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Preparation and invitro charectarization of nimuselide transdermal patch

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ABSTRACT

Conventional oral dosage forms have significant setbacks of poor bioavailability due to hepatic first pass metabolism, drug degradation and sever adverse effects are reported. To improve such character's transdermal drug delivery system (TDDS) was emerged, which will improve the therapeutic efficacy and safety of drugs by specific sites within the body, thereby reducing both the size and number of doses. Nimusulide is Non-steroidal Anti Inflammatory Drug (NSAID) with analgesic and antipyretic properties. It is used in the treatment of acute pain, the symptomatic treatment of osteoarthritis .It works by blocking the production of prostaglandins (a chemical associated with pain) thereby relieving pain and inflammation. But it is a poorly water-soluble drug. When compared to oral dosage forms, transdermal form of poorly water-soluble drug may act fast. This consideration is the basis for designing the transdermal drug delivery system. In present study Nimusulide patches were prepared by solvent casting method with the combination of hydrophobic polymer (Ethyl Cellulose) and hydrophilic polymer (Poly vinyl pyrollidine) polymers in different ratios without enhancer and with enhancer Di methyl sulphoxide (DMSO).the formulation is evaluated for various physicochemical parameters. Combination of a hydrophilic and hydrophobic polymer can be effectively used to modify and control the release of the drug. The formulation F4 containing PVP: EC (1:2) with Penetration enhancer increases the drug release.

Keywords: NSAID, Poly vinyl pyrollidone, Ethyl cellulose Di-methyl sulphoxide, TDDS.

INTRODUCTION [1-9]

Transdermal drug delivery is the delivery of the drugs through the skin to elicit a systemic effect. This makes it different from topical formulation, where the drug is expected to display only local activity.

Nimesulide is a relatively COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties used in the treatment of acute pain, the symptomatic treatment of osteoarthritis and it's works on COX 2 receptor by acting on prostaglandins to relieving pain and inflammation. [6]

Transdermal drug delivery systems are capable of controlling rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue. In response to these,

several transdermal drug delivery systems have been developed to achieve the objective of systemic medication through application on intact skin. Transdermal drug delivery system (TDDS) offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance, avoids first pass metabolism and minimizes harmful side effects of a drug caused from temporary over dose. Another advantage is convenience, especially notable in patches that require only once daily application. Such a simple dosing regimen can aid in patient adherence to drug therapy. [1-9]

MATERIALS AND METHODS

Materials

Nimusulide purchased from B.M.R Chemicals, remaining all chemicals were laboratory chemicals.

Preparation of transdermal patches

The patches were prepared by solvent casting method. The ingredients are shown in Table. Polymers (EC/PVP) was weighed accurately and dissolved in chloroform. Dibutyl phthalate and dimethyl sulphoxide were mixed uniformly and weighed amount of drug is added and do the volume make up with chloroform. The films were cast onto a suitable glass moulds and then dried in hot air oven at 50®C. The films were removed by using a sharp blade by inserting along the edges of the film. The dried films were wrapped in aluminum foil and stored in a closed container away from light and in cool place. [16]

Table 1: Composition of the transdermal patches

Ingredients	F1	F2	F3	F4	F5	F6
Nimesulide(mg)	100	100	100	100	100	100
Ethyl cellulose : Polyvinylpyrrolidone (mg)	1:2	1:5	1:3	1:2	1:5	1:3
Dibutyl phthalate (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Dimethyl sulphoxide (ml)	-	-	-	2	2	2
Chloroform (ml) q.s	10.0	10.0	10.0	10.0	10.0	10.0

EVALUATION OF TRANSDERMAL PATCHES

- Ttransdermal dosage forms are characterized by following methods
- Physicochemical evaluation &*In vitro* evaluation [15]

PHYSIOCHEMICAL EVALUATION

Calibration curve of nimusilide (Linearity and Range)

50 mg of nimusulide was accurately weighed and dissolved in sufficient ethanol to produce 100 ml. This stock solution was diluted with pH 7.4 phosphate buffer to get concentrations from 2 to 10 µg/ml. The absorbance of a 1 cm layer of this diluted solution was measured at 273 nm using a UV Spectrophotometer. The absorbance was plotted against concentration. [16]

Thickness

The thickness of transdermal film was determined by using a screw gauge micrometer at different points of the film. [16]

Uniformity of weight

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight. [16]

