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Research Article

Formulation and Evaluation of Betulin Loaded Transdermal Patches

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Abstract

Objectives: To develop and evaluate Transdermal patches of Betulin along with various polymers for controlled release action.

Method: Suitable method such as Solvent Casting Technique of Film Casting Technique are used for preparation of Transdermal patch.

Result: The prepared Transdermal patches were transparent, smooth, uniform and flexible. The method adopted for preparation of system was found satisfactory.

Conclusion: Various formulations were developed by using hydrophilic and hydrophobic polymers like HPMC E5 and EC respectively in single and combinations by solvent evaporation technique with incorporation of penetration enhancer such as dimethylsulfoxide and dibutyl phthalate as plasticizer. Formulation F7 containing equal ratio of HPMC E5: EC (5:5) showed maximum percentage drug content 95.44%. A suitable UV Spectroscopy method for the analysis of Betulin was developed. Betulin showed maximum absorption at wave length 215 nm in isotonic phosphate buffer (pH 7.4) solutions. The pre-formulation studies involving description, solubility, melting point, partition coefficient of the drug were found to be comparable with the standard. The Transdermal patch of Betulin was prepared successfully by solvent evaporation method. Transdermal patch of Betulin for Transdermal drug delivery was evaluated. Calibration curve was obtained; Transdermal film was prepared, overcome limitations regarding bioavailability of drug was done.

Keywords: Controlled DDS, Transdermal DDS, Betulin, Transdermal Patch, solvent evaporation method.

INTRODUCTION

Transdermal delivery system is currently available for treatment of various diseases such as cardiovascular diseases, Parkinson's disease, Alzheimer's disease, fungal diseases, depression, anxiety and Attention Deficit Hyperactivity Disorder (ADHD), skin cancer, female sexual dysfunction, post-menopausal bone loss and urinary incontinence. Transdermal drug delivery system constitutes one of the most important routes for new drug delivery system. Transdermal delivery of drug offers several advantages over conventional delivery methods. The controlled drug delivery is a newer approach is to deliver drug in to systemic circulation at a predetermined rate. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action. A novel drug delivery approach known as controlled release drug delivery system evolves, which facilitates the drug release into systemic circulation at a pre-determined rate.[1,2] A class of novel drug delivery systems is Transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate and maintain clinically effective concentrations over a prolonged period of time.[3,4,5]

Betulin, a pentacyclic triterpene and a plant pentacyclic triterpene metabolite, can be found in large quantities in the outer bark of the birches (*Betula*, Betulaceae). Betulin acid, obtained by betulin oxidation. Regarding the mode of action of Betulin, little is known about its antiproliferative and apoptosis-inducing mechanisms. It is found in the bark of several species of plants, principally the white birch (*Betula pubescens*) from which it gets its name, but also the ber tree (*Ziziphus mauritiana*), selfheal (*Prunella vulgaris*), the tropical carnivorous plants *Triphyophyllum peltatum* and *Ancistrocladus heyneanus*, *Diospyros leucomelas*, a member of the persimmon family, *Tetracera boiviniana*, the jambul (*Syzygium formosanum*), flowering quince (*Pseudocydonia sinensis*, former *Chaenomeles sinensis KOEHNE*), rosemary, and *Pulsatilla chinensis*. Also, Betulin acid was found active *in vitro* against neuroectodermal (neuroblastoma, medulloblastoma, Ewing's sarcoma and malignant brain tumors, ovarian carcinoma, in human leukemia HL-60 cells, and malignant head and neck squamous cell carcinoma SCC25 and SCC9 cell lines. Although the specific mechanism of action of betulin against malignant cells is still a subject of detailed research, the activity of betulin acid has been linked to the induction of the intrinsic pathway of apoptosis. As this process occurs with the sparing of non-cancer cells, and the induction of apoptosis can occur under conditions in which standard therapies fail, both substances seem as promising experimental anti-cancer drugs.[6-14]

In present study, attempt is made to prepare Transdermal patches containing an anti- inflammatory drug such as **Betulin** along with various polymers for controlled release action.

