetic stirrer. To the above mixture 30% of plasticizer was added and mixed well. Then the solution is poured on the glass plate inside the "o" ring, and left to dry for 48 hrs, at room temperature.

Formulation Table of Transdermal Drug Delivery System:-

Table 1: Formulation Table of Transdermal Drug Delivery System

Ingredients	Formulations								
	PDS1	PDS 2	PDS 3	PDS 4	PDS 5	PDS 6	PDS 7	PDS 8	PDS9
Prednisolone (mg)	100	100	100	100	100	100	100	100	100
Xanthum Gum (mg)	100	150	200	100	150	200	100	100	200
Guar Gum (mg)	300	250	200	-	-	-	100	200	100
Polyacrylamide	-	-	-	300	250	200	200	100	100
Glycerine	30%	30%	30%	30%	30%	30%	30%	30%	30%
Distilled water (QS)	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml

Evaluation of Transdermal patches:-

Physical appearance:- The prepared transdermal films were visually inspected for smoothness and clarity [**6**].

Thickness of patch:- The thickness of each patch was measured by using screw gauge at three different positions of the patch and the average was calculated [**7**].

Weight Uniformity:- Uniformity in weight was determined by taking 3 patches weighed on digital balance and analyzed for distinctions in weight [**8**].

Moisture content:- The film was weighed and kept in a desiccators containing calcium chloride at 40° C in a drier for at least 24 hr or more until it showed a constant weight and was reported in terms of percentage (by weight) moisture content [**9**].

Moisture Uptake:- The patches are weighed and kept for drying in desiccator at room temperature for 24 hr until a constant weight is recorded and then exposed to 84% relative humidity (saturated solution of potassium chloride) [**10**]

Folding endurance:- Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm x 2 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value. [**11]**

Drug polymer Interaction Study:- The infrared (IR) spectra were recorded, using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm–1. The spectra obtained for drug, polymers and physical mixtures of drug with polymers were compared. Disappearance of peaks or shifting of peak in any of the spectra was studied.[**12**]

Differential Scanning Calorimetry:- About 5 mg of sample was weighed and crimped into an aluminium pan and analysed at scanning range from 0 ºC - 300ºC at the heating rate of 5ºC/min under nitrogen flow of 25ml/min.[**13**]

Scanning electron microscopy:- Morphological details of the transdermal patches were determined by using a scanning electron microscope (SEM).[**14**]

X-RD Analysis: The spectra were recorded using a Philips, PW-171, Xray diffractometer with Cu-NF filtered CuK radiation. Quartz was used as an internal standard for calibration. The powder x-ray diffractometer was attached to a digital graphical assembly and computer with Cu-NF 25kV/20mA tube as a CuK radiation source in the 2θ range 0-50 ºC.[**15**]

Drug content determination:- It can be determined by completely dissolving a small area (1 cm2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.[**16**]

Diffusion study:- The glass Franz diffusion cell was used for release studies. The cellophane membrane was mounted between donor and receptor compartment. The transdermal patch was fixed in between donor and receptor compartments were clamped together and placed in a water bath maintained at 37 ± 0.5°C. The volume of receptor cell was 25 ml and the effective surface area available for permeation was 4.9062 cm2. The receptor compartment filled with pH 7.4 phosphate buffer. The hydrodynamics of the receptor fluid was maintained by stirring the fluid at 600 rpm with star head magnet. Samples 2 ml were withdrawn at specific interval of time. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 247nm UV-spectro-photometricaly.[**17**]

Determination of Kinetics Order of Drug Release:- The release mechanism of transdermal patch can be determined by the kinetics order of drug release. Zero order kinetics is determined by the plotting the percentage of release versus time (h), first order kinetics by plotting the logarithmic value of release versus time (h) and the Higuchi order kinetics is determined by making a percentage release of drug versus the square root of time.[**18**]

Stability Studies:- The stability studies of the formulated transdermal patches were studied on prepared film at different temperature and humidity 45- 50°C (75%RH) over a period of 45 days. The patches were wrapped in aluminum foil and stored in desiccators for stability study. The patches were tested for drug content and other parameters at regular intervals 45 days.[**15**]