Drug content

An accurately weighed portion of film was dissolved in 100 ml of methanol in which drug is soluble and then the solution was shaken continuously for 2 h in shaker incubator. Then the whole solution was sonicated. After sonication and subsequent filtration, drug in solution was estimated spectrophotometrically by appropriate dilution at 273

nm. The amount of aceclofenac was calculated using a validated calibration curve [4]

Content uniformity test

10 patches were selected and drug content was determined for individual patches. If 9 out of 10 patches have content between 85% and 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If these 20 patches have range from 85% to 115%, then the transdermal patches pass the test. [6]

2.4.6. Moisture content

The prepared films were weighed individually and kept in a desiccator containing calcium chloride at room temperature for 24 h. The films were weighed again after a specified interval until they show a constant weight. The percent moisture content was calculated using following formula.

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Moisture Uptake

Weighed films were kept in a desiccator at room temperature for 24 h. These were then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccator until a constant weight was achieved. % moisture uptake was calculated as given below. [5, 6]

$$\% \text{ moisture uptake} = \frac{\text{Final weight}}{\text{Initial weight}} \times 100$$

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip was cut from the center and two from each side of patches. The length of each strip was measured and variation in length was measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness. [5, 6]

$$\% \text{ constriction} = \frac{I_1 - I_2}{I_1} \times 100$$

I_2 = Final length of each strip
I_1 = Initial length of each strip

Folding Endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the films could be folded at the same place without breaking is folding endurance value. [5, 6]

In vitro- dissolution studies

The release-rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The dissolution studies of patches are very crucial, because one needs to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater than the drug concentration in the body, to achieve a constant rate of drug permeation.

The dissolution of patches was performed using USP basket type dissolution apparatus. The patches were placed in respective baskets with their drug matrix exposed to phosphate buffer pH 7.4. All dissolution studies were performed at 50 rpm, with each dissolution jar carrying 900ml of saline phosphate buffer pH7.4. Samples were withdrawn at different time intervals and analyzed using a Shumedzu Spectrophotometer at 240nm taking phosphate buffer solution pH 7.4 as blank. Cumulative amounts of drug released were plotted against time for different formulations [16]

Invitro- drug permeation study

The *in vitro* permeation studies were carried out using a modified Keshary-Chein diffusion cell. A 2.5 cm diameter patch was placed in intimate contact with diffusion membrane. Teflon bead was placed in the receptor compartment filled with 200 ml of pH 7.4 phosphate buffer. The whole assembly was kept on a magnetic stirrer, at a speed of 100 rpm and the temperature conditions controlled at 37^0C. The cell contents were stirred with a magnetic stirrer. Sample of 3 ml was withdrawn at time interval of 30 min for 8 h and simultaneously replaced with equal volume of fresh pH 7.4 phosphate buffers. The samples were withdrawn and filtered through Whatman filter paper. The absorbance of the solution was measured spectrophotometrically at 273 nm. [5, 6, 17]

RESULTS & DISCUSSION

Calibration Curve

The values for the absorbance at different concentration are shown in Table 2 and Fig 6. The calibration curve constructed for samples covered a range of concentrations from 1 to 5 µg/ml and was found to be linear.

Table 2: Calibration curve nimesulide using buffer solution

Sl.No	Concentration (µg/ml)	Absorbance
1	**0**	**0**
2	**1**	**0.221**
3	**2**	**0.430**
4	**3**	**0.624**
5	**4**	**0.842**
6	**5**	**1.032**

