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Design and *In-Vitro* Formulation and Evaluation of Transdermal Patches Containing Voglibose

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ABSTRACT

Transdermal patches of Voglibose were prepared by the solvent evaporation method using ethyl cellulose, PVP, and HPMC K15M using different ratios. The physicochemical parameter such as Weight variation, Thickness, Moisture content, Moisture uptake, Folding endurance, and Tensile strength was evaluated for the prepared patches. The formulation exhibited Weight, Thickness Moisture content, Moisture uptake, Folding endurance, Tensile strength, and good drug content (91.30-94.22). The *in-vitro* studies were carried out using Franz diffusion cell and formulation followed the Higuchi's model. The formulation containing EC and PVP as polymers showed a Faster release rate (Hydrophilic and Hydrophobic polymers) compared to HPMC K15M or a combination of hydrophilic and hydrophobic polymers (EC and PVP). The stability studies indicated that all the patches maintained good physicochemical properties and drug content after storing the patches in different storage conditions. In- vitro studies showed that Voglibose helps in decreasing the effect of blood sugar. Hence, the present study aimed to prepare the sustained release formulation (Transdermal patches) of the drug-using different blend of polymers. The formulated patches containing the hydrophobic and hydrophilic polymers showed the best release rate of the drug.

INTRODUCTION:

Transdermal drug delivery systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin [1, 2]. Conventional systems of medication that require multi-dose therapy have numerous problems and complications. The design of a conventional dosage form, whether a tablet, an injection, or a patch, to deliver the right amount of medicine at the right target site becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient [3, 4]. Redesigning the modules and means to transport medicine into the body is a less demanding and more lucrative task. To address these problems, a controlled release drug delivery system, a novel drug delivery approach evolves, which facilitates the drug release into systemic circulation at a pre-determined rate [5]. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period [6].

The transdermal drug delivery system not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into the systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery systems such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems, etc. In comparison to conventional pharmaceutical dosage forms, TDDS offers many advantages, such as elimination of the first-pass metabolism, enhancement of therapeutic efficiency and (maintenance of steady plasma level of the drug sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance [7].

Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients. They are intended to be applied to the unbroken skin to deliver the active ingredient to the systemic circulation after passing through the skin barriers. TDDS which produce comparable smaller patches with a more controlled and sustained release [8].

MATERIALS AND METHODS:

MATERIALS:

Voglibose obtained as a gif sample from NPL ltd. Bara, Nepal. Ethylcellulose, PVP, HPMC K15M were obtained from SD Fine-chemical Limited, Mumbai. Propylene glycol, Methanol,

and PEG-400 were obtained from Thermo Electron Lls, Mumbai. All other chemicals and reagents used were of analytical reagent grade.

METHODS:

Formulation of transdermal patches

In the present study, the matrix type of transdermal patches of Voglibose was prepared by the solvent evaporation method. A flat square-shaped having surface area 2x2 cm^2.

Method of preparation of Transdermal patches

Transdermal films of Voglibose were prepared by the solvent evaporation method. The solution of PVP with EC, HPMC, were dissolved in 10 ml mixture of methanol in the ratio as per the formulation table. PEG 400 was added in the required amounts as per the formulation chart to the prepared solution and stirred well. The accurately weighed drug was mixed with the above mixture and mixed well to obtain a homogenous mixture. After proper mixing, the solution was kept for stabilization and complete removal of air bubbles. Then the above mixture was cast in a glass mold of 9cm^2 previously coated with a thin layer of glycerine to prevent the adhesion of formed patch to the mold. The rate of evaporation was controlled by inverting a glass funnel over the glass mold. The mold was kept aside for drying at room temperature for 24hrs. After 24 hrs the dried films were carefully removed from the mold and stored in a desiccator.

Table No. 1: Composition of Voglibose transdermal patches

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
HPMC K15M (mg)	100	-	-	50	-	50	75	25	-
EC (mg)	-	100	-	50	50	-	25	75	75
PVP (mg)	-	-	100	-	50	50	-	-	25
Propylene glycol (mg)	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Methanol (mg)	9	9	9	9	9	9	9	9	9

Evaluation Parameters

1. The thickness of the patch[9]

The thickness of the drug prepared patches is measured by using a digital micrometer at different points of the patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patches.