Results:-

IR Spectral Analysis

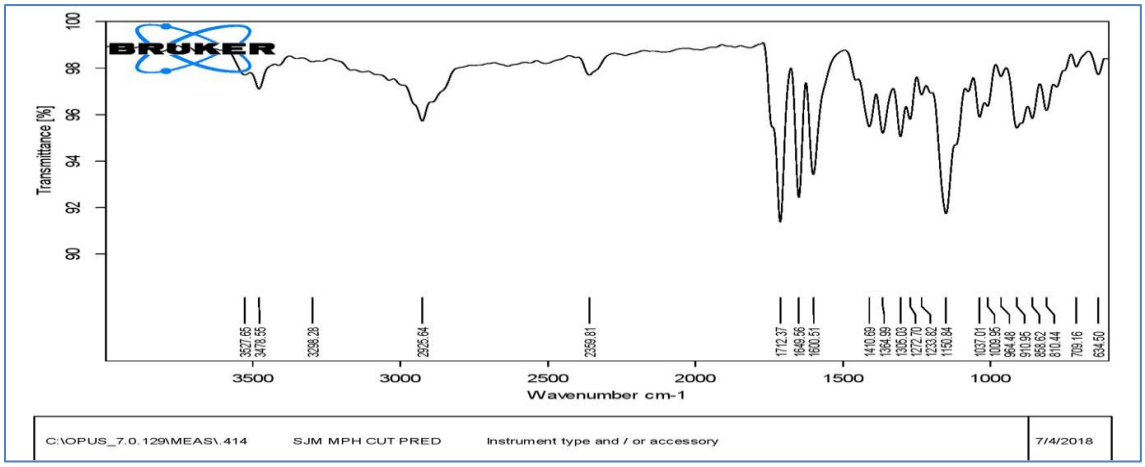

Figure 1: IR Spectra of Prednisolone

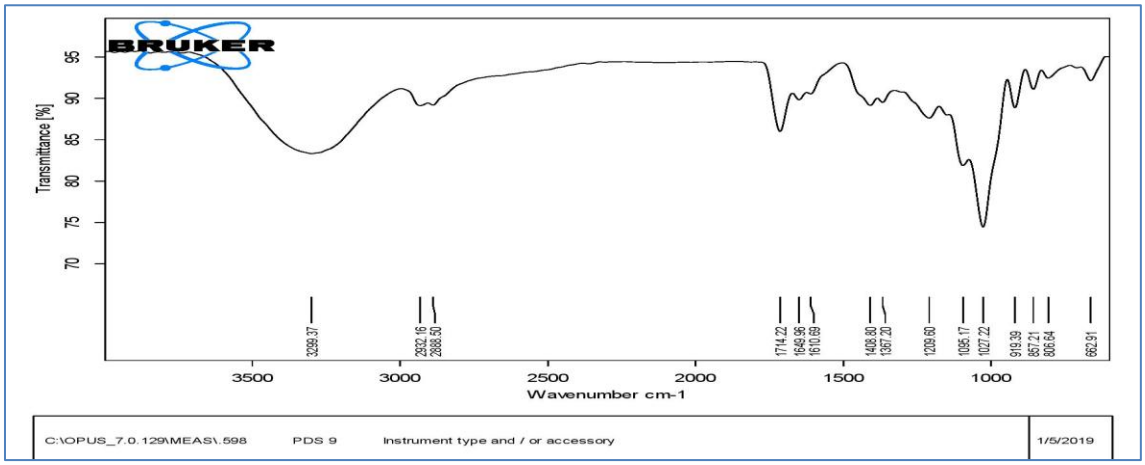

Figure 2: IR Spectra of PDS 9 [Drug] Formulation