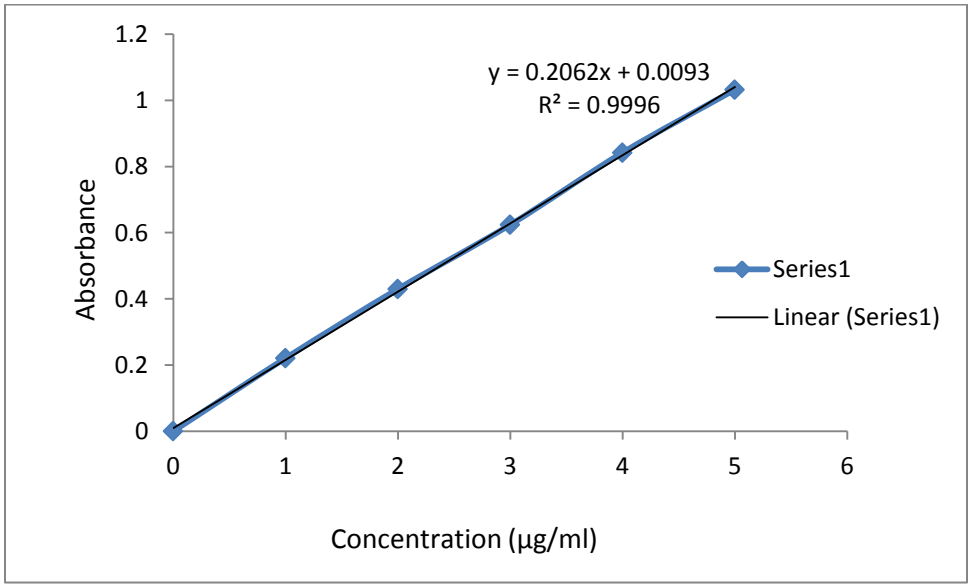

Fig 1: Calibration graph of Nimesulide in Phosphate buffer pH 7.4

Table 3:Calibration curve of nimesulide by using octanol

SL.NO	Concentration (µg/ml)	Absorbance
1	**0**	**0**
2	**1**	**0.250**
3	**2**	**0.453**
4	**3**	**0.661**
5	**4**	**0.868**
6	**5**	**1.091**

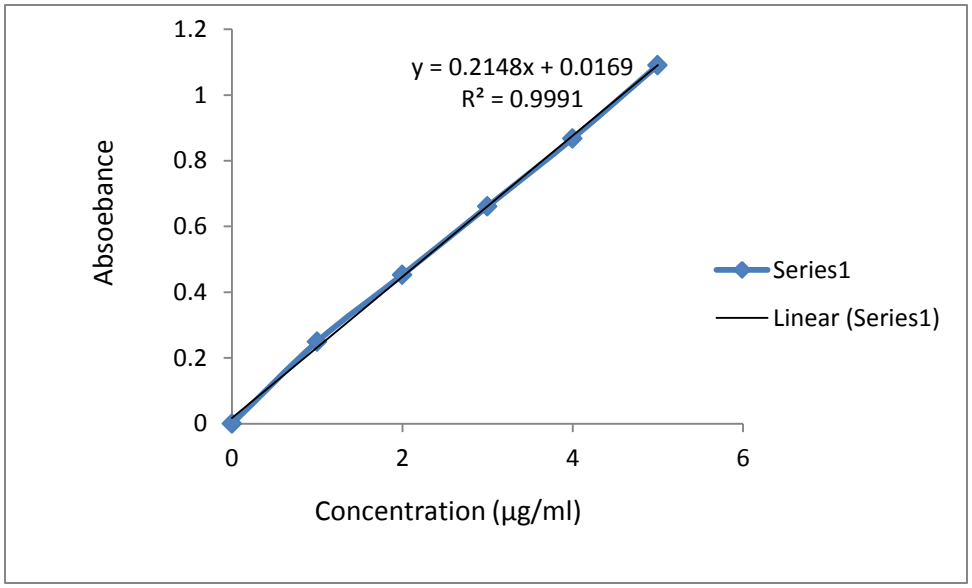

Fig 2: Calibration graph of Nimesulide in Octanol

PREFORMULATION STUDIES

Physical mixture is examined for FTIR and results were shown below

Physiochemical evaluation

In the present investigation various polymeric transdermal patches of nimesulide were prepared. The effect of permeability enhancer (PVP) on the permeability of drug from ethyl cellulose patches were studies. It was found to be satisfactory with respect to weight variation, thickness, folding endurance, moisture content, moisture uptake and drug content. The polymeric combinations showed good film forming properties. The method of casting on glass substrate was found to give good films. Low S.D valued were found in the patches, which ensured uniformity of thickness of each film.

Table 4: Evaluation of patches

Formulation	Thickness (mm)	Uniformity of Weight (%)	Drug content (%)	Uniformity of drug content (%)
F1	0.109	0.040	98.5	90.1-102.3
F2	0.116	0.041	99.2	92.6-103.4
F3	0.331	0.114	98.8	93.6-103.9
F4	0.101	0.043	98.0	92.6-101.4
F5	0.103	0.045	98.1	90.1-102.4
F6	0.107	0.041	98.5	93.2-101

Table 5: Evaluation of patches

Formuation	Moisture Content (%)	Moisture Uptake (%)	Flatness	Folding endurance
F1	7.3	11.9	0	129
F2	2.5	5.6	0	142
F3	8.6	13.5	0	79
F4	7.3	8.3	0	83
F5	8.1	4.5	0	91
F6	8.2	9.6	0	123