MATERIALS & METHODS

Materials

For the preparation and evaluation of the gel, basic reagents used are summarized in table.

Table 1: List of chemicals used in the experiment

S. No.	Chemicals	Manufacturer/Supplier
1.	Betulin	Sigma Aldrich (Merck)
2.	Hydroxypropyl methylcellulose E5	Loba Chemie
3.	Ethylcellulose	Loba Chemie
4.	Dimethyl sulphoxide	Hi-Media
5.	Dibutylphthalate	CDH Chemicals
6.	Potassium chloride	CDH Chemicals
7.	Fused calcium chloride	CDH Chemicals
8.	Glycerol	Loba Chemie
9.	Absolute Ethanol	Loba Chemie
10.	HPLC grade Acetonitrile	Spectrochem
11.	HPLC grade Methanol	Spectrochem
12.	HPLC grade water	Rankem
13	Aluminium foils	Sigma-Aldrich
14.	Chloroform	CDH Chemicals

Methods

Suitable method such as Solvent Casting Technique of Film Casting Technique are used for preparation of Transdermal patch.

1. Pre-formulation studies

A. Determination of melting point

Melting point of the drug was determined by taking small amount of drug in a capillary tube closed at one end and placed in a melting point apparatus This was performed thrice and average value of temperature at which drug melts was noted.

B. Determination of solubility

An excess amount of drug was taken and dissolved in a measured volume of distilled water in a volumetric flask to get a saturated solution and kept for 24 hours at room temperature for the attainment of equilibrium. These solutions were kept for sonication and then supernatant were filtered using a 0.45-micron whatmann filter paper, to separate the undissolved drug particles and diluted suitably and the concentration of Betulin in the filtrate was determined spectrophotometrically by measuring at 300 nm.[15,16,17]

C. Determination of partition coefficient

The partition coefficient of the drug was determined by taking equal volumes of 1-octanol and aqueous solution in a separating funnel. In case of water-soluble drugs, a drug solution was prepared in distilled water, and in case of water-insoluble drugs, a drug solution of was prepared in 1-octanol. Standard solution of the drug was prepared in this phosphate buffer pH 7.4 solution. Octanol (10 ml) was added to equal volume of this standard drug solution in a separating funnel and was kept for 24 h at 37±°C with intermittent shaking. Finally, the buffer solution was separated, clarified by centrifugation and assayed for drug content.[18]

2. Determination of drug-excipients compatibility

FT-IR: FT-IR spectroscopy was employed to ascertain the compatibility between Betulin and the selected polymers. The pure drug and drug with excipients were scanned separately.

Procedure: Potassium bromide was mixed with drug and/or polymer and the spectra were taken. FT-IR spectrum of Betulin was compared with FT-IR spectra of Betulin with polymer. Disappearance of Betulin peaks or shifting of peak in any of the spectra was studied.[19]

3. Procurement of standard drug

Betulin was procured from Sigma Aldrich (Merck).

4. Characterization of Betulin

A. DSC of Betulin

Purity profile of drug was determined by using differential scanning calorimetry (DSC). The latter can be assessed by the melting behavior observed in the recorded thermogram. The main application of DSC to purity relies on the notion that impurities reduce the melting temperature of the drug. The melting temperature is a strong indication of drug purity.[20] For carrying out DSC of the model drug, 2 mg of sample was placed in aluminum pan. The pan was crimped using punching press. The sample pan was placed in pan holder of the DSC machine. The sample was run at a ramp rate of 10°C/min from 25°C to 300°C with a flow rate of 60 ml/min for nitrogen.