SEM Analysis:- PDS 9 Formulation

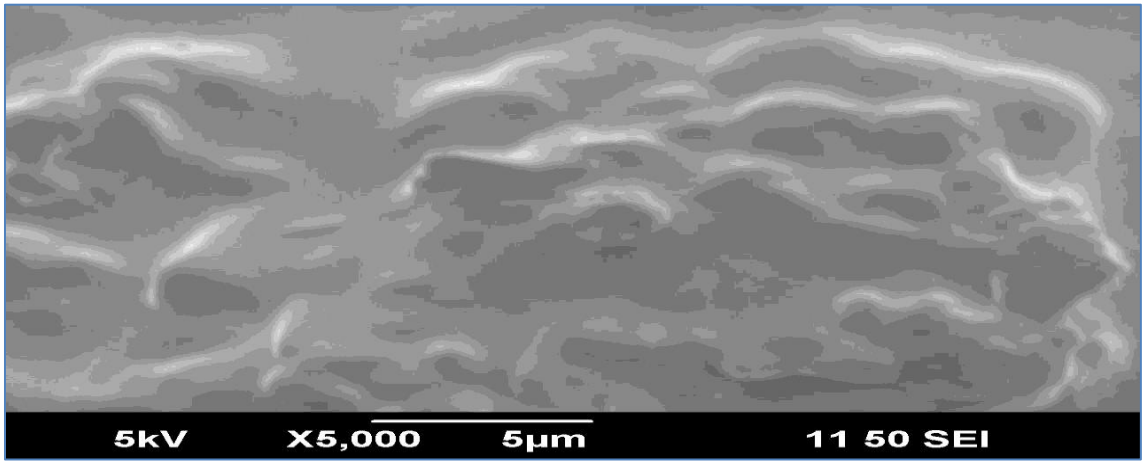

Figure 3: SEM Image of PDS 9 Formulation at 5 µm.

DSC Analysis

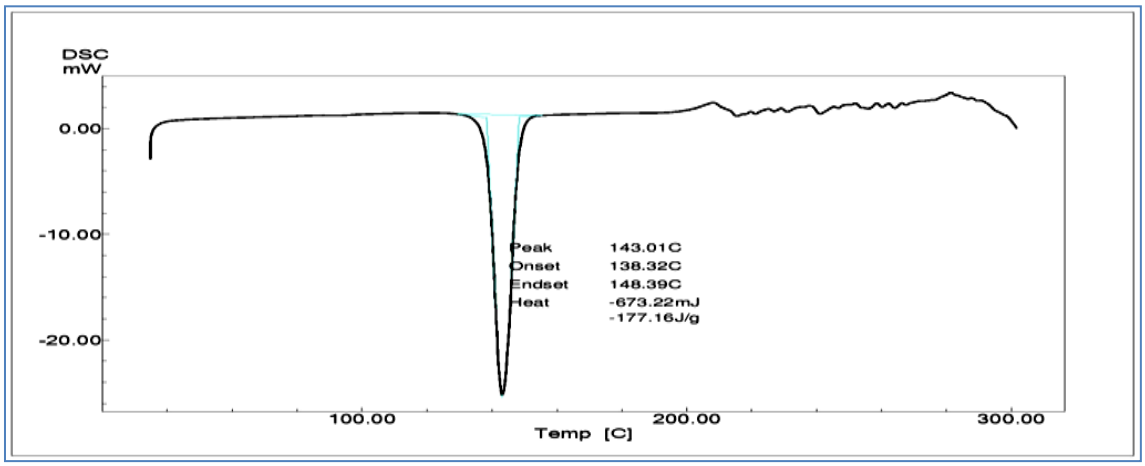

Figure 4: DSC graph of Prednisolone.

