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Formulation and Evaluation of Transdermal Patch Containing Naproxen

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***Abstract*: Transdermal route is most popular route for deliver the specific amount of drug through the skin into the blood stream .an advantage of transdermal route of drug delivery avoid the first pass metabolism and controlled release of medication. The present study was aimed to formulate transdermal patch of NSAID, naproxen used to cure the pain, inflammation, by using solvent evaporation technique. Naproxen transdermal patches were prepared using different concentration of HPMC and methylcellulose. DMSO permeation enhancer, polyethylene glycol as a plasticizer and finally methanol: dichloromethane (2:1) ratio used as solvent altering the two polymeric concentrations. We can formulate different formulations by keeping drug constant dose (f1 to f7) and evaluate parameter to get optimizing good releasing formulation.**

***Keywords*: Naproxen, HPMC, Solvent evaporation technique, Patch, Methanol.**

ABBREVIATION

Hydroxy propyl methyl cellulose (HPMC)
Dimethyl Sulphoxide (DMSO)
Nonsteroidal Anti-Inflammatory Drug (NSAID).

1. Introduction

A. Controlled Drug Delivery

One of the most quickly developing fields of study in which chemists and chemical engineers are boosting human health care is controlled medication delivery technologies. When compared to conventional dosage forms, such delivery methods have a number of benefits, such as improved patient care, decreased toxicity, increased efficacy, and convenience. [1]

The different classification of controlled drug delivery systems (CDDS) can be given as follows [2], [3]:

1. Rate-pre -programmed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery systems

Oral course is the most well -known course of medication conveyance framework however it has a few hindrances including first pass digestion, drug debasement and so on in gastrointestinal plot because of chemicals, PH. and so on. To defeat these issues, a clever medication conveyance framework was created by Chien in 1992, Banker in 1990, and Guy in 1996. It was Transdermal patches or Transdermal conveyance framework. In this framework sedated cement patches are arranged which convey restoratively powerful measure of medication across the skin when it put on skin [4], [5].

Transdermal patch by and large alludes to skin application conveys specialists to sound flawless skin either for restricted treatment of tissues fundamental the skin or for foundational treatment. Transdermal Patch offers many benefits over the conventional dosage forms or controlled release oral systems. Transdermal patch gives steady blood levels, stays away from first pass metabolism, expanded patient consistence, and avoid dose dumping [6], [7].

The transdermal conveyance can likewise kill beat section into the fundamental flow, which could frequently cause unfortunate secondary effects [8].

Naproxen is a nonsteroidal anti-inflammatory drug, which relieves pain and swelling. It is utilized to treat migraines, muscle hurts, spinal pains, tendonitis, dental agony, feminine spasms, joint inflammation, or gout. This medication works by hindering the protein that makes prostaglandins. Diminishing prostaglandins assists with lessening agony and expanding. The objective of the present study was to overcome the harmful side effects of naproxen a non-steroidal anti-inflammatory drug [NSAID] which causes severe gastro intestinal bleeding while taken orally [9]. The utilization of the majority of the NSAIDS by oral course connected with potential weaknesses like peptic ulceration and gastric dying. This severe drawback creates a potential need for development of transdermal patches of NSAIDS. The major advantage of transdermal delivery system is the ability to avoid first-pass metabolism and also to circumvent the hostile environment of the gastrointestinal tract [10].

Definition:

Transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream [11].

Advantages:

Conveyance through the transdermal route is an intriguing choice on the grounds that the transdermal route is helpful and safe.

- Evasion of first pass metabolism.

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- Evasion of gastro digestive contrariness.
- Unsurprising and expanded span of the action.
- Limiting unwanted secondary effects.
- Keeping away from the variance in drug levels.
- They can keep away from gastrointestinal medication assimilation.
- More prominent patient consistence because of the end of various dosing profiles.
- The action of medications having a beginning half-life is reached out through the repository of medication in the helpful conveyance framework and its controlled delivery.
- Drug treatment might be ended quickly by expulsion of the application from the outer layer of the skin.
- Further developed bioavailability.
- More uniform plasma levels and keep up.
- Plasma accumulating of extreme Medication.
- Diminished responses and improved medicines [12]-[16].

