DESIGN AND IN-VITRO EVALUATION OF TRANSDERMAL PATCHES CONTAINING EMPAGLIFLOZIN

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Abstract

The transdermal drug delivery system of Empagliflozin has been formulated by using the solvent evaporation method using polymers such as Ethyl cellulose PVP, and HPMC K15M in different proportions. PEG-400 is used as a plasticizer and propylene glycol is used as a penetration enhancer.

The IR studies confirmed the compatibility between the drug and the polymers. All the patches were uniform concerning physiochemical evaluation. The effect of polymer concentration on physiochemical parameters of prepared formulations like thickness, weight variation, folding endurance, moisture content, moisture uptake, tensile strength, drug content, and in-vitro release was evaluated.

The purpose of this research was to develop a matrix type of transdermal therapeutic system containing Empagliflozin with different ratios of hydrophilic and hydrophobic polymeric concentration by the solvent evaporation method. The prepared patch showed satisfactory physiochemical characteristics of weight uniformity, thickness, folding endurance, moisture uptake, tensile strength, and moisture absorption for the stability of the formulation, and drug content was uniform in all patches. In vitro study done by Franz diffusion cell having semi-permeable membrane to determine the amount of drug present in the formulated patch. In formulation based on the present study formulation , F5 shows 92.29% drug was released within 6 hrs.

Conclusion: the study concludes that transdermal patches can extend the release of Empagliflozin for many hours with the help of polymer ethyl cellulose and PVP further it also helps in avoiding first-pass metabolism.

Keywords: transdermal drug delivery, Empagliflozin, HPMC, EC, and PVP.

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1. INTRODUCTION

The transdermal drug delivery system adheres to the body surface and delivers the drug. Across the skin at a controlled rate into the bloodstream. A transdermal drug delivery system is a self-contained discrete dosage form. A transdermal drug delivery system is also known as a transdermal patch or skin patch that delivers a specific medication dose to the systemic circulation. It is a medicated adhesive patch. The transdermal drug delivery system is a novel drug delivery system and it aims to achieve a programmed delivery of the therapeutic products when applied on the skin for optimal beneficial effects while avoiding the side effect of drugs. The transdermal drug delivery system is topically administered medicaments. In the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device that provides an alternative route for administrating medication. [1]

Transdermal patches are flexible pharmaceutical preparation of varying sizes, containing, one or more active ingredients to the systemic circulation after passing through the skin barriers. [2]. A transdermal patch is also known by the name of a skin patch which is used to deliver a specific amount of dose through the skin and it directly goes into the bloodstream. 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. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc. is that it provides a controlled release of the medicament into the patient. A wide variety of drugs are delivered by transdermal patches. A new crystal reservoir technology has come out successfully with the advancement in TDDS which produce comparable smaller patches with a more controlled and sustained release [3].

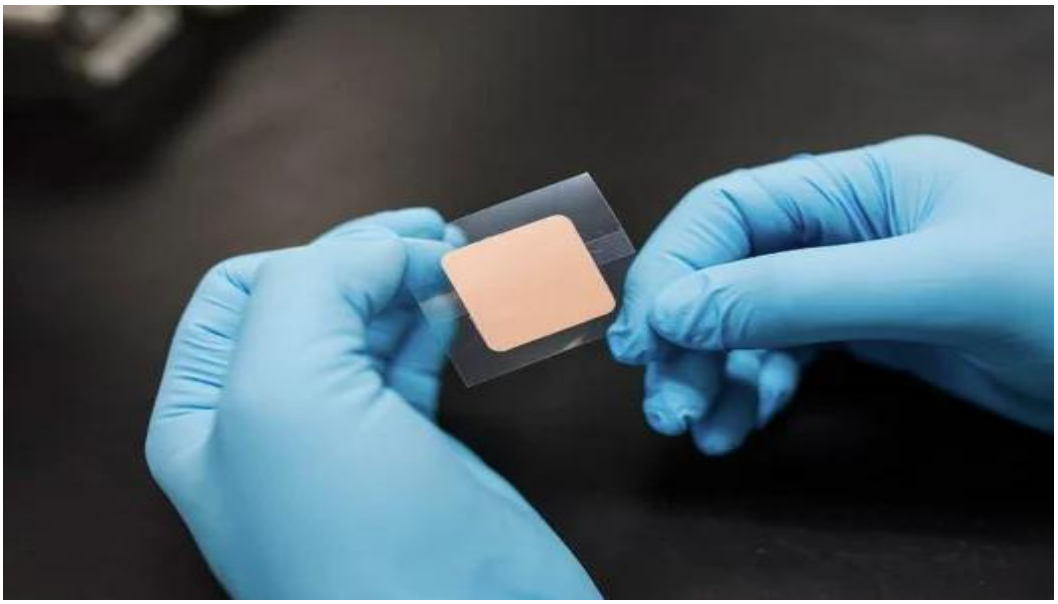

Fig.no.1: Transdermal patch

Advantage of transdermal drug delivery system

- Eliminate hepatic first-pass metabolism.
- Provide steady delivery.
- Increase compliance.
- Reduce systemic drug interaction
- Permit dose discontinuation via removal.
- Improved bioavailability.
- Longer duration of action.
- More uniform plasma levels.
- Self-administration is possible.
- Minimal inter and intra-patient variation because the composition of skin structurally and biologically is the same in almost all humans.
- Avoidance of gastrointestinal incompatibility.