2. Weight uniformity[10]

The prepared patches were 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 the digital balance. The average weight and standard deviation values were calculated from the individual weights.

3. Folding endurance[11]

Specific areas of patches were cut and repeatedly folded at the same place till it broke. The number of times the film was folded without breaking gave the value of folding endurance.

4. Percentage moisture content [12]

The prepared patches were weighed individually and were kept in a desiccator containing fused calcium chloride at room temperature. After 24 hrs the films were reweighed and determine the percentage moisture content by using the below formula.

Percentage moisture content = [Initial weight- Final weight / Final weight] x 100

5. Drug content [13]

A specified area of patches was dissolved in methanol in a specific volume. Then the solution is to be filtered through a filter medium and analyzed the drug contains the suitable method UV-Spectrophotometer. Then take the average of three different samples.

6. *In-vitro* drug permeation studies[14]

In-vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 150 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into a size of 2x2cm^2 and placed over the drug release membrane and the

receptor compartment of the diffusion cell was filled with phosphate buffer Ph 7.4. 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 37 ± 0.5 0C. The samples of 1 ml were withdrawn preset time points up to 24 hrs, analyzed for drug content spectrophotometrically at 282 nm against a blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal.

7. Kinetics studies[15]

To study the release kinetics of in-vitro drug release, data obtained from in-vitro release study were plotted in various kinetic models: Zero-order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer- Peppas as log % drug released Vs log time and Hixson-Crowell as (% drug retained)1/3Vs time. By comparing the r-values obtained, the best-fit model was selected.

8. Stability studies[16]

The stability studies were carried out on the most satisfactory formulations at 40±2oC/70±5 % RH for two months to assess their stability as per ICH guidelines. At fixed time intervals of 30 days and 60 days, the formulation was evaluated for the physicochemical properties and in vitro drug release. There was no significant difference in the physicochemical parameters and in vitro drug release profiles and were found to be superimposable with the initial observations.

RESULTS AND DISCUSSION:

Transdermal patches of Voglibose were prepared by the solvent evaporation technique as per the formulation table using polymers such as PVP, EC, PEG-400, HPMC K15M in different proportions. The effect of polymer concentration on physicochemical parameters of prepared formulations like thickness, weight variation, folding endurance, tensile strength, moisture content, drug content, In-vitro release profile, and stability studies was evaluated.

Determination of solubility

Voglibose is very slightly soluble in distilled water and freely soluble in methanol and soluble in Phosphate buffer pH7.4.

Compatibility studies

The incompatibility between the Drug and Excipients were studied by FTIR spectroscopy. The spectral data of pure drug and various drug-excipient mixtures are presented in Fig. no. (5 to 8). The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation.

Evaluation studies of Voglibose transdermal Patches

The Voglibose transdermal patches have been developed by using HPMC K15M, EC, and PVP. The results of the prepared patches have been illustrated briefly as follows.

Weight Variation

Weight variation for all the formulations (F1-F9) were found to be 120mg, 116mg, 115mg, 122mg, 124mg, 120mg, 118mg, 118mg, and 119mg respectively. The results are shown in Table no. 2.

Thickness

In thickness variation test, thickness variation values of the formulations (F1-F9) prepared with HPMC K15M, EC and PVP are 0.14mg, 0.13mg, 0.12mg, 0.2mg, 0.21mg, 0.2mg, 0.14mg, 0.14mg and 0.19mg respectively. The result shown in Table no. 2.

Folding endurance

Folding endurance numbers of formulations (F1- F9) prepared with HPMC K15M, EC and PVP are 96, 89, 92, 95, 99, 87, 92, 90, and 98. The highest folding endurance number in the case of was shown of formulation F5 due to its more hydrophilic nature. The folding endurance numbers decreased with a decrease in HPMC K15M concentration. This data revealed that the patches had good strength along with good flexibility. The results are shown in Table no. 3.

Estimation of drug content

The drug content of formulations (F1-F9) has in the range of 91.30% to 94.22%. The results of content uniformity indicated that the drug was uniformly dispersed in all transdermal patches. The results of drug content for formulations (F1-F9) are shown in Table no. 2.