5. Calibration curve of Betulin

The standard calibration curve was constructed to obtain a regression line equation to be used for finding out the concentration of drug in samples. Two calibration curves of drug were plotted; one by RP-HPLC method and one by UV spectrophotometer.[21] Calibration curve by RP-HPLC method was used for assay of drug in gel matrix for entrapment efficiency studies. The other one was plotted by UV spectrophotometer using Ethanolic phosphate buffer (pH 7.4) for carrying out *in-vitro* drug release studies.

6. Morphology studies (SEM analysis)

The surface morphology of pure drug and its treated counterpart, Drug-PC complex was performed using scanning electron microscopy (SEM).

Evaluation of Transdermal patches

A. Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

B. Thickness uniformity

To check the uniformity of thickness of the formulated films. The thickness of the film was measured at 3 different points using a digital caliper and average thickness of three reading was calculated.

C. Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated.[22,23]

D. Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (5 x 5 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.[24,25,26]

E. Percentage moisture absorption

The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 3 days, the films were taken out and weighed. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula: [27,28]

Percentage moisture absorption = Final Weight –Initial Weight/ Initial Weight X 100

F. Percentage moisture loss

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The moisture loss was calculated using the formula: [27,28]

Percentage moisture loss = Final Weight –Initial Weight/ Initial Weight X 100

G. Water vapors transmission rate

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 gm of fused calcium chloride was taken in the vials & the polymer films of 1.44 cm^2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 hours. The vials were removed and weighed at time interval of 24 h for three consecutive days to note down the weight gain. [29,30,31]

Water vapour transmission rate =

Final Weight –Initial Weight/ Time X Area X 100

H. Tensile strength

Tensile strength of the film was determined with Universal strength testing machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 gram. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows; [32,33,34]

Tensile strength = Tensile load at Break/ Cross Sectional Area

I. Drug content uniformity of films

The patches (1cm^2) were cut and added to a beaker containing 100ml of phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (containing no drug) at 215 nm spectrophotometrically.[23]

J. In vitro drug release studies

In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1cm^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 ± 0.50C. The samples of 1ml were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h, analyzed for drug content spectrophotometrically at 215 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.[31,35,36]

RESULTS AND DISCUSSION

Standard drug Melting point range of Betulin is 316 to 318 °C.

RESULTS

Table 2: Pre-formulation Studies

S.No.	Drug	Melting Point	Solubility	Partition Coefficient(P)
1.	Betulin	318.32 ºC	5mg/ml	4.6