- Avoidance of hazards and discomfort associated with parenteral therapy.
- Improves patient compliance, as it is easy to apply.
- Steady and optimum blood concentration-time profile achieved.
- Release of a drug for a prolonged time with a single application which extends the duration of activity.
- Elimination of typical multiple dosing [4].

Disadvantage of transdermal drug delivery system

- Local irritation is a major problem.
- Drugs requiring high blood levels are unsuitable.
- Drugs with long half-lives can- not be formulated in TDDS.
- Uncomfortable to wear.
- Daily dose of more than 10 mg is not possible.

Diabetes

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes from Overtime eating. Insulin well glucose then stays in your blood and does not reach your cell Over time, having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can take steps to manage your diabetes and stay healthy sometimes people call diabetes "a touch of sugar" or" borderline" diabetes. These terms suggest that someone doesn't have diabetes or has a less serious case but every case of diabetes is serious.

The most common type of diabetes is type 1, type 2, and gestational diabetes.

Type 1 diabetes.

In type 1 diabetes, the body doesn't make insulin. The immune system attacks and destroys the cell in the pancreas that make insulin. type1 diabetes is usually diagnosed in children and young adults, although it can appear at any age people with type 1 diabetes need to take insulin every day to stay alive

Type 2 diabetes.

In type -2 diabetes, the body doesn't make or use insulin well. Type 2 diabetes can be developed at any age. even during childhood. However, this type of diabetes occurs most often in middle-aged and older people Type 2 is the most common type of diabetes. It comes as a tablet.

Gestational diabetes

Gestational diabetes develops in some women when they are pregnant. Most of the time, this type of diabetes goes away after the baby is born. However, if you've had gestational diabetes, you have a greater chance of developing type 2 diabetes later in life. Something diabetes diagnosed during pregnancy is type 2 diabetes. [5].

2. MATERIALS AND METHODS

Table 1: list of materials used

S. No	Name of chemicals	Suppliers/manufactures
1.	Empagliflozin	Vega pharmaceutical
2.	EC	SD Fine Chemical Limited
3.	HPMC	SD Fine Chemical Limited
4.	PVP	SD Fine Chemical Limited
5.	Eudrajit RS100	Thermo electrons Lls, Mumbai
6.	Propylene glycol	SD Fine Chemical Limited
7.	Chloroform	SD Fine Chemical Limited
8.	Methanol	SD Fine Chemical Limited

Table no.2: List of Equipment used.

S. No	Name of equipment's	Suppliers
1.	Analytical balance	Shimadzu AX
2.	Hot air oven	Analytical technologies
3.	FTIR	FTIR-8300, Shimadzu
4.	U.V Spectrophotometer	Systronics 117
5.	Vernier calipers	Optics technology
6.	Franz diffusion cell	A-one scientific solution
7.	pH meter	Optics technology

Methods:

Preformulation studies:

It is one of the important prerequisites in the development of any drug delivery system. Preformulation studies were performed on the drug. Which are melting point determination, solubility, and compatibility studies.

Description: Empagliflozin was physically examined for color and odour

Solubility: The solubility of the selected drug was determined in methanol and phosphate buffer 6.8 pH using the standard method.

Melting point: fine powder of Empagliflozin was filled in a glass capillary tube (previously sealed at one end) and kept in electrical melting point apparatus. The melting temperature was found.

Estimation of Empagliflozin: A spectrophotometric method based on the measurement of extinction at 272 nm in methanol was used for the estimation of empagliflozin.

Fourier transforms infrared radiation (FTIR):

Prior to the development of dosage forms the compatibility study was carried out. The Fourier Transform Infra-Red (FT-IR) spectroscopy studies were carried out for pure drug alone and along with polymers to check the compatibility between drug (Empagliflozin) and HPMC, EC, Eudragit RS100, which are used to formulate transdermal patches.

The drug spectrum peak was compared with the drug and polymer mixture spectrum peaks. an instrument was used for the study using KBr pellets. The major sharp and significant peaks (functional groups) of the drug and drug-polymer mixture were noted.