Moisture absorption and Moisture loss study

The moisture absorption and moisture loss of formulations F1 to F9 is (7.86 to 10.21) and (8.56 to 11.46) respectively. The results revealed that the moisture absorption and moisture loss was found to decrease due to the different concentration of hydrophilic polymer HPM K15M. The small moisture content in the formulations helps them to remain stable. The results of moisture absorption and moisture loss studies were shown in Table no. 2.

***In-vitro* drug release profile**

The results of *in-vitro* drug release studies from Transdermal patches are depicted in the table. The cumulative percentage of drug release from the various formulations was found to vary between 82.58 to 86.99 Formulation F1, F2, exhibited greatest 98.17 and 91.70 percentage of drug release compared to other formulations and drug release was found to be less in formulations F5 and F9. The drug release from all the films was rapid in the initial hours (up to 12 hrs), which could be due to the presence of drugs on the surface of the films. Later the drug was released slowly from the patches. The result is shown in Table No. 3.

Kinetics of drug release

The results of dissolution data were fitted to various kinetic equations to analyze the release mechanism. All the selected formulations were found to follow Higuchi kinetics.

The optimized formulation F5 treated with different kinetic equations to interpret the order of release of Voglibose and the coefficient of determination (r^2) was determined. Results indicate that in the selected F5 formulation, the calculating regression coefficients for Zero order, First order, Higuchi plot, and Korse Mayer Peppas models were 0.7615, 0.7703, 0.9252 and 0.5678 respectively. Therefore, the release seems to fit in the Higuchi plot model indicating the release of drugs from the matrix as a square root of time-dependent process based on Fickian diffusion.

The kinetic values obtained for selected formulations are tabulated in Table No.4.

Stability studies

The stability studies were carried out on the most satisfactory formulations F5 at 40±2oC/70±5 % RH for two months to assess their stability as per ICH guidelines. At fixed

time intervals of 30 days and 60 days, the formulation was evaluated for the physicochemical properties and in vitro drug release. There was no significant difference in the physicochemical parameters and in vitro drug release profiles and were found to be superimposable with the initial observations. The results are shown in table no. 5.

Table No. 2: Physicochemical evaluation parameters

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Weight variation (mg)	120	116	115	122	124	120	118	118	119
Thickness (mg)	0.14	0.13	0.12	0.2	0.21	0.2	0.14	0.14	0.19
% Moisture uptake	9.86	9.15	7.69	9.52	10.21	8.53	9.25	9.78	7.86
% Moisture content	10.72	10.62	8.56	11.11	11.46	9.78	10.11	11.12	8.96
Folding endurance	96	89	92	95	99	87	92	90	98
Tensile strength (kg/mm^2)	0.473	0.463	0.449	0.435	0.421	0.432	0.409	0.394	0.365
% Drug content	92.38	92.87	91.99	91.30	94.22	93.26	91.40	93.65	93.55

Table No. 3*: In-vitro drug* release profile of Voglibose transdermal patch: F1-F9

Time in hrs	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	45.85	47.58	51.40	33.21	52.29	46.39	50.55	48.18	50.26
2	49.07	51.40	56.41	37.30	56.41	49.67	56.11	53.49	56.43
3	51.40	55.52	63.74	45.80	61.96	51.40	60.22	56.11	59.07
4	53.49	62.85	67.86	51.40	65.63	56.41	64.95	60.22	72.31
5	56.11	63.15	73.76	56.41	67.86	63.15	66.72	64.95	73.48
6	62.85	66.72	75.79	61.96	73.76	66.72	69.05	67.86	76.71
7	63.74	73.76	77.57	63.15	76.09	69.05	70.83	69.05	78.47
8	66.72	75.79	79.94	66.72	78.47	74.95	73.76	71.11	79.36
9	71.11	77.57	82	67.86	84.02	75.79	74.95	72.01	83.17
10	75.25	79.94	83.17	71.11	86.99	76.09	76.68	73.18	84.02
11	80.80	82	84.02	74.95	91.70	77.57	78.47	74.06	88.43
12	82.58	86.99	88.43	75.83	98.17	79.6	82	78.47	91.70