Drug excipients compatibility studies

FT-IR Spectrum and values

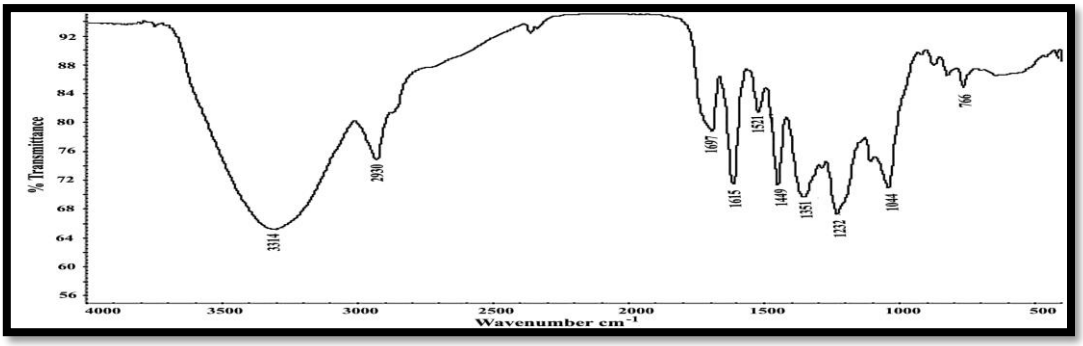

Figure 1: IR Spectrum of Pure Betulin

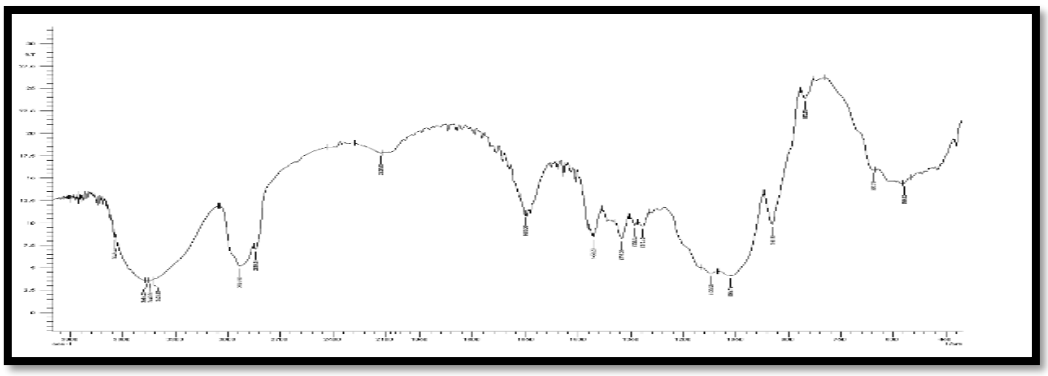

Figure 2: IR Spectrum of Pure HPMC E5

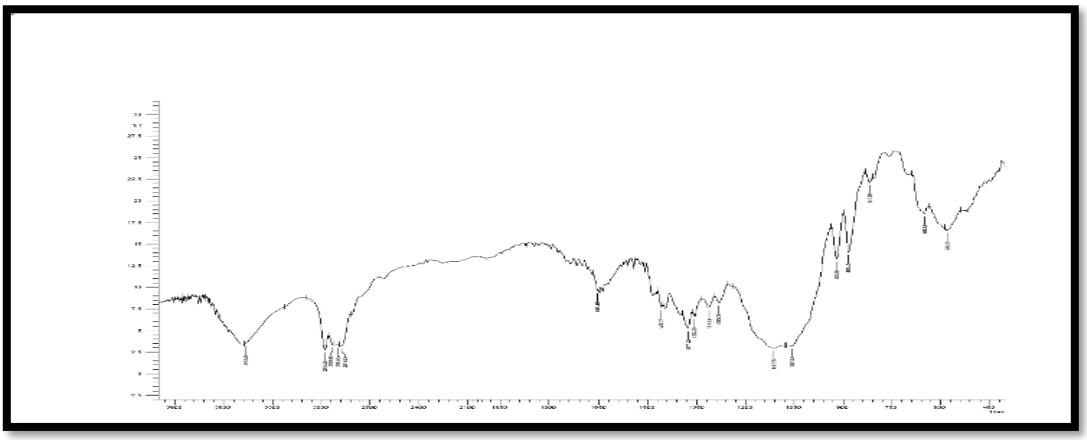

Figure 3: IR Spectrum of Pure EC

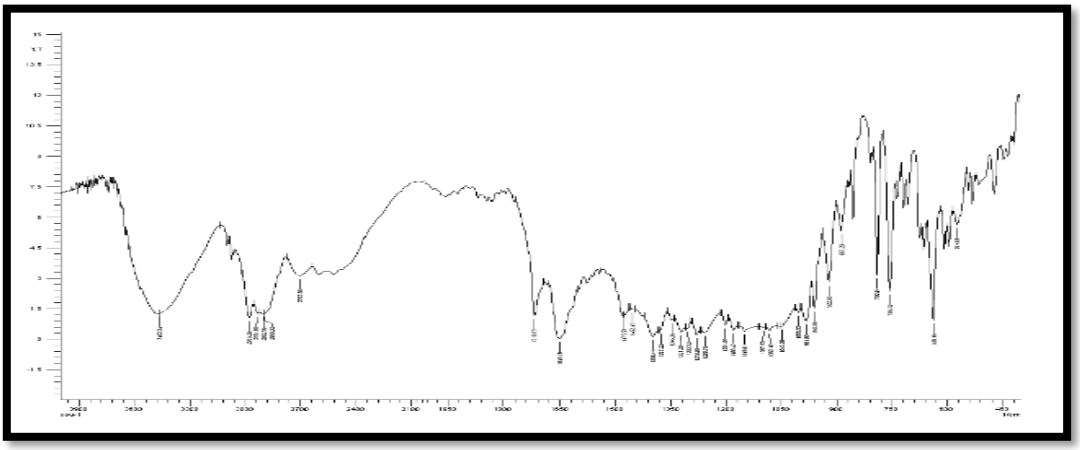

Figure 4: IR Spectrum of Betulin +HPMC E5+EC mixture

Formulation of Transdermal patches

Compositions of different formulations containing Betulin

Table 3: Compositions of different formulations

Formulations	F1	F2	F3	F4	F5	F6	F7
Betulin, mg	30	30	30	30	30	30	30
Ethylcellulose,mg	300	*	30	60	90	120	150
HPMC E(5cps),mg	*	300	270	240	210	180	150
Dibutylphthalate (2drop),ml	0.12	0.12	0.12	0.12	0.12	0.12	0.12
DMSO,ml	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Chaloroform:Ethanol (1:1),ml	5	5	5	5	5	5	5

*No ingredient used,HPMC=Hydroxypropyl Methylcellulose, DMSO=Dimethyl sulfoxide

Evaluation of Transdermal Patches

a) Thickness Uniformity

Table 4: Thickness Uniformity

S.No.	Formulation code	Average Thickness (mm)			
		Trial 1	Trial 2	Trial 3	Mean±S.E.M.
1.	F1	0.20	0.18	0.22	0.202±0.04
2.	F2	0.19	0.21	0.21	0.204±0.02
3.	F3	0.18	0.21	0.21	0.208±0.03
4.	F4	0.20	0.17	0.22	0.198±0.05