Evaluation

Parameters

Thickness:

The thickness of transdermal patches is measured by a traveling microscope, dial gauge, screw gauge, or micrometer at three different points of the patch and the average of the three is taken as the thickness of the patch a uniformly thick patch will have an equal thickness at every point. The variation of thickness within the patch and patch can be calculated.[6]

Folding endurance:

Folding endurance is calculated by continuously folding the strip of the patch/film of a specific area at the same place until it breaks or is folded up to 300 times. The number of times of folding the patch without breaking gives the folding endurance of the patch. The folding endurance determines the flexibility of the patch.[7]

Drug content determination:

An accurately weighed portion of the film (about 10mg) is dissolved in 10 ml of phosphate buffer of pH 6.8 and then the solution is shaken continuously for 24 hrs in shaker incubator. Then the whole solution is sonicated. After sonication and subsequent filtration, the drug in solution is estimated spectrophotometrically by appropriate dilution. [8]

Weight variation:

This was done by weighing three different patches of individual patches taking the uniform size (3cm*3cm) at random

And calculating the average weight of 3. The tests were performed on films that were dried at 60^0c for 4hrs prior to testing. [9]

Moisture content:
The prepared film is weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24hrs. the films are weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using the following formula.[9]
% moisture content = final weight x 100

Moisture uptake: weighed films are kept in a desiccator at room temperature for 24 h. these are then taken out and exposed to 84% relative humidity using a saturated solution of potassium chloride in a desiccator until a constant weight is achieved. %moisture uptake is calculated as given below.[10]
% moisture uptake = final weight -initial weight X100

Percent Elongation break test:
The percentage elongation break is to be determined by nothing the length just before the breaking point, the percentage elongation can be determined from the below-mentioned formula. Elongation percentage = L1-L2 X100 L2, Where, L1 is the final length of each strip and L2 is the initial length of each strip. [11]

Stability studies:
A stability study is conducted to determine the time period for which the patch remains viable and usable. In unstable patch formulations drug starts degrading gradually so stability is tested according to ICH guidelines at 400/75% RH for 6 months. Samples are taken at 0,30, 60,90, and 180 days and tested for its stability. [12]

In vitro drug permeation studies:
The drug release study was carried out using a modified diffusion assembly. The transdermal patch ($3x3cm^2$) was adhered to the cellulose acetate membrane and tied firmly to the diffusion tube. This assembly was lowered in a beaker containing 100 ml of PSB so that the membrane assembly just touches the solution in the beaker. The whole assembly was kept on a magnetic stirrer and the study was conducted at a temperature of 37 ± 2^0C. the contents in the beaker were stirred using a Teflon bead at a constant speed. Samples of 5 ml were collected at a predetermined time and replenished with fresh prewarmed medium. The drug content in the samples was estimated using a UV/visible spectrophotometer at 272nm. The cumulative percentage of the released drug was calculated and plotted against time.

Kinetics of drug release:
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, Kors Meyer - Peppas as log % drug released Vs log time. by comparing the r- values obtained, the best–fit model was selected. [13]

3. RESULT

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

Determination of Solubility
Empagliflozin is very slightly soluble in distilled water and freely soluble in methanol.

Melting point determination
The melting point of empagliflozin was evaluated three times. The average value is shown in the table.

Table no. 3: melting point determination

S No.	Melting point (^{0}c)
Trail 1	151
Trail 2	152
Trail 3	150
Average	151^0c

Calibration curve of Empagliflozin:
The method was developed for the estimation of Empagliflozin by scanning in UV-spectrophotometer and showed maximum absorption at a wavelength of 272 nm in methanol. The standard calibration curve obeyed Beer's law at the given concentration range of 5ug/ml.
The absorbance values obtained were shown in Table 4.

Table no. 4: spectrophotometric data for a standard curve of empagliflozin in methanol.