Disadvantages:

A few patients foster contact dermatitis at the site of use from at least one of the framework parts, requiring suspension.

- Greater expense.
- Shouldn't utilize the ionic medication.
- May cause hypersensitive responses.
- Just strong medications are reasonable possibility for transdermal patch on account of the regular furthest reaches of medication section forced by the skin's imperiality.
- A few medications for example scopolamine transdermal fix set behind the ear, it is awkward.
- Long time stick is troublesome [17]-[21].

Care taken while applying transdermal patch:

The piece of the skin ought to be appropriately cleaned before use of patch. Cutting the patch annihilates the medication conveyance framework in this manner patch ought not be cut. It ought to be ensured that the old patch is eliminated from the site prior to applying another patch. Care should be taken while applying or removing the patch to the site of administration [22].

B. Anatomy of the Skin

Skin is the biggest organ of the human body comprising around 16% of the complete body weight. In a sound grown-up man, length of skin is 1.5-2 m2 and gauging around 6-10 kg. 14 Skin is comprised of various layers of cells; cell epidermis, fundamental dermis and the subcutaneous layer being the significant layers.

Layers of the skin:

1) Epidermis:

It is the peripheral layer of the skin portrayed by presence of defined squamous epithelium tissues, principally containing keratinocytes in moderate phases of separation. Keratinocytes are the building cells of the epidermis. Being connective in nature, epidermis depends on dermis for supplement conveyance and garbage removal through the cellar film.

Epidermis is separated into four layers; be that as it may, the piece of the body where the skin is thick, epidermis has five layers.

i. Layer Basal (layer germinativum).
ii. Layer spinosum (prickle cell layer).
iii. Layer granulosum.
iv. Layer lucidum.
v. Layer corneum.

2. Dermis:

Dermis is the layer present beneath the epidermis yet is a lot thicker than the epidermal layer (1-5mm thick). Dermis assumes a fundamental part to maintain and uphold the epidermis. The connective tissues in the dermis are principally made of collagen strands alongside some elastin. It is the house to a few particular cells like pole cells and fibroblasts and designs like veins, lymphatics, sweat organs and nerves. Dermal layer is made out of two primary layers of connective tissues.

- Papillary layer: It is the slim layer uncovered towards the outside containing free connective tissues.
- Reticular layer: It is fewer cells, a lot thicker and more profound layer including thick connective tissue/heaps of collagen filaments.

3. Hypodermis:

It is otherwise called the subcutaneous layer/fat or the Panniculus layer. It is the layer present beneath the dermis which interfaces the skin to the basic belt (stringy tissue) of the bones and muscles. Hypodermis is comprised of very much vascularized, free, areolar connective tissues and fat tissues that go about as an energy hold, protect the body to forestall heat misfortune, and act as a pad to safeguard basic designs from injury consequently, going about as a safeguard. It is joined with veins and nerves and is the greatest amount of site for capacity of fat in the body [23]-[27].

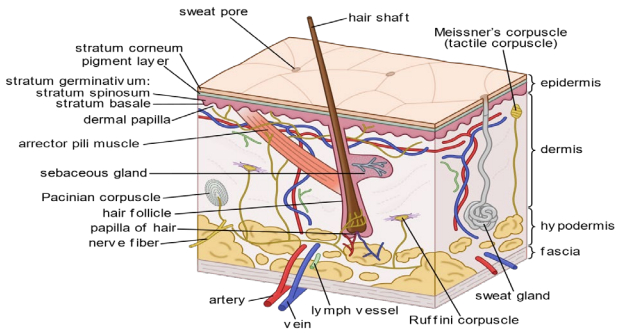

Fig. 1. Structure of skin

C. Basic Components of T. D. D. S (Baker RW et al., 1989)

1) Polymer matrix

The Polymer controls the arrival of the medication from the gadget.