5.	F5	0.15	0.14	0.17	0.156±0.03
6.	F6	0.20	0.22	0.20	0.204±0.02
7.	F7	0.17	0.18	0.20	0.192±0.03

Standard Error Means , n=3

a) Weight Uniformity

Table 5: Weight Uniformity

S.No.	Formulation code	Average Weight			
		Trial 1	Trial 2	Trial 3	Mean±S.E.M.
1.	F1	0.40	0.43	0.42	0.418±0.03
2.	F2	0.38	0.36	0.36	0.368±0.02
3.	F3	0.40	0.38	0.37	0.384±0.03
4.	F4	0.41	0.39	0.38	0.394±0.03
5.	F5	0.35	0.41	0.38	0.382±0.06
6.	F6	0.38	0.34	0.36	0.362±0.04
7.	F7	0.43	0.40	0.41	0.414±0.03

Standard Error Means, n=3

b) Folding Endurance

Table 6: Folding Endurance

S.No.	Formulation code	Folding Endurance			
		Trial 1	Trial 2	Trial 3	Mean±S.E.M.
1.	F1	116	110	107	112.10± 9.0
2.	F2	53	63	50	55.66±13.0
3.	F3	60	67	73	66.64±13.0
4.	F4	74	84	88	82.22±14.0
5.	F5	85	79	94	86.00±9.0
6.	F6	78	91	85	84.66±13.0
7.	F7	93	104	90	95.66±13.0

Standard Error Means, n=3

c) Percentage Moisture Absorption

Table 7: Percentage Moisture Absorption

S.No.	Formulation code	Percentage moisture absorption			
		Trial 1	Trial 2	Trial 3	Mean±S.E.M.
1.	F1	4.65	6.97	9.30	6.97±4.65
2.	F2	0.00	2.63	2.78	2.70±0.15
3.	F3	0.00	2.98	2.74	2.86±0.24
4.	F4	2.78	2.60	5.50	3.62±0.18
5.	F5	2.43	2.48	4.87	3.26±2.44
6.	F6	2.78	5.46	5.40	4.54±2.68
7.	F7	4.76	7.14	7.24	6.38±2.48