S. No	Concentration (ug/ml)	Absorbance (At 272nm)
0	0	0
1	5	0.199
2	10	0.455
3	15	0.629
4	20	0.817
5	25	1.016

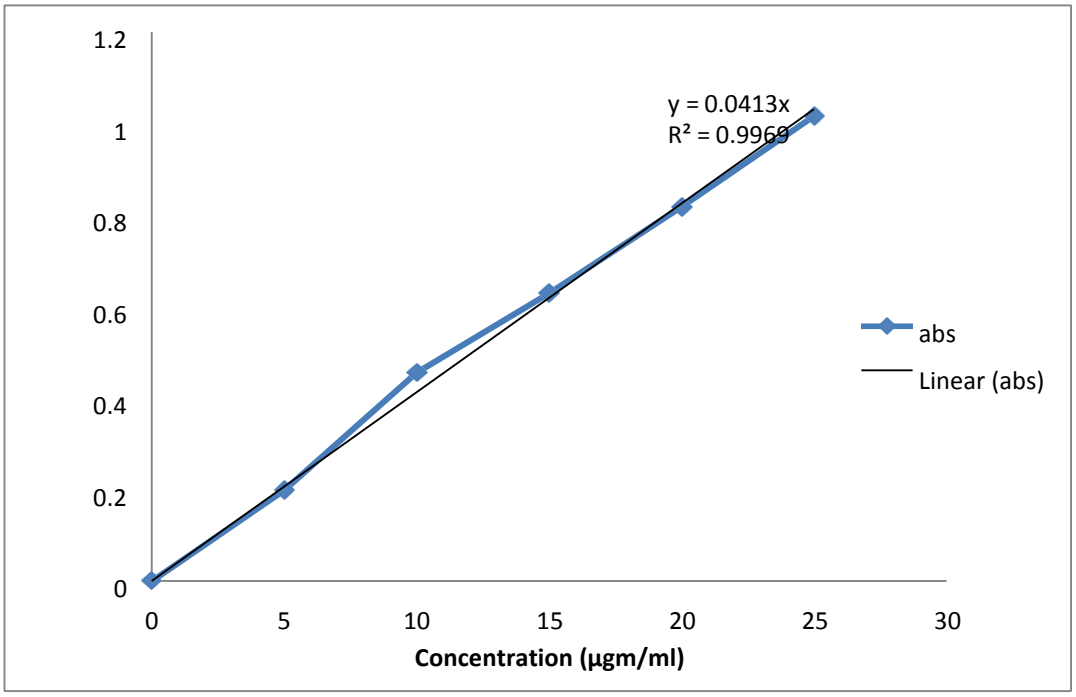

Fig. No. 2: standard calibration curve of empagliflozin

FTIR compatibility studies:
The FTIR spectra of pure drug and physical mixture of drug and polymer were obtained and compared for confirming the compatibility of the drug with the polymers used for formulation. The absorption spectra and their principal peaks at or around the corresponding range of the pure drug. It is inferred that there was no interaction between the drug and polymer and other additives. The integrity of the drug was maintained in all physical mixtures.
The spectra showed no incompatibility between the polymer and Empagliflozin.