a) Natural Polymers: Cellulose derivatives, Zein, Gelatine, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc. Acrylonitrile, Butyl rubber, Styrenebutadieine rubber, Neoprene etc.
b) Synthetic Polymers: Poly vinyl alcohol,

Polyvinylchloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinyl pyrrolidone.

c) Synthetic Elastomers: Poly butadiene, Hydrinrubber, Polysiloxane, Silicone rubber, Nitrile, Polymethyl methacrylate, Epoxy etc.

2) Drug

For effectively fostering a transdermal drug delivery system, the drug ought to be picked with extraordinary consideration. Coming up next are a portion of the positive properties of a medication for transdermal conveyance.

Physicochemical properties:

- The medication ought to have a sub-atomic weight not exactly roughly 1000 Dalton's.
- The medication ought to have proclivity for both - lipophilic and hydrophilic stages. Outrageous dividing qualities are not helpful for fruitful medication conveyance by means of the skin.
- The medication ought to have low softening point. Alongside these properties the medication ought to be powerful, having short half - life and be non - disturbing.
- Penetration Enhancers (Cal K et al., 2000)

These are intensifying which advance skin porousness by modifying the skin as an obstruction to the motion of an ideal penetrant. These may advantageously be characterized under the accompanying fundamental classes:

a) Solvents

These mixtures increment entrance perhaps by gulping the polar pathway as well as by fluidizing lipids.

Models:

Water alcohols - methanol and ethanol;

Alkyl methyl sulfoxides: dimethyl sulfoxide,

alkyl homologs: methyl sulfoxide dimethyl acetamide

Pyrrolidones: 2 pyrrolidones.

Factors Affecting Transdermal Patches:

There are different variables which influences the activity of transdermal patches. These are given beneath:

a. Physicochemical Properties

i. Partition coefficient
ii. Atomic size
iii. Dissolvability/softening point
iv. Ionization

b. Physiological and Pathological Conditions of Skin

i. Supply impact of horny layer
ii. Lipid film
iii. Skin hydration
iv. Skin temperature
v. Local variety
vi. Obsessive wounds to the skin
vii. Cutaneous self-digestion [28].

D. Types of Transdermal Patches

1) Single layer drug in adhesive

Here, the glue [adhesive] layer contains the medication. The cement layer not just sticks the different layers together and furthermore answerable for the delivering the medication to the skin. The glue layer is encircled by an impermanent liner and a backing [29], [30].

2) Multi - layer drug in adhesive

This framework is like the single layer however it contains a quick medication discharge layer and other layer will be a controlled delivery alongside the glue layer. The glue layer is answerable for the arrival of the medication. This fix likewise has an impermanent liner-layer and an extremely durable sponsorship layer [30].

3) Vapour patch

Here, the job of adhesive layer not just sticks to the different layers together yet in addition discharges fume. The fume [vapour] patches are new and are normally utilized for delivering of medicinal ointments in decongestion. Different sorts of fume patches are likewise accessible in the business sectors which are utilized to work on the nature of rest and diminish the cigarette smoking [29].

4) Reservoir system

Here, the drug reservoir is installed between an impenetrable support layer and a rate controlling film. The medication delivers just through the rate controlling film, which can be either miniature permeable or non - permeable. In the medication repository compartment, the medication can be as an answer, suspension or scattered in a strong polymer lattice. Hypoallergenic cement polymer can be applied as external surface polymeric layer which is viable with drug [31,32].

5) Matrix system

a. Drug-in-glue [adhesive] system:

Here, the medication supply is framed by scattering the medication in a glue polymer and afterward spreading the cured adhesive polymer by dissolvable projecting or softening on an impenetrable sponsorship layer. On the highest point of repository, unmediated glue polymer layers are applied for insurance purpose [31], [33].

b. Matrix-dispersion system:

Here, the medication [drug] is scattered homogenously in a hydrophilic or lipophilic polymer matrix. This medication containing polymeric circle is fixed to an occlusive base plate in a compartment manufactured from a medication impermeable sponsorship layer. Cement is spread alongside the circuit to frame a segment of glue edge.