Table No. 4: Release kinetic profile of F5 formulation

Formulation code	Mathematical value (r^2 value)				Best fit model
	Zero-order	First-order	Higuchi	Peppas	
F5	0.7615	0.7703	0.9252	0.5678	0.9252

Table No. 5: Dissolution of Formulations F5 after stability studies

FORMULATION	0 DAYS	30 DAYS	60 DAYS
F5	98.17%	97.85%	96.55%

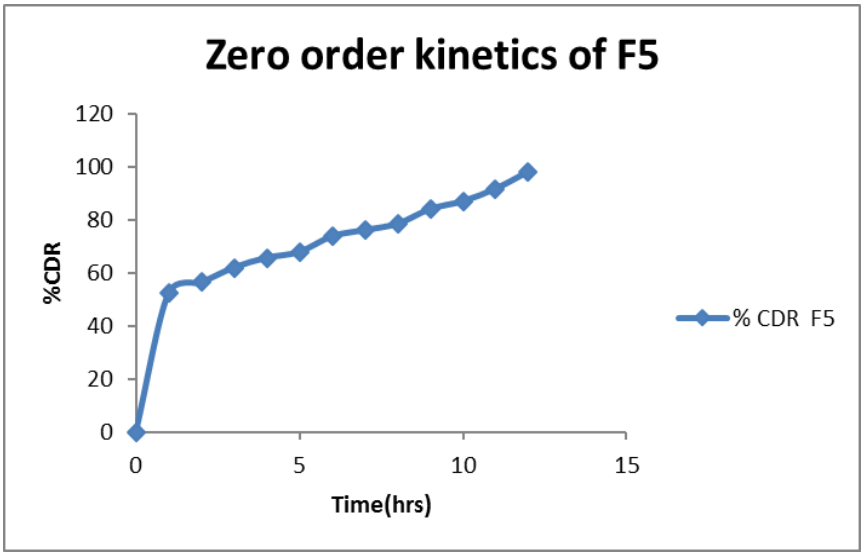