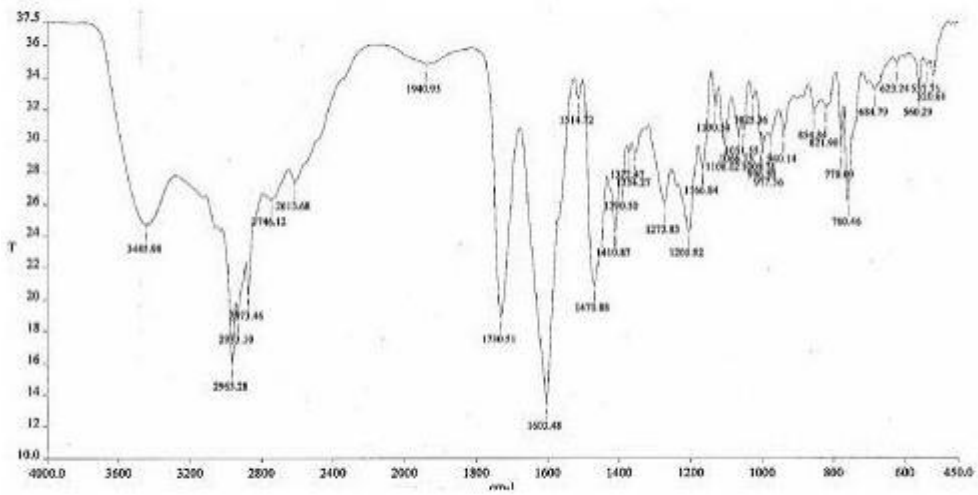

Figure No.3: FTIR Spectra of pure drug

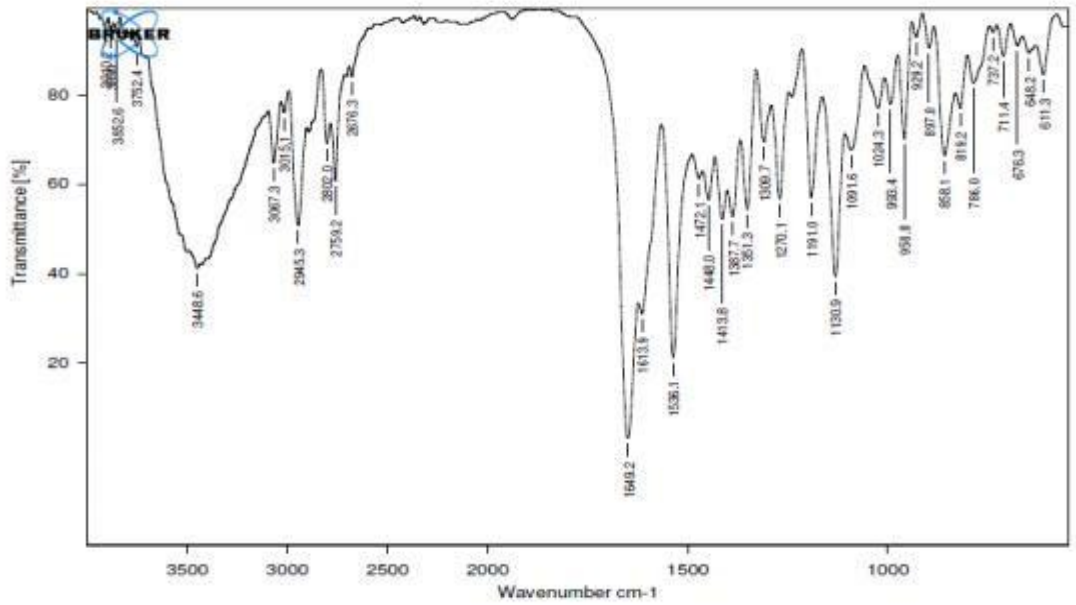

Figure no. 4: FTIR spectra of pure drug+HPMC

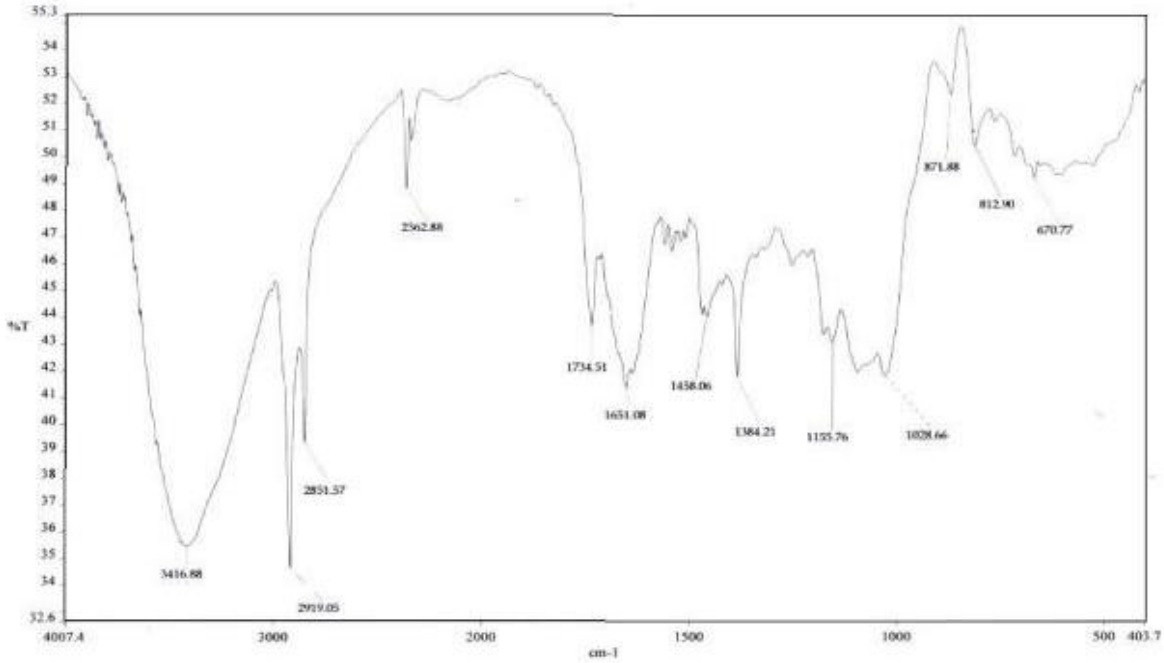

Figure No.5: FTIR spectra of pure drug ethyl cellulose

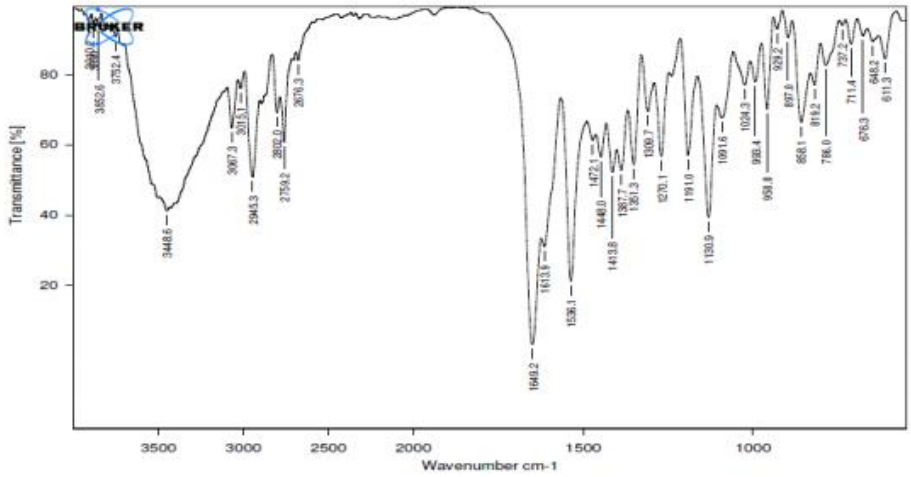

Figure No.6: FTIR Spectra of pure drug+PVP

Evaluation studies of Empagliflozin transdermal patches

Thickness and weight variation:
There was very little variation in the weight of any formulation, and all the films displayed similar weight and thickness. The homogeneity of weight and thickness between batches suggests that the polymeric solution containing the medication is evenly distributed throughout the patches. The results of thickness variation of 0.11 to 0.13 and weight variation of 119 to 124 were displayed in table no. 5

Drug content uniformity:

All the prepared formulations were found to have uniform drug content which is in the acceptable range of IP. The drug content analysis of the formulation has showed that process employed for the mixing and preparation of the films were capable of giving films with uniform drug content with minimum batch variability. The drug content of the formulation were found to vary between 91.1 to 95.12. the results were shown the table no.6

Folding Endurance:
The folding endurance was found to be in the range of 179 to 197. The values for all formulations were shown in table no.6. this data

revealed that the patches had good mechanical strength along with flexibility.

Moisture content:
Moisture content can cause significant changes in properties such as reduced crushing strength, and increased pore diameter in the patches containing hydrophilic polymer. But the moisture in the prepared patches was found to be low and it varied very little in the formulation. The little moisture content helps the formulation to be stable and prevents them from becoming a completely dried, brittle

Percentage of elongation:
Information on how much a specimen may extend before breaking can be found in the percentage elongation of films. The scale is used to measure the percentage elongation at the breaking point, and the results show that it falls between the range of 23.7 to 35.55.

In vitro drug release profile:
Table No. 7 shows the outcomes of investigations on the in vitro release of drugs from transdermal patches. It was discovered that the range of the cumulative percentage of drug release from the different formulations was 91.79 to 92.29. In comparison to other formulations, drug release was found to be greatest in formulations F9 and F5, and to be least in formulations F3 and F7. The drug is released from all the presence of the drug on the surface of the films. Later the drug was released slowly from the patches.

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 the Higuchi model.
The kinetic value obtained for selected formulations are tabulated in Table No. 21 and kinetic plots are shown in table no. 8.

Stability studies:
The most effective formulation F5 underwent two months of stability experiments at 40+20C and 70+5% RH to evaluate its stability by ICH recommendations. The formulation was shown to be superimposable with the original data at fixed time intervals of 30 days and 60 days, where there was no discernible variation in the physiochemical parameters and in vitro drug release profiles. The outcome is displayed in Table No. 9.

Table No.5: physicochemical evaluation parameters

Formulation code	Parameters			
	Weight variation (mg)	**Thickness (mg)**	**%moisture uptake**	**%moisture content**
F1	120	0.11	4.18	2.21
F2	119	0.10	4.19	3.21
F3	120	0.12	5.25	3.23
F4	119	0.11	5.18	3.01
F5	124	0.13	4.09	2.65
F6	122	0.12	3.12	2.72
F7	121	0.11	4.16	3.32
F8	120	0.12	3.18	2.65
F9	123	0.13	3.14	2.82

Table No.6: Physicochemical evaluation parameters

Batch code	Parameters		
	Folding endurance	**%Elongation break test**	**%Drug content**
F1	195	31.1	91.4
F2	186	32.2	91.9
F3	179	33.66	91.1
F4	189	28.1	92.4
F5	181	32.8	95.12

F6	179	35.55	92.1
F7	197	23.7	93.2
F8	184	25.3	92.41
F9	181	24.5	94.21

Table No. 7: in-vitro drug release profile of empagliflozin transdermal patches: F1-F9

PERCENTAGE OF DRUG RELEASE

Time in hour	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	50.02	29.26	44.43	30.20	46.37	30.26	50.61	53.60	44.43
2	53.66	33.33	46.71	33.97	53.78	39.09	51.61	57.49	49.14
3	56.89	35.86	50.02	36.14	59.96	39.43	59.37	59.36	56.19
4	61.13	39.85	57.95	38.55	79.94	42.02	74.46	67.60	73.48
5	79.07	40.67	79.36	42.02	83.47	43.88	79.36	73.98	78.76
6	75.25	47.14	87.59	52.96	92.29	50.37	81.08	77	91.79

Table No. 8: Release kinetics profile of F5 formulation.

Formulation code	**Mathematical value (r^2 value)**				**Best fit model**
F5	**Zero-order**	**First order**	**Higuchi**	**Peppas**	0.9806
	0.8743	0.9312	0.9806	0.7759	

Table No. 9: Dissolution of formulation F5 after stability studies.