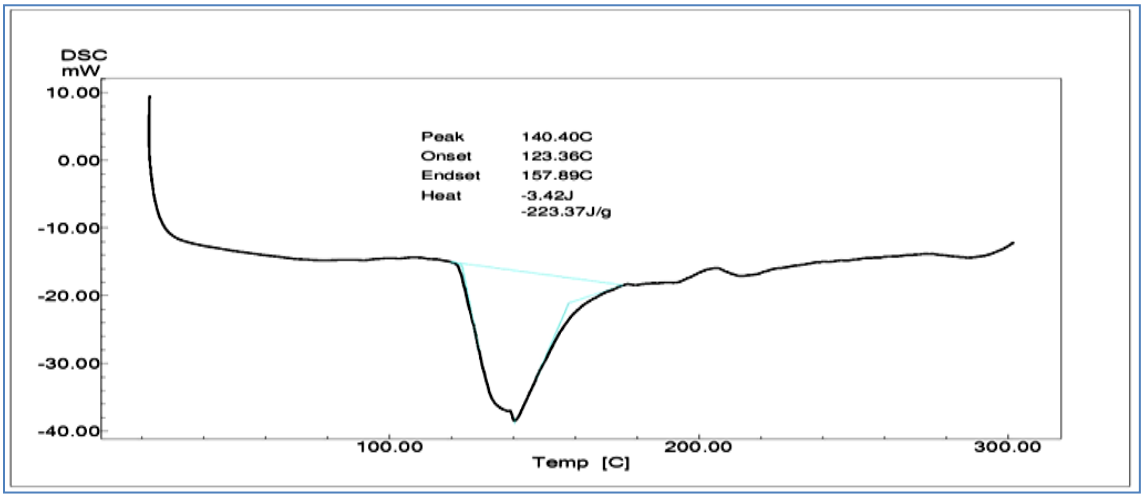

Figure 5: DSC graph of PDS 9[Drug] Formulation.

XRD Analysis

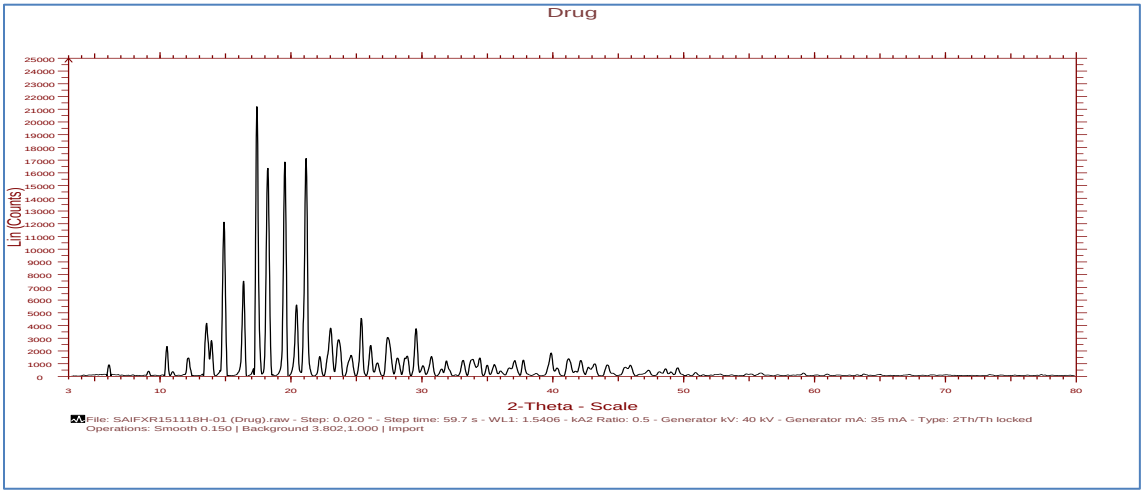

Figure 6: XRD Graph of Prednisolone.

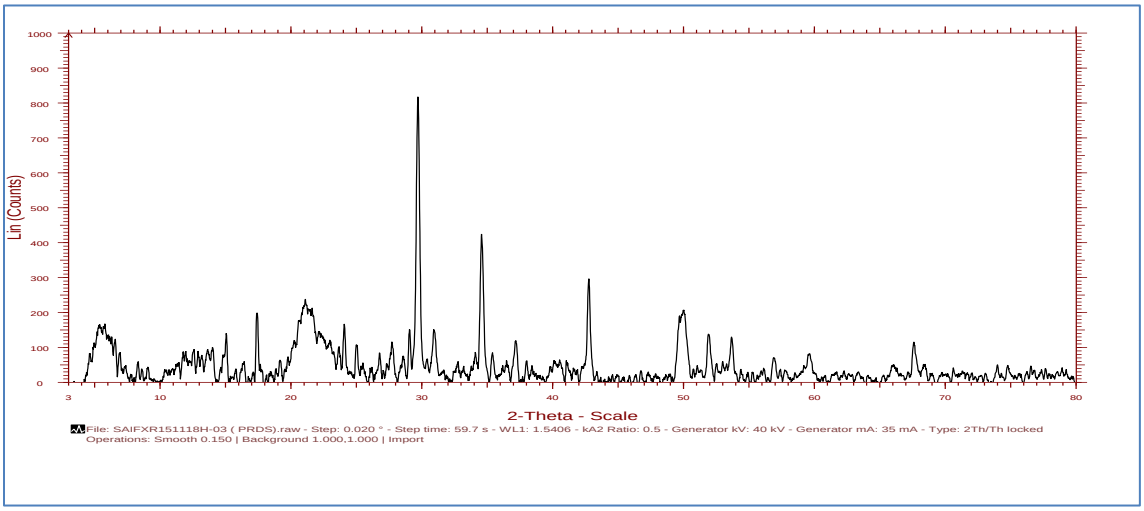

Figure 7: XRD Graph of PDS 9 [Drug] Formulation.