Figure No. 1: Zero-order kinetics of F5

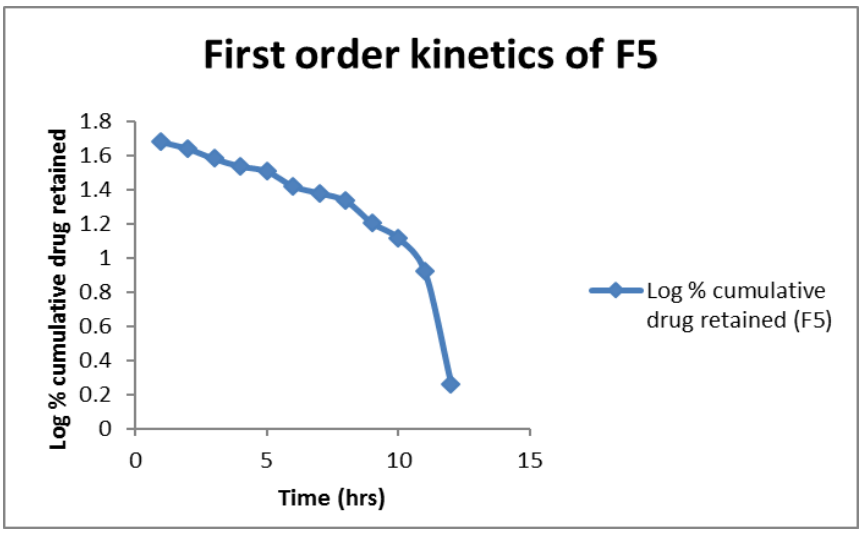

Figure No. 2: First-order kinetics of F5

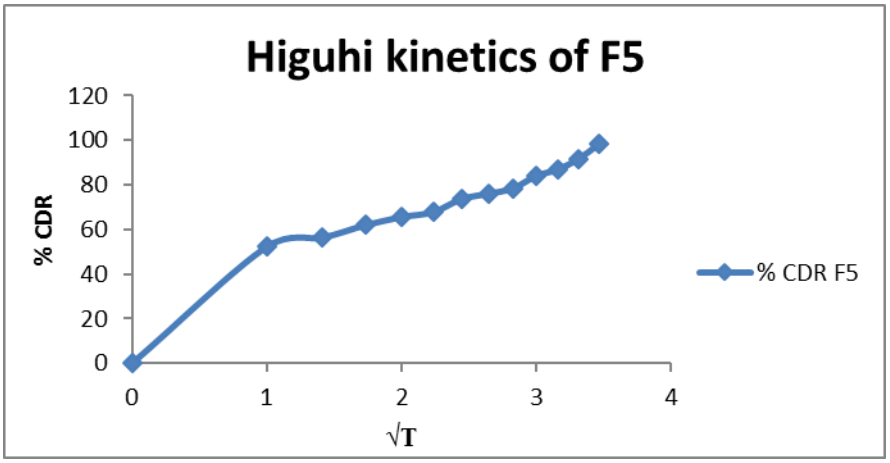

Figure No. 3: Higuchi kinetics of F5

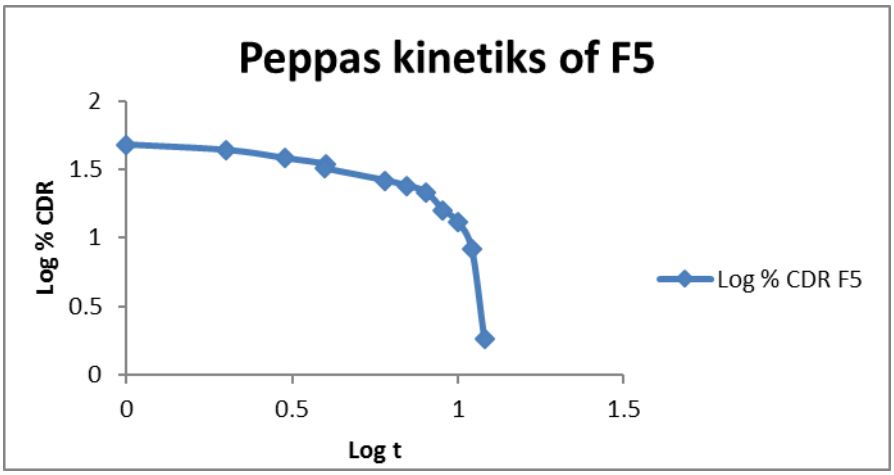

Figure No. 4: Peppas kinetic from F4-F6

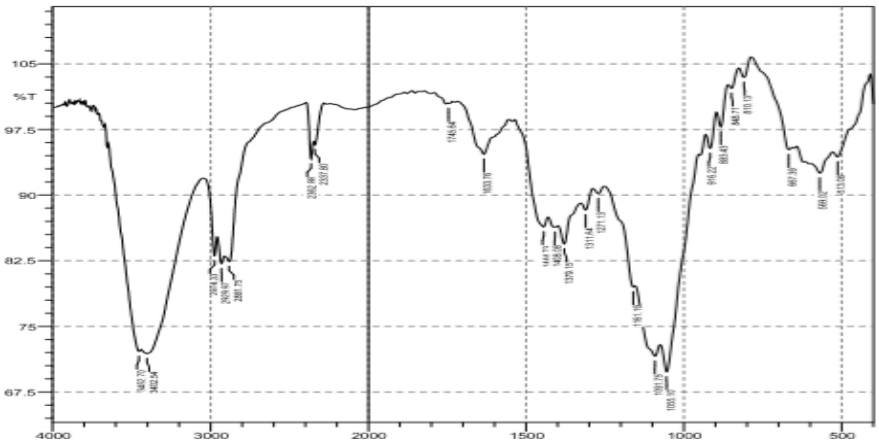

Figure No. 5: FTIR Spectra of a pure drug (Voglibose)

