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Research Article

Formulation and Evaluation of herbal TDDS for the Treatment of Inflammation

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Abstract

Natural remedies are more acceptable in the belief that they are safer with fewer side effects than the synthetic ones. Herbal formulations have growing demand in the world market. The purpose of the work was to formulate and evaluate the herbal transdermal patches with natural permeation enhancer for the controlled delivery of the drug in the body. Patches were formulated using various ratios of polymer $HPMCK_{15}M$, ($PVPK_{30}$) Polyvinyl Pyrrolidone and Ethyl Cellulose. Transdermal patches were formulated by solvent evaporation method. Transdermal patches were evaluated for various parameters like thickness, folding endurance, percentage moisture loss, percentage moisture absorption, drug content uniformity, stability studies, *in vitro* skin permeation and skin irritation test. All formulations possess excellent physicochemical properties and exhibited negligible skin irritation with good physical stability. Permeation study was performed by using modified Franz diffusion cells. On the basis of drug release and physicochemical values, formulation F5 with natural permeation enhancer was shows higher percentage of drug release at 24 hours. Release kinetics studies revealed that the drug release from formulations followed Higuchi kinetics

Keyword : Natural remedies, Transdermal patches, Polymer, $HPMCK_{15}M$, *In vitro*.

Introduction : Medicinal plants contain inherent active ingredients to cure disease or relieve pain. The use of traditional medicines and medicinal plant in most developing countries as therapeutic agent for the maintenance of good health has been widely observed. The world health organization estimated that 80% of the population of developing countries relies on traditional medicines, mostly herbal plant drugs for their primary health care. The medicinal property of plant could be based on the anti-oxidant, antimicrobial, antipyretic effect of the phytochemicals present. Traditionally, herbs have been considered to be non-toxic and have been used for treating various problems by the general public and/or traditional medicine doctors worldwide. Although, the literature has documented several toxicity resulted from the use of herbs on many occasions, still the potential toxicity of herbs has not been recognized by the general public or by professional groups of traditional medicine. The use of medicinal plants as raw materials in the production of drug is gaining popularity.[1,2]

Transdermal route is, therefore, a better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens. To provide continuous drug infusion through an intact skin, various transdermal systems have been designed for topical application and it control the delivery of drug and its permeation via the skin tissue. Historically, developments related to TDDS have been incremental, concentrating on overcoming issue related with the skin barrier properties, minimizing skin irritation and improving the outlook related with passive patch systems. TDDS defined as self-contained, discrete dosage form applied to the unharmed skin then it deliver the drug, via skin at controlled manner in the systemic circulation. Transdermal drug delivery via the skin provides a suitable route of administration for a various clinical indications. A pharmaceutical scientist focuses the development of transdermal drug delivery over the last 25 years. The skin offers a large and easily penetrable surface for drug delivery. Transdermal routes, from that of other routes are quite non-invasive, like simple adhesion of a "Patch" similar as that of application of a Band-Aid. A transdermal drug delivery systems transfer a precise dose of drug through the skin and into systemic circulation.

Transdermal delivery is important because it is a non-invasive procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration, gastric irritation and discomfort associated with parenteral drug administration can be avoided. Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin-the largest and most accessible organ of human body-through its layers, to the circulatory 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 and minimizes harmful side effects of a drug caused from temporary overdose.[3-6]

Materials and Methods[7-14]

Collection of plant: *Ipomoea carnea* The stem barks of *Commiphora wightii* were collected from local market of gwalior. The plant was washed, chopped in to small

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pieces and dried under shade then powdered coarsely with a mechanical grinder. The powder was passed through sieve No. 40 and stored in an airtight container for further use.

About 200 gm of coarsely powdered plant material was successively extracted by Soxhlet extraction method using solvents with increasing polarity viz. petroleum ether and methanol. Each time before extracting with next solvent, the powdered material was dried in hot air oven (mentioned temp range). Each extract was then concentrated by distilling off the solvent by evaporation to water bath. All the extracts thus obtained were stored in air-tight bottles at 4ºC for further experiments.[7]

Ultra Sonicate : After the extraction the extracts were dissolved in minimum quantity of ethanol and placed for 15 mint in ultra sonicator bath machine (Elmasonic S150 **)** for complete dissolution after that this sonicated extract solution used for formulation.