Table 2: Thickness, Weight variation, % Moisture content, % Moisture uptake, % Drug content and Folding endurance of the Transdermal patches.

Sr. No.	Formulation	Thickness (mm)	Weight variation (mg)	% Moisture content	% Moisture uptake	% Drug content	Folding Enduraance
1	PDS 1	0.14 ± 0.016	365 ± 2.08	9.85 ± 0.28	5.19 ± 0.03	85.84 ± 0.21	124 ± 1
2	PDS 2	0.19 ± 0.014	671 ± 6. 27	7.81 ± 0.08	5.56 ± 0.27	67.92 ± 0.22	122 ± 1
3	PDS 3	0.15 ± 0.021	833 ± 4.5	6.73 ± 0.16	5.56 ± 0.27	85.84 ± 0.21	120 ± 1
4	PDS 4	0.20 ± 0.016	550 ± 2.94	7.69 ± 0.29	4.79 ± 0.01	67.92 ± 0.14	125 ± 1
5	PDS 5	0.24 ± 0.005	348 ± 3.16	6.59 ± 0.25	3.7 ± 0.08	82.23 ± 0.22	123 ± 1
6	PDS 6	0.19 ± 0.008	602 ± 2.08	8.49 ± 0.15	5.14 ± 0.04	85.84 ± 0.21	123 ± 1
7	PDS 7	0.13 ± 0.008	365 ± 2.08	5.97 ± 0.1	6.53 ± 0.08	64.38 ± 0.09	124 ± 1
8	PDS 8	0.14 ± 0.016	610 ± 2.16	6.93 ± 0.12	4.47 ± 0.02	64.38 ± 0.09	126 ± 1
9	PDS 9	0.12 ± 0.005	406 ± 1.63	4.64 ± 0.4	3.56 ± 0.22	96.53 ± 0.22	127 ± 1

***In-Vitro* Diffusion Profile of PDS 1 to PDS 9**

Table 3: *In-Vitro* Diffusion Profile of PDS 1 to PDS 9.