Table No:6 Dissolution profile of transdermal patches

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	18.98 ± 0.426	14.56± 0.525	16.84± 0.127	21.05± 0.3535	22.35± 0.120	20.45 ± 0.446
2	21.04 ± 0.278	16.64± 0.187	19.86 ± 0.624	27.603± 1.31	29.09±0.390	28.28± 1.353
3	24.70 ± 0.221	20.53± 0.654	24.39± 1.76	33.11± 0.162	32 ±0.303	31.11± 0.465
4	26.00 ± 0.543	24.67 ± 0.451	28.16± 0.833	39.63 ± 1.004	36.2 ±1.536	39.08± 1.373
5	29.46 ± 0.372	27.68± 0.171	33.41± 0.638	46.52± 0.346	42.35±0.240	42.64 ± 0.330
6	36.92 ± 0.195	29.63± 0.218	36.13± 0.438	49.45 ± 0.502	49.27±1.156	46.2± 0.244
7	42.54 ± 1.83	31.52± 0.573	40.16± 0.325	54.07± 0.707	53.3 ±0.249	53.18 ± 0.104
8	48.77 ± 0.252	33.87± 0.612	43.04 ± 1.22	67.27 ± 0.608	59.04 ±0.285	61.24± 0.9

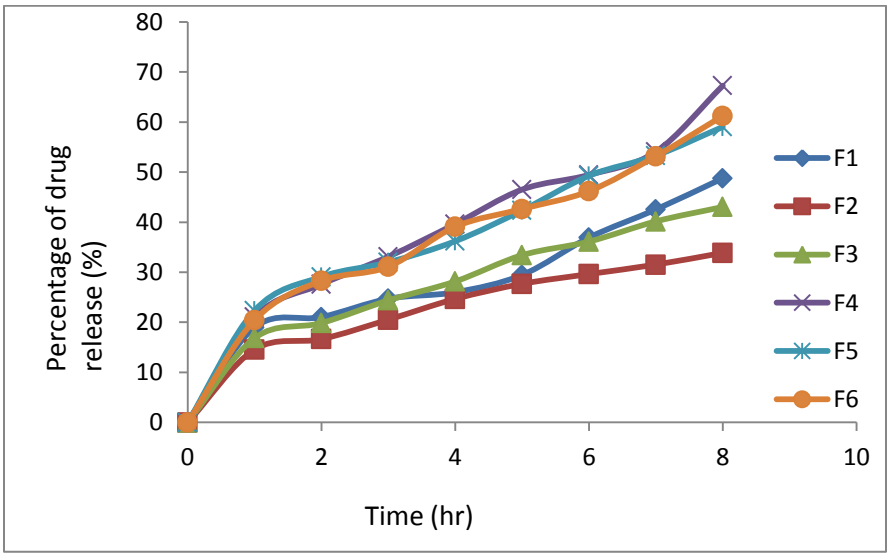

Fig 3: Dissolution graph of the prepared patches

Table No.7: Diffusion profile of transdermal patches

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	20.529± 0.202	19.87 ± 0.326	18.611± ± 0.226	24.19± 0.574	20.39± 0.212	16.85± 0.261
2	24.543± 0.404	21.93 ± 0.408	22.02 ± 0.420	29.27 ± 0.567	22.76± 0.456	21.30 ± 0.912
3	30.102± 0.182	26.22 ± 0.434	24.166 ± 0.152	38.05± 0.647	24.51± 0.168	29.31± 0.622
4	34.35± 0.521	28.23 ± 0.306	29.051 ± 0.456	45.64 ± 0.716	28.28± 0.454	38.05± 0.289
5	40.36± 0.258	34.242± 0.452	35.187 ± 0.598	48.60± 1.696	39.41 ± 0.498	45.62 ± 0.636
6	43.31 ± 0.404	37.278± 0.427	42.142 ± 0.422	55.82± 0.735	45.11± 0.584	49.83 ± 0.021
7	48.39± 0.08	42.283± 0.355	46.28 ± 0.736	57.32± 0.424	49.01± 0.113	53.99± 0.240
8	51.399 ± 0.09	46.473± 0.598	49.293± ± 0.858	60.13± 0.247	53.89± 0.459	57.96± 0.318