Standard Error Means, n=3

e) Percentage Moisture Loss

Table 8: Percentage Moisture Loss

S.No.	Formulation code	Percentage moisture loss			
		Trial 1	Trial 2	Trial 3	Mean±S.E.M.
1.	F1	10.6	12.5	15.8	12.90±5.2
2.	F2	7.89	10.52	10.51	9.64±2.63
3.	F3	7.50	10.06	10.00	9.16±2.56
4.	F4	2.50	5.06	7.50	5.00±5.00
5.	F5	2.85	2.85	5.71	3.82±2.14
6.	F6	0.00	5.26	7.89	4.38±2.63
7.	F7	6.97	9.30	11.62	9.28±4.65

Standard Error Means, n=3

f) Water Vapour Transition Rate

Table 9: Water Vapour Transition Rate

S.No.	Formulation code	Water vapour transition rate			
		Trial 1	Trial 2	Trial 3	Mean±S.E.M.
1.	F1	.043	.046	.046	.045±.006
2.	F2	.020	.031	.028	.026±.008
3.	F3	.026	.032	.034	.030±.006
4.	F4	.028	.023	.034	.028±.006
5.	F5	.031	.031	.028	.030±.002
6.	F6	.037	.034	.046	.037±.006
7.	F7	.049	.043	.037	.042±.008

Standard Error Means, n=3

g) Tensile Strength

Table 10: Tensile Strength

S.No.	Formulation code	Tensile strength Kg/mm^2			
		Trial 1	Trial 2	Trial 3	Mean ± S.E.M.
1.	F1	3.85	3.96	3.71	3.84±0.25
2.	F2	2.85	2.96	3.07	2.96±0.22
3.	F3	3.05	3.14	3.13	3.13±0.09
4.	F4	3.18	3.29	3.21	3.22±0.11
5.	F5	3.22	3.31	3.28	3.27±0.09
6.	F6	3.27	3.39	3.36	3.34±0.12
7.	F7	3.32	3.47	3.44	3.41±0.15

Standard Error Means, n=3

h) Drug Content

Table 11: Drug Content

S.No.	Formulation Studies	Concentration Mean ± SEM*(mg/cm^2)	Percentage drug content
1.	F1	1.178±0.072	92.67
2.	F2	1.156±0.072	87.68
3.	F3	1.084±0.048	90.26
4.	F4	1.085±0.056	90.27
5.	F5	1.114±0.076	92.86
6.	F6	1.116±0.038	92.87
7.	F7	1.118±0.038	95.44

Standard Error Means, n=3

Characterization of standard drug:

A single endothermic peak in case of Betulin at 317.32 ° C.