Time	% CDR								
	PDS 1	PDS 2	PDS 3	PDS 4	PDS 5	PDS 6	PDS 7	PDS 8	PDS 9
0	0	0	0	0	0	0	0	0	0
0.5	5.86 ± 0.22	5.86 ± 0.14	4.23 ± 0.14	5.86 ± 0.14	1.63 ± 0.14	5.86 ± 0.12	3.45 ± 0.22	4.01 ± 0.14	6 ± 0.14
1	7.19 ± 0.21	6.86 ± 0.18	6.2 ± 0.22	7.19 ± 0.22	4.24 ± 0.18	7.51 ± 0.22	4.67 ± 0.21	10.93 ± 0.18	10.87 ± 0.22
1.5	10.9 ± 0.22	9.17 ± 0.09	7.53 ± 0.09	7.86 ± 0.09	6.21 ± 0.09	9.5 ± 0.21	7.55 ± 0.22	16.81 ± 0.09	16.78 ± 0.09
2	14.81 ± 0.14	11.22 ± 0.14	9.19 ± 0.22	8.87 ± 0.22	7.54 ± 0.14	10.25 ± 0.14	11.66 ± 0.14	29.19 ± 0.14	18.2 ± 0.22
3	16.85 ± 0.22	14.97 ± 0.21	2.44 ± 0.21	10.59 ± 0.21	9.19 ± 0.21	19.61 ± 0.22	16.81 ± 0.22	40.05 ± 0.21	26.71 ± 0.21
4	19.68 ± 0.09	19.26 ± 0.22	17.47 ± 0.22	15.62 ± 0.22	10.95 ± 0.22	20.75 ± 0.09	18.57 ± 0.09	42.79 ± 0.22	40.72 ± 0.22
5	22.92 ± 0.22	20.67 ± 0.13	19.46 ± 0.14	22.56 ± 0.14	19.43 ± 0.13	22.3 ± 0.22	20.96 ± 0.22	45.71 ± 0.13	46.37 ± 0.14
6	31.9 ± 0.21	22.99 ± 0.15	23.83 ± 0.22	26.87 ± 0.22	24.29 ± 0.15	26.45 ± 0.21	26.9 ± 0.21	46.09 ± 0.15	48.77 ± 0.22
7	35.69 ± 0.18	30.63 ± 0.23	28.7 ± 0.09	27.13 ± 0.09	40.25 ± 0.23	29.34 ± 0.18	36.32 ± 0.18	46.93 ± 0.23	50.53 ± 0.09
8	37.21 ± 0.13	36.05 ± 0.2	37.34 ± 0.22	36.9 ± 0.22	41.04 ± 0.2	32.44 ± 0.13	39.3 ± 0.13	52.73 ± 0.2	53.11 ± 0.22
9	43.07 ± 0.21	38.06 ± 0.12	42.06 ± 0.21	38.39 ± 0.21	41.82 ± 0.12	41.25 ± 0.21	44.4 ± 0.21	57.89 ± 0.12	53.71 ± 0.21
10	46.12 ± 0.12	45.29 ± 0.15	47.98 ± 0.18	42.6 ± 0.18	47.08 ± 0.15	42.95 ± 0.12	46.79 ± 0.12	61.64 ± 0.15	53.08 ± 0.18
11	51.09 ± 0.15	51.22 ± 0.2	53.34 ± 0.13	48.26 ± 0.13	51.55 ± 0.2	45.94 ± 0.15	53.08 ± 0.15	61.76 ± 0.2	53.78 ± 0.17
12	57.00 ± 0.21	55.54 ± 0.17	57.37 ± 0.21	53.01 ± 0.21	53.78 ± 0.17	48.64 ± 0.18	55.93 ± 0.21	62.74 ± 0.17	56.54 ± 0.13
18	64.53 ± 0.2	62.18 ± 0.21	63.17 ± 0.12	65.19 ± 0.14	61.06 ± 0.21	61.48 ± 0.21	65.58 ± 0.2	75.41 ± 0.21	78.8 ± 0.17
24	72.31 ± 0.18	69.03 ± 0.13	65.79 ± 0.15	75.55 ± 0.16	72.29 ± 0.13	75.51 ± 0.14	78.74 ± 0.18	85.44 ± 0.13	92.1 ± 0.12

Table 4: Release Kinetics Data of Prednisolone Transdermal patches

Formulation	Zero order		First order		Higuchi	Peppas	
	R^2	N	R^2	N	R^2	R^2	N
PDS 1	0.9205	3.1661	0.9799	0.056	0.9654	0.9820	0.7496
PDS 2	0.9179	3.1220	0.9643	0.053	0.9450	0.9804	0.7914
PDS 3	0.8647	3.2453	0.9153	0.053	0.8991	0.7760	0.9637
PDS 4	0.9565	3.3674	0.9920	0.060	0.9472	0.9699	0.8560
PDS 5	0.8915	3.3675	0.9609	0.057	0.9214	0.9508	1.0112
PDS 6	0.9650	3.1406	0.9912	0.056	0.9657	0.9857	0.7558
PDS 7	0.9782	3.4746	0.9095	0.065	0.9413	0.9729	0.9005
PDS 8	0.8269	3.2228	0.9717	0.074	0.9658	0.9069	0.5781
PDS 9	0.8801	3.5187	0.9378	0.092	0.9648	0.9487	0.6389

Table 5: Short term stability result of Drug content, *In-Vitro* Diffusion study and Folding endurance.

Sr. No.	Stabilty Results	Formulation PDS 9		
		% Drug Content	% CDR	Folding endurance
1	Before stability test	96.53 ± 0.17	92.1081 ± 0.22	127±1
2	After stability test	95.97 ± 0.21	91.9573 ± 0.18	127±1

Discussion:

IR spectrum for pure drug and physical mixture of drug-polymers were obtained and characterized. The intense Peaks at 3299.37 is shown due to O-H stretching, 1714.22 is shown due to C=O, C-H stretching, 1649.96 is shown due to C=C stretching, 1027.22 is shown due to C-O stretching, 919.39 is shown due to C=C bending. It indicates that there is no interaction between Xanthan gum, Guar gum, polyacrylamide and the drug Prednisolone. The results are given in the **Figure 1 and 2.**

The DSC thermogram of Prednisolone exhibited a single sharp endothermic peak at 143.01˚C and drug containing formulation (PDS 9) shows peak at 140.40˚C in the DSC thermogram. This indicates that there is no interaction between the drug and polymer. The results are given in the **Figure 4 and 5**.