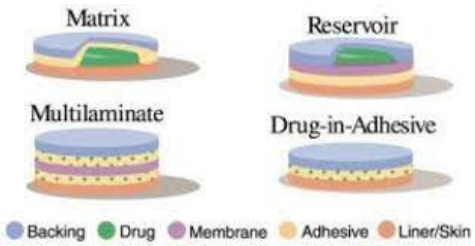

Fig. 2. Types of transdermal patch

6) Micro-reservoir system

Here, the drug delivery system is a combination of reservoir and matrix-dispersion system. The reservoir is framed by first suspending the medication in a fluid arrangement of water dissolvable polymer and afterward distributing the arrangement homogeneously in a lipophilic polymer to shape great many

Table 1
Formulation design

Formulation	Methyl cellulose	HPMC	Ratio	Drug mg	Solvent		Polyethylene glycol 400 0.50%	DMSO ml
					Methanol	dichloromethane		
F1	400	100	4:1	200	20	10	1ml	0.05
F2	350	150	3.5:1.5	200	20	10	1ml	0.05
F3	300	200	3:2	200	20	10	1ml	0.05
F4	250	250	2.5:2.5	200	20	10	1ml	0.05
F5	100	400	1:4	200	20	10	1ml	0.05
F6	150	350	1.5:3.5	200	20	10	1ml	0.05
F7	200	300	2:3	200	20	10	1ml	0.05

tiny circles of medication repository. This thermodynamically unsound scattering is settled rapidly by promptly cross-connecting the polymer in situ by cross connecting agents [33].

2. Materials and Methods

Naproxen, methyl cellulose, HPMC, PEG-400.di-butylpthalate, methanol, dimethyl sulfoxide. All the ingredients and reagents were used analytical grade.

Preparation of transdermal patch of naproxen by using solvent evaporation method

Preparation of Transdermal Patch by the solvent evaporation technique was used for the formulation of naproxen loaded patches, with MC (methyl cellulose) and HPMC as rate-controlling polymers at different concentrations (Table-1). The polymers were weighted accurately using an analytical weighing balance, placed in a solvent system (30 mL) comprising Methanol and dichloromethane (2:1) and allowed to swell for 6 h. The plasticizer used was PEG-400 and 0.05ml of DMSO as permeation enhancer. A 5 mL volume of methanol was taken in a beaker, and a proper amount of naproxen was added. The drug and polymers were mixed homogeneously by slow stirring. A uniform dispersion was poured in Petri dishes. The Petri dishes were placed in an oven at 40 ◦C for 12 h.

Fig. 3. Transdermal patch

3. Evaluation

A. Weight Uniformity

The pre-arranged patches are dried for 4 hours at 60 degree C prior to playing out the test. A particular piece of a clear aspect is cut from different pieces of the fix and burdened a computerized balance. The typical weight and standard deviation values are then determined [33], [34].

B. Thickness of Patch

The thickness of each patch was estimated by utilizing screw gauge at five unique places of the fix and the normal was determined [35].

C. Percentage Moisture Content

The medication stacked patches are weighed separately and kept in a desiccator containing melded calcium chloride at room temperature for 24 hrs. After 24 hrs, the patches are rechecked. Decide the rate dampness content from the underneath referenced equation:

% Moisture content = [Initial Weight-Final weight/Final weight] ×100 [36], [37].

D. Percentage Moisture Absorbed

The medication stacked patches are gauged and kept in a desiccator at room temperature for 24 hrs containing immersed arrangement of potassium chloride to keep up with 84% RH. After 24 hrs, the patches are rechecked and the percentage moisture absorbed determined from the beneath referenced equation:

% Moisture absorb = [Final weight- Initial weight/initial weight] ×100 [33], [38], [39].