Different concentrations & their absorbance by UV Spectroscopy

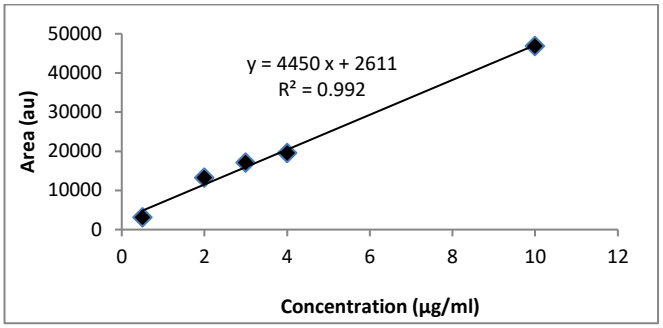

Figure 5: Calibration curve of Betulin by HPLC

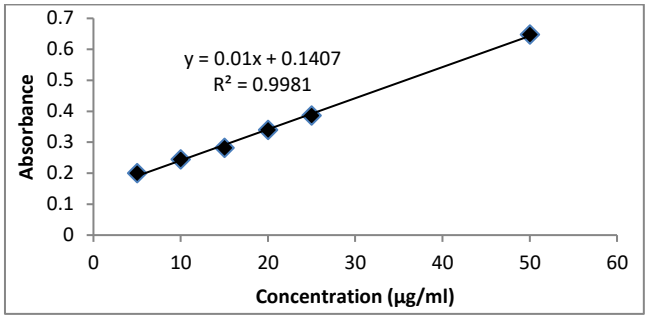

Figure 6: Calibration curve of Betulin by UV spectroscopy

Morphology studies (SEM analysis)

The pure drug exists in the form of irregular crystalline structures with sharp edges.. D-PC complexes were found to be free flowing particles. The average diameter of D-PC complex was in the range 9.28 to 17.44 µm.

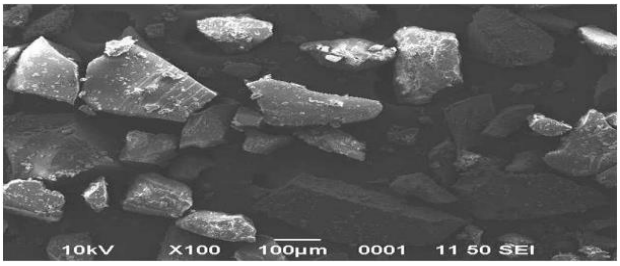

Figure 7: SEM picture of Betulin

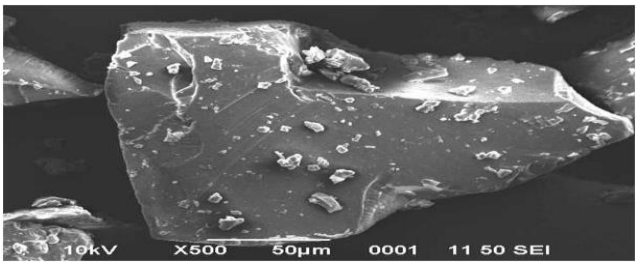

Figure 8: SEM picture of D-PC complex

DISCUSSION

The present study was designed to investigate the possibility of preparing Transdermal patches of a known herbal bio-active compound Betulin to combat poor solubility and poor bioavailability profile. The transdermal patch was made by solvent casting technique using a D-PC complex (drug-phosphatydicholine complex). DSC studies revealed that there is no interaction between the different components of Transdermal films. Hence it indicated the stability of the patches. It holds an immense potential for development of topical herbal anti-inflammatory formulation comparable to topical NSAIDs. One of the additional advantages of the formulation is better stability profile. The formulated Transdermal film in the study is simple in preparation without using any special or costly excipients thus making it cost effective also.

Betulin is insoluble in water, phosphate buffer pH 7.4, chloroform, methanol and ethanol. The mean concentration of the drug dissolved in the ethanol was 5mg/ml .

The partition coefficient value was experimentally found to be 4.6. The results obtained indicate that the drug possesses sufficient lipophilicity, which fulfill the experiment of formulating the selected drug into a Transdermal film.

FT-IR: Chemical interaction between drug and the polymeric material was studied by using FT-IR. IR spectra of Betulin, HPMC E5, EC alone and their combinations are shown in Figures. The peaks can be considered as characteristic peaks of Betulin confirming the purity of the drug and prominently observed in IR spectra of Betulin along with polymers. This indicates there is no interaction between Betulin and polymers. The IR results suggest that the drug and polymers are compatible.

Physical appearance; The prepared Transdermal patches were transparent, smooth, uniform and flexible. The method adopted for preparation of system was found satisfactory.