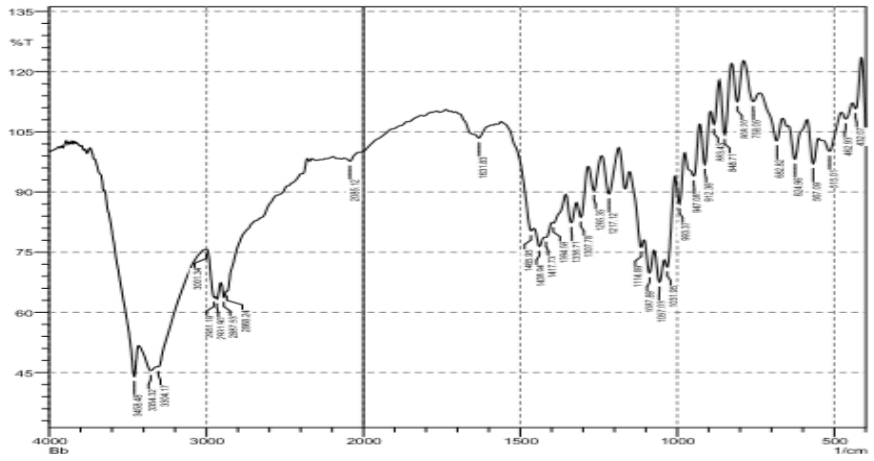

Figure No. 6: FTIR Spectra of Voglibose +HPMC K15M

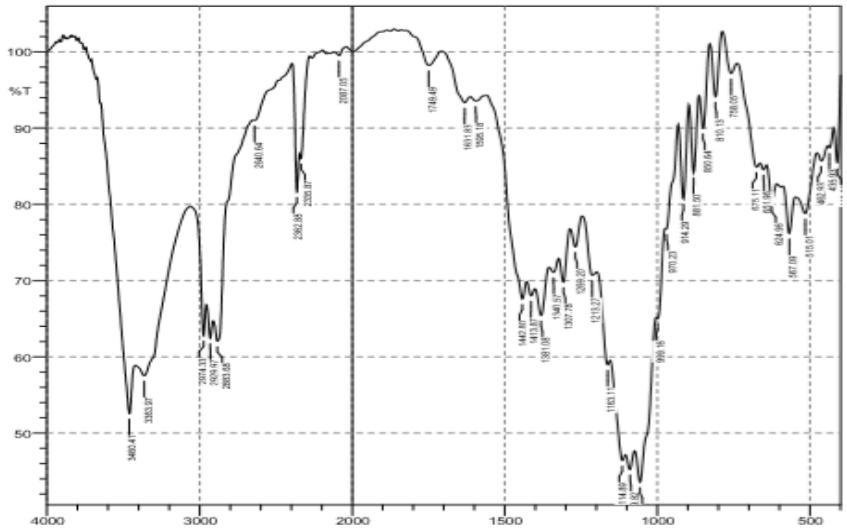

Figure No. 7: FTIR Spectra of Voglibose +Ethyl cellulose

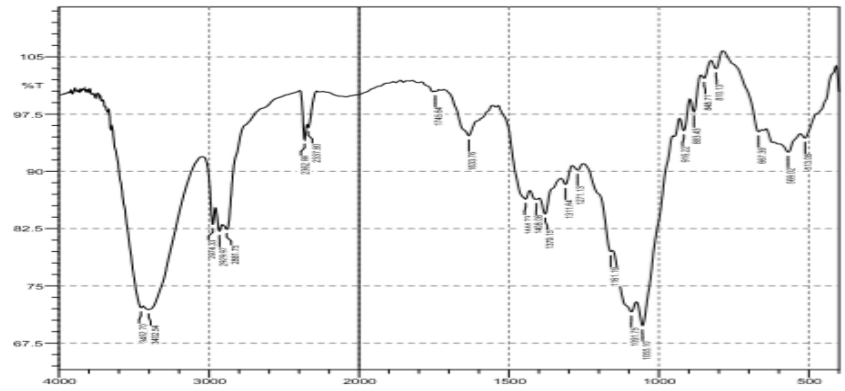

Figure No. 8: FTIR Spectra of Voglibose + HPMC K15M+Ethyl cellulose

CONCLUSION:

The prepared transdermal patches were evaluated for their physicochemical characteristics such as physical appearance, weight uniformity, thickness, folding endurance; moisture content, drug content was suitable. The polymer-drug interaction study did not show any incompatibility. The formulations F5 exhibited the highest Cumulative amount of drug 98.17% in 12hr. So the results indicate that Voglibose transdermal patches can be suitable for sustain release throughout 12 hrs for the management of Diabetes mellitus.

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