E. Folding Endurance

A segment of explicit aspect is cut equitably and more than once collapsed at a similar spot till it brakes. The quantities of times the film was folded at a similar spot without breaking give the worth of the Folding endurance. [40]-[42]

F. Drug Content

A predetermined area of patch is to be disintegrated in a reasonable dissolvable in volumetric flask. The arrangement is then separated through a filter medium and investigated utilizing reasonable strategy (UV or HPLC technique) [31, 33, and 43].

4. Results and Discussion

The spectrum of UV analysed by UV/V is spectroscopy and λ_{max} found to be 235 nm at 7.4 pH with R^2 value of 0.9911.

Table 2

Concentration(µg/ml)	Absorbance
10	0.014
20	0.029
30	0.056
40	0.071
50	0.097

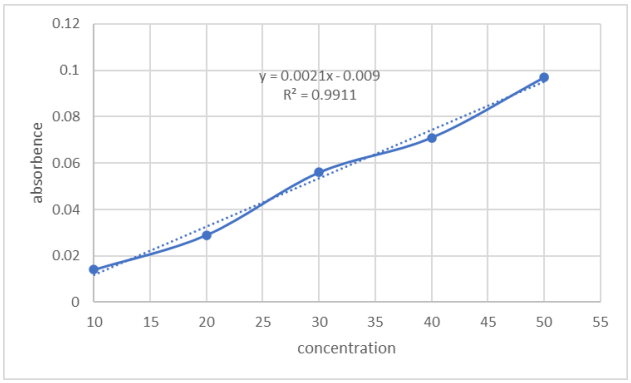

Fig. 4. Standard cure of Naproxen

Table 3
Evaluation of naproxen transdermal patch

Formulation	Weight variation (mg)	Thickness (mm)	Folding endurance
F1	59±0.32	0.72±0.2	66
F2	60±0.18	0.73±0.2	64
F3	62±1.12	0.75±0.2	60
F4	61±1.17	0.80±0.2	69
F5	70±0.56	0.87±0.2	71
F6	69±0.19	0.84±0.2	72
F7	68±0.45	0.83±0.2	70

Table 4
Evaluation of transdermal patch

Formulation	% Moisture absorbed	% Moisture Content	Drug contains (mg/cm²)
F1	13.026±1.12	6.31±0.52	39
F2	12.28±1.32	8.12±0.36	42
F3	12.58±1.62	8.64±0.23	40
F4	11.18±1.44	9.11±0.49	42
F5	12.44±1.22	9.85±0.26	44
F6	11.65±1.56	4.33±0.63	44
F7	11.23±1.24	5.13±0.44	45

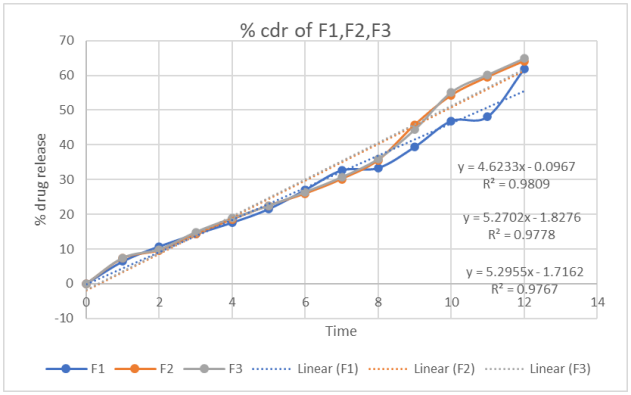

Fig. 5. % Cumulative drug release (F1 to F3)