Transdermal patches of Prednisolone were prepared by Glass substrate method using polymers, such as Xanthan gum, Guar gum, and Polyacrylamide. The patches were transparent/translucent, smooth and flexible. The patches PDS 1 to PDS 9 exhibited uniform weight ranging from 348mg to 833mg and thickness of PDS 1 to PDS 9 are ranging from 0.12mm to 0.24mm. Among the various patches, the uniformity weight and thickness indicates that the polymeric solution of the drug is well dispersed in the patches, the moisture content and moisture uptake ratio was found to be low in formulation PDS 9. All the formulations exhibited fairly uniform drug content ranging from 67.9% to 96.53% respectively. Folding endurance of the prepared formulations PDS 1 to PDS 9 varied from 120±1 to 127±1. The highest folding endurance was noted for PDS 9. Data was recorded in **Table 2**. This was satisfactory to ensure that the patches would maintain integrity when attached to skin.

The SEM of formulation PDS 9 reveals that the surface of the film was smooth and free from air bubbles. The results are shown in the **Figure 3**.

XRD graph of Prednisolone had shown the characteristic peaks at 2θ of 14.805˚, 17.329˚, 18.105˚, 19.453˚, 21.085˚ etc.., due to its crystalline nature. However the peaks observed in prednisolone are not found in the formulation PDS 9. This indicates that the drug is in amorphous form in the formulation. The graph of drug and formulation is shown in **Figure 6 and 7.**

The *in vitro* Diffusion study of patches conducted using cellophane membrane barrier was carried

out using Franz's diffusion cell. The results of *in vitro* permeation studies are shown in the **Table 3**. The cumulative percentage of drug diffusion from PDS 1 to PDS 9 formulations ranges from 65.79% to 92.1%.

The release kinetics was evaluated by making use of Zero order, First order, Higuchi's and kosmeyer-Peppa's equation. The drug release through the transdermal patches of Prednisolone follows First order kinetics with diffusion controlled mechanism. By fitting in the Korsemeyer-Peppa's equation the release kinetics follows non-Fickian kinetics. The data is shown in **Table 4**.

The Short term stability studies were carried out on the most satisfactory formulation PDS 9 at 45-50°C (75%RH) for a period of 45 days to assess Stability as per ICH guidelines. At fixed time, the formulation was evaluated for Drug content, Folding endurance and any changes in their physical appearance. There was no significant change in the drug content, *in vitro* drug release profile, folding endurance and appearance of the patches. The results are shown in the **Table 5.** Therefore PDS9 is a stable formulation.

Conclusion

The preformulation studies involving description of solubility, melting point, of the drug. Based on all above preformulation studies the drug was suitable for making the transdermal formulation. Based on all the factors the transdermal drug delivery system PDS 9 is having lower moisture content and moisture uptake, and greater folding endurance and % drug release. The Formulation PDS 9 shows better extended release up-to 24 hrs when compared to other formulations because the combination of two natural polymers show better retardation efficiency than the combination of two natural polymers and one synthetic polymer. So it was concluded that the formulation PDS 9 prepared by using Xanthan gum, Guar gum and Polyacrylamide (in ratio 2:1:1) is the better formulation for control release of drug upto 24 hr. However by the pharmacokinetic studies it indicates that *in vitro* drug release of the formulation PDS 9 follows first order kinetics and the mechanism followed non- Fickian diffusion. The formulation PDS 9 was found to be stable in short term stability studies, so it can be suggested that there is further scope for *in-vivo* and pharmacokinetic study.

From the results it indicates that biocompatible and cost effective polymers like Xanthan gum, Guar gum and Polyacrylamide can be used to formulate efficient transdermal patches with good percentage entrapment efficiency and controlled release upto 24 hr.

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