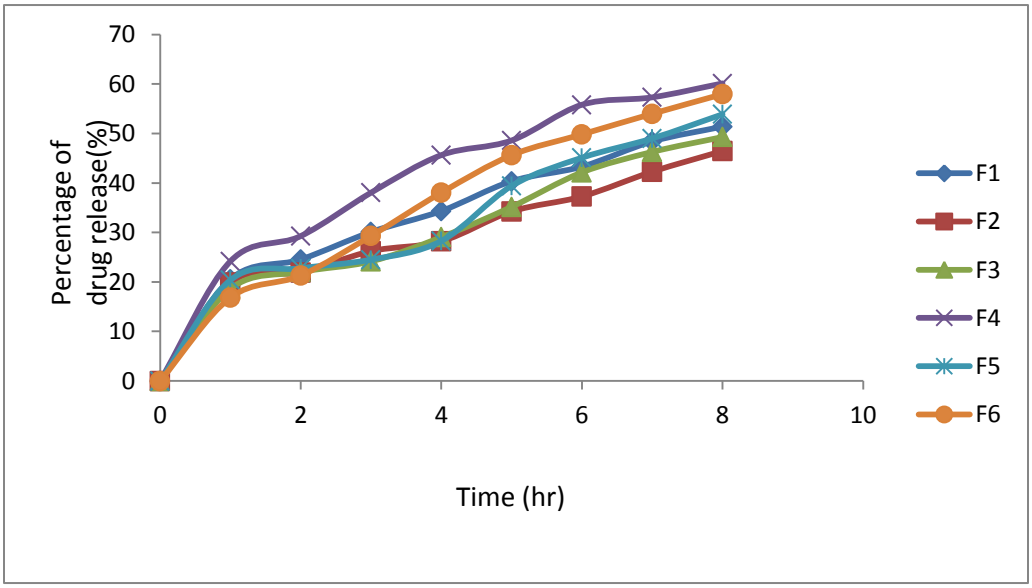

Fig 4: Diffusion graph of transdermal patches

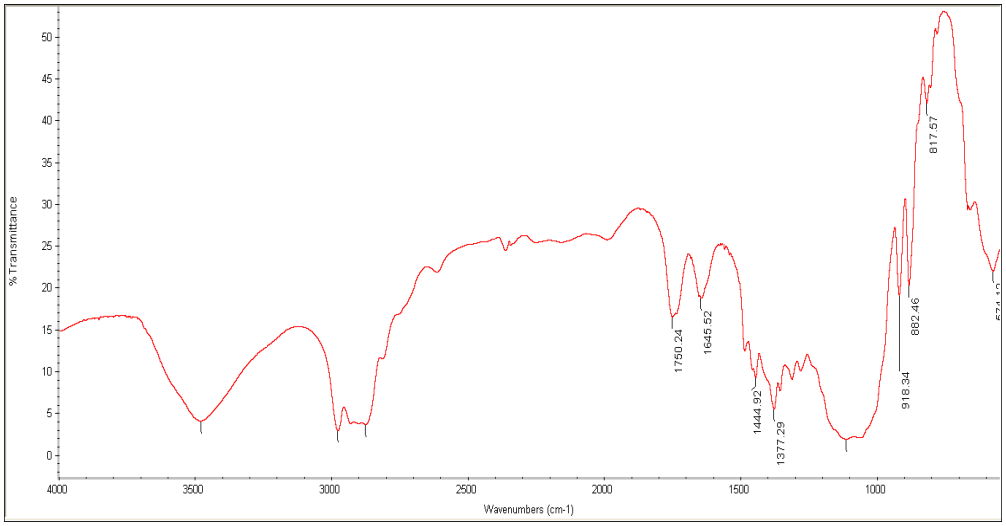

Fig.5: FT-IR: Ethyl cellulose

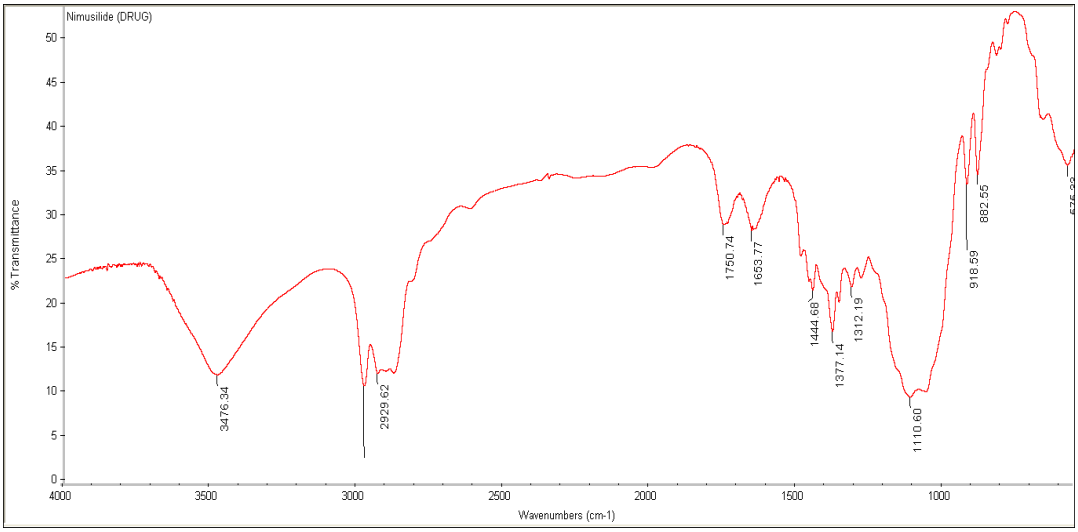

Fig.6 : FT-IR. Nimusulide

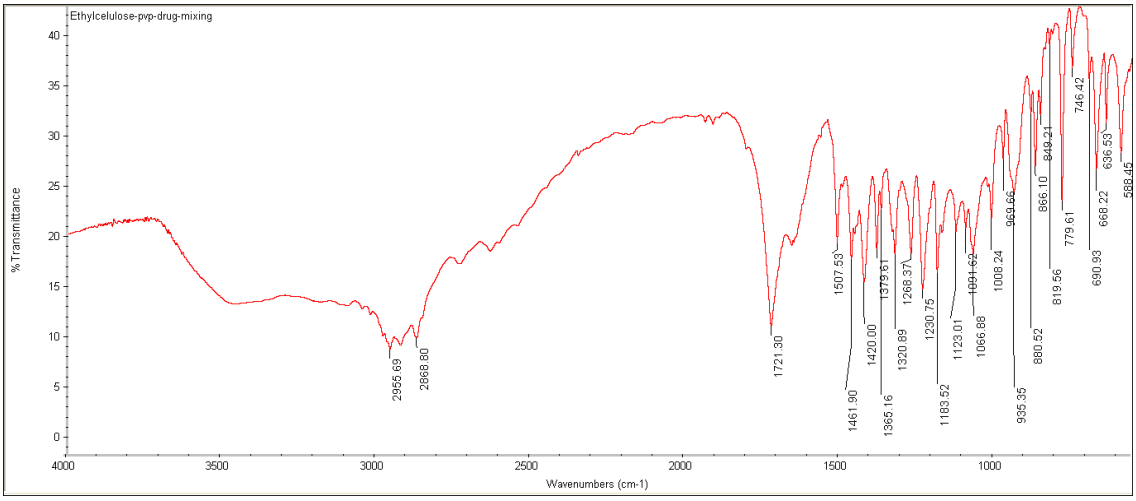

Fig.7 : FT-IR: Ethyl cellulose, pvp and drugs

CONCLUSION

Transdermal drug delivery is a most suitable system for long term treatment because transdermal patches are prepared for a long period of time in a single dose providing treatment from a day to even up to seven days. Transdermal also increases the bioavailability of drugs by avoiding first pass metabolism and increases the therapeutic efficacy of drugs by reaching into the systemic circulation.

Polymers like ethyl cellulose and PVP were selected based on their adhering property and non toxicity. Nimesulide patches were prepared with combination of these polymers and evaluated for physical characteristics and release profile. From these evaluations it was found that thickness, drug content, moisture uptake, moisture content and folding endurance were suitable. The diffusion study results showed controlled release of the drug from the patches.

In view of the overall results, it shows that a combination of a hydrophilic and hydrophobic polymer can be effectively used to modify and control the release of the drug. In this study ethyl cellulose was chosen as the hydrophobic polymer in combination with PVP which is a hydrophilic polymer. The formulation F4 with Penetration enhancer increases the drug release In accordance with other studies it was seen that as the ratio of hydrophobic polymer decreased there was a significant increase in the release of the drug. Nimesulide can be effectively formulated in the matrix type transdermal drug delivery system to control the release of the drug for chronic administration.

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