Table 5
Cumulative drug release

Time	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	3.2	3.657143	3.714286	3.142857	3.657143	3.942857	3.085714
2	5.35619	4.815238	4.933333	4.980952	4.872381	5.205714	7.834286
3	7.127619	7.139048	7.432381	6.825714	7.826667	8.084762	8.917143
4	8.780952	9.278095	9.438095	8.812381	10.41714	9.797143	11.82762
5	10.73905	11.25238	11.21714	10.57238	12.45714	11.90095	12.54
6	13.49619	12.96857	13.18857	12.32476	14.78286	14.1219	15.49238
7	16.30571	15.07333	15.32857	14.89619	17.31619	16.54762	16.44476
8	16.65238	17.7781	17.95524	16.82667	19.77619	19.09714	19.27048
9	19.68	22.84381	22.16857	19.34952	21.87238	21.22952	22.08857
10	23.42095	27.08952	27.53333	22.74	24.24762	25.72857	23.89619
11	24.03905	29.74	30.05524	23.91048	30.7381	30.18571	25.97143
12	30.88381	32.02381	32.40571	30.46952	31.99333	32.48095	30.97905

Table 6
% Cumulative drug release

Time	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	6.4	7.314286	7.428571	6.285714	7.885714	7.314286	6.171429
2	10.71238	9.630476	9.866667	9.961905	10.41143	9.744762	15.66857
3	14.25524	14.2781	14.86476	13.65143	16.16952	15.65333	17.83429
4	17.5619	18.55619	18.87619	17.62476	19.59429	20.83429	23.65524
5	21.4781	22.50476	22.43429	21.14476	23.8019	24.91429	25.08
6	26.99238	25.93714	26.37714	24.64952	28.24381	29.56571	30.98476
7	32.61143	30.14667	30.65714	29.79238	33.09524	34.63238	32.88952
8	33.30476	35.55619	35.91048	33.65333	38.19429	39.55238	38.54095
9	39.36	45.68762	44.33714	38.69905	42.45905	43.74476	44.17714
10	46.8419	54.17905	55.06667	45.48	51.45714	48.49524	47.79238
11	48.0781	59.48	60.11048	47.82095	60.37143	61.47619	51.94286
12	61.76762	64.04762	64.81143	60.93905	64.9619	63.98667	61.9581

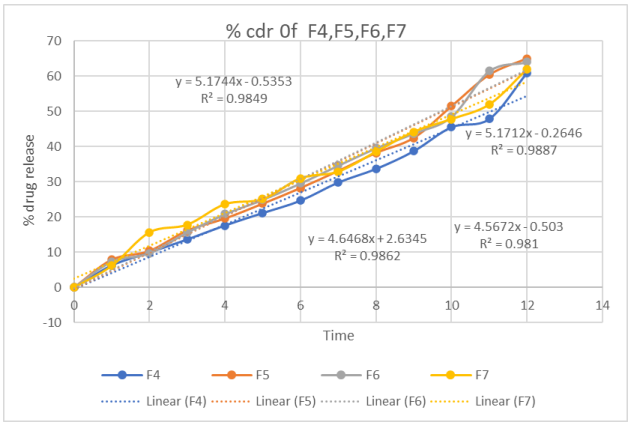

Fig. 6. Cumulative drug release (F4 to F7)

FT-IR Studies:

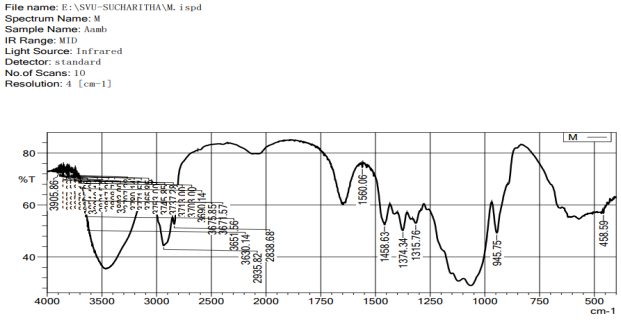

Fig. 7. Methylcellulose

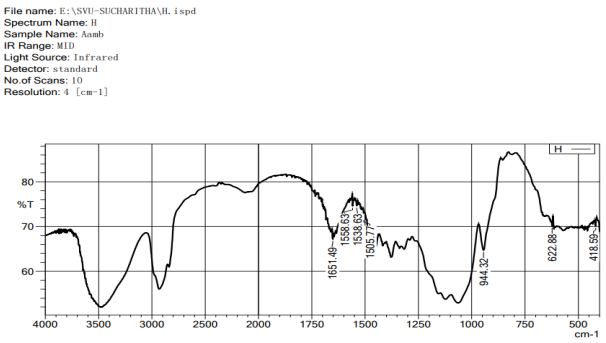

Fig. 8. HPMC

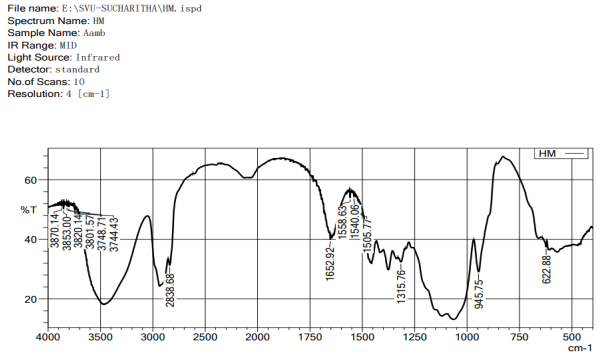

Fig. 9. HPMC + Methylcellulose

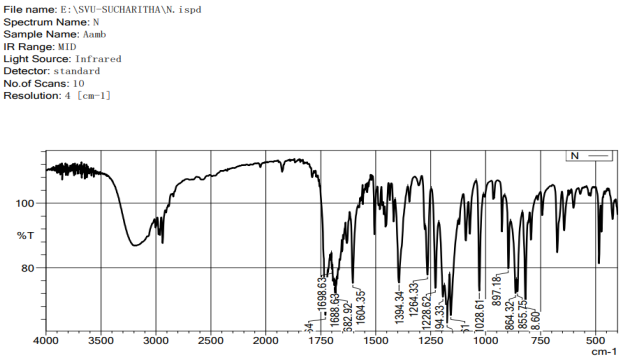

Fig. 10. Naproxen

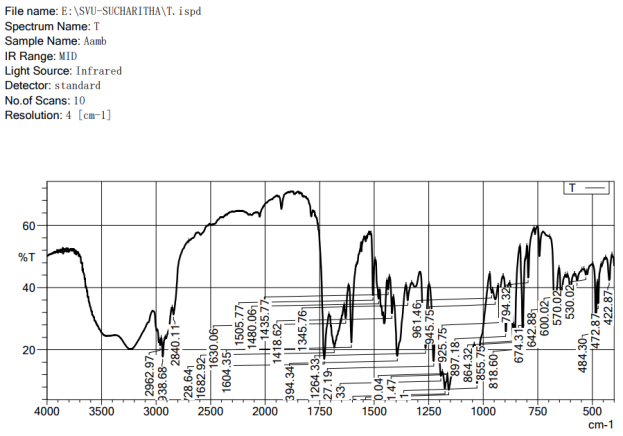

Fig. 11. Naproxen + HPMC + Methyl Cellulose

5. Discussion

Naproxen is a Non-steroidal Anti-inflammatory drug is used for treatment of some disease like cute gout, ankylosing spondylitis, bursitis, polyarticular juvenile idiopathic arthritis, osteoarthritis, tendonitis, rheumatoid arthritis, pain, and primary dysmenorrhea. On oral administration, the dose of the drug should be increased due to high metabolic degradation but the drug has long half-life (12-15hr) due to this reason, we cannot control release the drug by oral administration and it finally leads to several side effects. And also, naproxen has high protein binding capacity leads to saturation of protein takes place on high doses.by considering all these parameters and adverse effects the naproxen should be formulated as film/ patch to apply directly at site needed and also, we can control release the drug 12-24 hr. Following this we can reduce the amount of drug as compared with oral dose of drug by direct targeting the site and decrease the side effect.