Formulation	**0 Days**	**30 Days**	**60 Days**
F5	92.29%	91.85%	90.55%

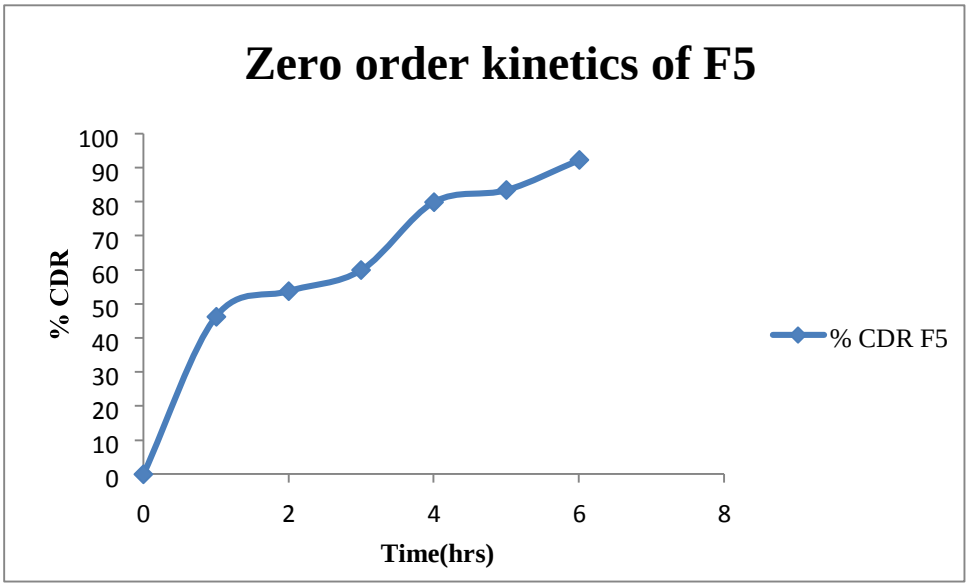

Figure no.7: Zero order kinetics of F5

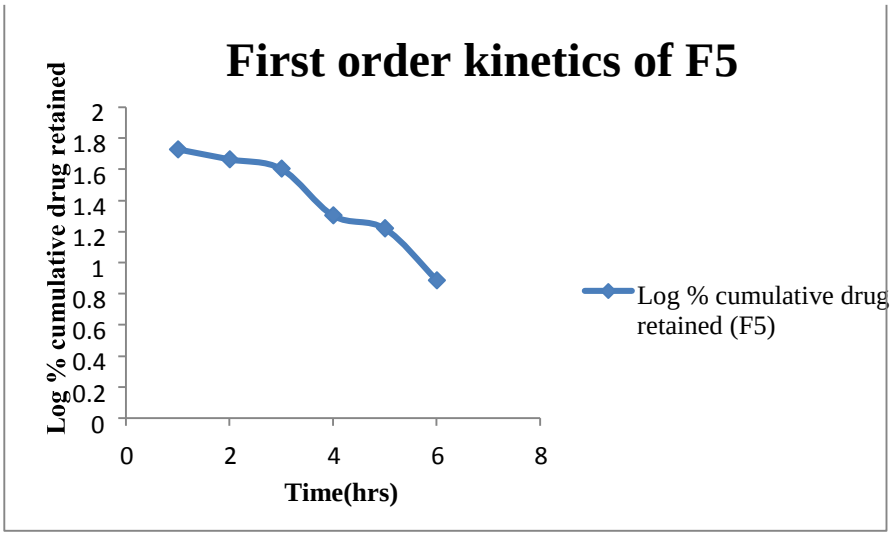

Figure No.8: first order kinetics of F5

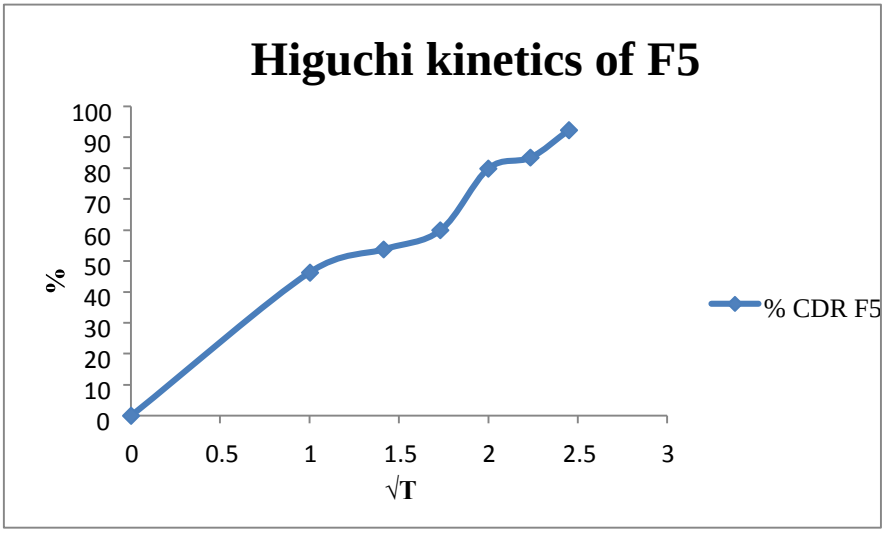

Figure No.9: Higuchi kinetics of F5

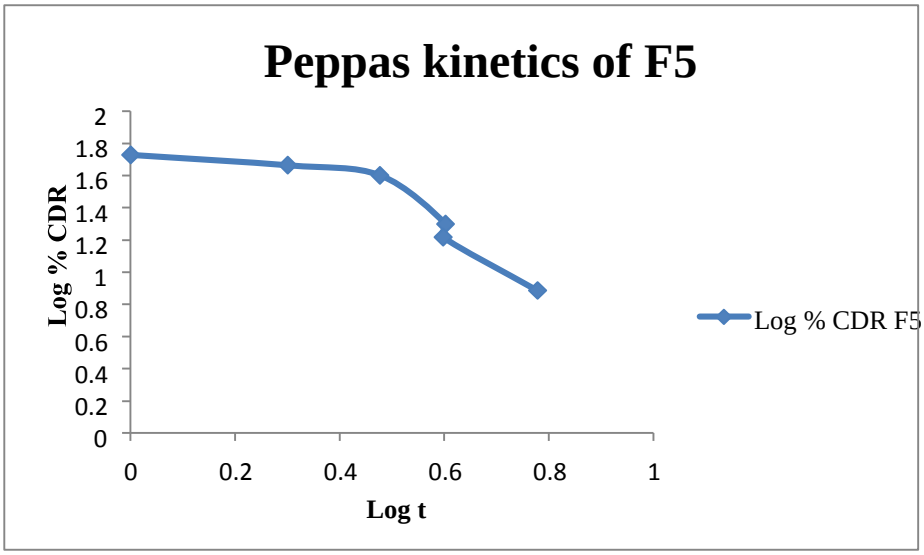

Figure No.10: Peppas kinetics of F5

4. CONCLUSION

The result of pre-formulation studies involving physiochemical characteristics, description, solubility, and the melting point of the drug, Estimation of Empagliflozin, and standard curve of Empagliflozin, were found to be authenticated with literature. The drug and excipients compatibility studies were carried out by FTIR for the drug alone and the drug with polymers. The studies showed that there is no interaction between drugs and polymers. Based on the above all pre-formulation studies confirmed that the drug might be an ideal candidate for making the transdermal patch. 9 such formulations of transdermal patches of Empagliflozin with different proportions of hydrophilic polymers and hydrophobic polymers were successfully formulated. All the formulations were studied for their thickness, weight uniformity, folding endurance, moisture uptake, moisture content, and tensile strength.

The folding endurance value of matrix films was found within 179-197 numbers of folds, indicating good strength and elasticity and that the patch would maintain integrity with general skin folding when applied. The thickness of all the formulations indicates physical uniformity among the prepared patches. The value of drug content shows minimum batch variability.

Hydrophilic polymer like PVP with increased concentration showed an increase in% moisture absorption as it was able to retain water in the patch. Hydrophobic polymers like EC with increased concentration showed a decrease in value, as it was able to repel water.