Thickness uniformity; With the help of digital caliper, the thickness of film was measured at different points and the average thickness was noted. The result indicates that there was no much difference in the thickness within the formulations and it was found to vary from 0.156 ± 0.03 to 0.208 ± 0.03 mm with low standard Mean error. The results are given in Table and order of the thickness of films is F5 < F7 < F4 < F1 < F2 < F6 < F7.

Weight uniformity; Three different films of the individual batch were weighed and the average weight was ranging from 0.362 ± 0.04 to 0.418 ± 0.03 g with low standard deviation values. The order of the weight of films is F6 < F2 < F5 < F3 < F4 < F7 < F1.

Folding endurance; The recorded folding endurance of the films was > 150 times. The order of the folding endurance was F2 < F3 < F4 < F6 < F5 < F7 < F1. This test is important to check the ability of sample to withstand folding, which gives an indication of brittleness; less folding endurance indicates more brittleness.

Percentage moisture absorption; The moisture absorption studies carried out in desicator. All the patches showed least percentage moisture absorption. The order of the percentage moisture absorption is F1<F7<F6<F4<F3<F5<F2 (1.70 ± 0.15 to 6.97 ± 4.65) and the data is presented in the Table. The moisture uptake of the formulations was low, which could protect the formulations from microbial contamination and reduce bulkiness.

Percentage moisture loss; The moisture loss studies were carried out at 80 – 90% relative humidity. All the patches showed least percentage moisture loss. The order of the percentage moisture loss is F1<F2<F3<F7<F6<F4<F5 (3.82 ± 2.14 to 12.90 ±5.2)

Tensile strength; The tensile strength measures the ability of a patch to withstand rupture. Presence of dibutyl phthalate and dimethyl sulfoxide has shown good tensile strength. Both the combination show significant tensile strength. The mean value was found to vary between 2.96 ± 0.22 to 3.84 ± .025 kg/mm^2.

Drug content; For the various formulations prepared drug content was found to vary between 1.084 ± 0.048 mg to 1.178 ± 0.072 mg. Drug distribution was found to be uniform in the polymeric films.

CONCLUSION

The following conclusions were drawn from results obtained.

- A suitable UV Spectroscopy method for the analysis of Betulin was developed. Betulin showed maximum absorption at wave length 215 nm in isotonic phosphate buffer (pH 7.4) solutions. The R^2 value for the standard curve was found to be 0.998, which showed linear relationship between drug concentrations and absorbance values. The R^2 value for the standard curve by HPLC method was found to be 0.992, which showed linear relationship between drug concentrations and absorbance values. Based on the all the above pre-formulation studies the drug was suitable for making the Transdermal formulation. Drug-polymer compatibility studies by FT-IR and DSC gave confirmation about their purity and showed no interaction between the drug and selected polymers. Various formulations were developed by using hydrophilic and hydrophobic polymers like HPMC E5 and EC respectively in single and combinations by solvent evaporation technique with incorporation of penetration enhancer such as dimethylsulfoxide and dibutyl phthalate as plasticizer. As HPMC concentration increases showed higher WVTR. Patches exhibited higher tensile strength as the concentration of HPMC was increased. Most of the batches shows high folding endurance values .From the results of the drug content determination, it was inferred that there was proper distribution of drug in the patches and the deviations were within the acceptable limits.
- In vitro studies concluded that HPMC E5 patches has better release than that of EC patches. An attempt was made to incorporate HPMC E5 and EC to the monolithic system for better release and prolong the duration of release.
- Formulation F7 containing equal ratio of HPMC E5: EC (5:5) showed maximum percentage drug content 95.44%. Kinetic models were used to confirm release mechanism of the formulations. Betulin release from the patches F1 to F7 followed non Fickian diffusion rate controlled mechanism.

The Transdermal patch of Betulin was prepared successfully by solvent evaporation method. The present work can further be preceded with in-vivo study on healthy animals to evaluate the pharmacokinetic profile.

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Conflicts of Interests

There are no conflicts of interest.

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Authors Contributions

All the authors have contributed equally.

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