The main aim of this study is to formulate the control release transdermal patch of Naproxen for topical administration. Hear we can control the amount of drug release by using the two different polymers like HPMC and Methylcellulose as controlling agents, DMSO as permeation enhancer, Polyethylene glycol as a plasticizer and finally methanol: Dichloromethane (2:1) ratio used as a solvent. By altering the amount of two polymeric concentrations we can formulate different formulation by keeping drug constant Dose (F1 to F7) and evaluate their parameters to get optimized good releasing formulation.

Physicochemical assessment of Naproxen-Loaded Transdermal Patches:

All formulated naproxen patches are under go for physico-chemical characterisation. Evaluation results of various patches formulation (F1 to F7) reveals the sticky nature transparency, thickness, pH, drug contains, *invitro* release folding endurance to know the stability and release pattern of formulated patch. When comes to the pH of patch the all-formulated patches should be within the range of pH 5.0-5.9.so skin irritation does not occur and thickness of all formulated patches should be in range of 0.72±0.2 to 0.87±0.2 but by increase in the concentration of HPMC the thick ness should be increased and folding endurance should be pass by the all-formulated patch (F1 to F7) range should be 60 -72.the folding endurance should be more when compare to expected value. The weight variation should be calculated and deviation should be range of 59±0.32 to 70±0.56. When it comes to the moisture absorbance and percentage moisture, Moisture absorbance should be increased when methyl cellulose concentration increased in formulation, from F1 to F4 moisture absorbance should be in range of 13.026±1.12 to 11.18±1.44, from F5 to F7 moisture absorbance should be in 12.44±1.22 to 11.23±1.24. Percentage moisture be within the standard range of 4.33±0.63 to 9.85±0.26.

All formulated patches showed uniformity in drug content that was quite good and ranged between 39 % and 45 %. The results of this study show that the formulated patches could produce transdermal matrix-type patches with uniform drug contents. The plasticizer used was PEG-400 to reduce the brittleness of the patches. The current study indicates that the addition of PEG-400 at 0.5% w/w of polymers produces uniform, flexible and smooth patches. Patches formulated with the addition of PEG-400 as plasticizer were found to be best for tensile strength and folding endurance properties.

Invitro Dissolution Studies:

Invitro dissolution studies are carried out by using a Franz diffusion cell volume of 60 ml and 7.4 pH buffer used as media and maintain temperature 37±0.5 ^{0}C.egg membrane used as permeation barrier. Percentage drug release should be calculated for all formulated patches (F1 to F7), 1 cm2 patch should be used for invitro studies. In vitro drug release studies are needed for predicting the reproducibility of the rate and duration of drug release. % Drug release should different at different ratio of polymeric concentrations but high concentration of HPMC and Methyl Cellulose shows altered drug release but when comes to the drug release compared to the all formulation F6 formulation show good release pattern. Due to unequal concentration of Methyl cellulose and HPMC (1.5:3.5) based on KorsMeyer–Poppa's equation drug release pattern should be (R^2 =0.995122) and (n =1.059903). The controlled drug release of naproxen found over a period of 12 h. The optimized formulation for the current study was F6. Thus, F6 releases the drug at the predefined rate for a prolonged period of time into the systemic circulation or applied site leading to minimal dose frequency and adverse effects.

6. Conclusion

The results of naproxen contain methyl cellulose and hydroxy propyl methyl cellulose patches shows the different release patterns at different polymeric concentrations. All the formulated patches (F1 to F7) are shows good evaluation parameters but when comes to release study F6 formulation shows good controlled release of drug over 12 hours period of time. We have no standard patch for this formulation, but when compared with tablet formulation of naproxen here we can formulate the tablet into controlled release manner it leads to high adverse effect by expose to long period of time for NSAIDS. In patch formulations we can controlled release the drug and reduce the dose of drug, avoid the multiple dosage regimen and toxic effect of drug.

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