The in-vitro release studies diffusion studies were conducted for all the formulations by using the Franz diffusion cell and the result was evaluated for release kinetics.

From the above parameters, out of all 9 formulations one formulation i.e., F5 were given satisfactory result and they were selected for further studies. The formulation F5 was given satisfactory results and they were selected for further studies. The formulation F5 containing hydrophilic polymer & hydrophobic polymer (PVP and EC) showed a maximum release of 92.29% at 6hrs of in-vitro drug release studies.

The release profile suggested that an increase in hydrophobic polymer content led to a decrease in the release rate of the drug. When the amount of EC was raised, they were able to maintain the release for a protracted period of 12 hours after an initial burst release of roughly 50% of the material occurred within 3 hours at a lower concentration of hydrophobic polymer. Thus, it was determined that the best materials for the transdermal systems of empagliflozin were PVP, EC, and PEG 400 as plasticizers.

According to ICH criteria, stability experiments were conducted over a two-month period on the most effective F5 formulations. The physicochemical characteristics and in vitro drug release patterns showed no discernible differences. All the selected formulations followed Higuchi's model.

By reviewing the results obtained, on the basic chemical and in-vitro characterization it was concluded that Empagliflozin can be developed as a transdermal dosage form by using polymers such as EC, HPMC, and PVP. Further work is to focus on the therapeutic utility of this system through pharmacokinetic and pharmacodynamic studies on animals or human beings, which are required for the safety and efficiency of the developed formulation.

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