Preparations of Transdermal patches

The transdermal patches of composition listed in Table no.2 were prepared by solution casting technique employing a glass substrate (Bangles wrapped with aluminium foil). Membrane type transdermal systems with containing 100 mg Commiphora wightii prepared by employing various proportions of natural permeation enhancer as well as anti-inflammatory agent :Oleic acid, camphor, Menthol & clove oil and $HPMCK_{15}M$, $PVPK_{30,}$ & Ethyl Cellulose. The polymers was accurately weight and dissolved in a suitable solvent mixed until clear solution formed with magnetic stirrer then plant extract and natural penetration enhancer added .This mixture Placed for 30 mint in ultra sonicator bath machine (Elmasonic S150**)** for complete dissolution after that this sonicated solution mixed with PEG400 as a plasticizer .The polymer solution was poured into bangles placed in a suitable level, hard rigid surface and patches were dried at a room temperature in a dust free environment for 24 hrs. An inverted funnel was covered over the bangles to avoid fast evaporation of the solvent. Patches of 3.14 cm^2 were prepared by cutting and packed in an aluminum foil and kept in a desiccator.[8-13]

Evaluation of Transdermal Patches

Thickness of patches

The thickness of Patches were measured by digital vernier calipers with least count 0.001mm at three different sites average of three reading was taken with standard deviation.

Weight variation

The three disks of 3.14 cm^2 were cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Drug content

Accurately weighed patches were individually dissolved in minimum quantity of methanol and made volume up to 100 ml with PBS pH 7.4 solutions; 10 ml was transferred to flask and made volume 100 ml. The absorbance was recorded. The blank solution was made in the same manner except the patches without drug were used.

Percentage Moisture content

The films were weighed & placed in desiccators containing calcium chloride at 40^0c in a dryer for at least 24 hrs or more until it gives a constant weight. The % of moisture content was the difference between constant weight taken and the initial weight and as reported with percentage by weight moisture content.

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

Percentage Moisture absorption/uptake

The films of which the size 3.14cm^2 were put in a desiccators with silica gel for 24 hrs and weighed the patches were transferred to another desiccators containing saturated solution of KCL(84% RH) after equilibrium was attained. Patches were taken out and weighed. Moisture uptake was calculated with following formula

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

Swelling index

The patches of 3.14 cm^2 were weighed and added into Petri dish which contains 10 ml double distilled water and were permeated to absorb moisture at a fix time interval check the increase weight of the patches. Continue this process till same weight observed until weight remaining the same over a period of time. Swelling index (% S) was determined by applying the formula.

S (percentage) = Wt – Wo / Wo x 100

Where, S percent swelling, Wt patch weight at time t.

Wo patch weight at time zero.

Folding endurance

This was obtained by constantly folding one patch at the same place without breaking gave the value of folding endurance. This test performed to check folding ability of transdermal patches also indicate brittleness of patches, more brittle patch when folding endurance value

Table1: Composition of Transdermal patches

Formulation	Drug (mg)	HPMCK15M (mg)	PVPK3 (mg)	EC (mg)	PEG-400 (ml)	Solvent (M:DCM) (1:1) (ml)
F1	100	50	250	100	0.2	4
F2	100	50	250	100	0.2	4
F3	100	50	250	100	0.2	4
F4	100	50	250	100	0.2	4
F5	100	50	250	100	0.2	4
F6	100	50	250	100	0.2	4
F7	100	50	250	100	0.2	4

HPMC: Hydroxypropyl methyl cellulose, PVP: Polyvinyl pyrolidone, PEG : Polyethylene glycol, DMSO: Dimethyl sulphoxide, *M: Methanol *DCM: Dichloromethane

Table: 2 Composition of Natural penetration enhancer in Transdermal patches

Formulation Code	Natural Penetration Enhancer in parentage			
	Oleic acid	**Camphor**	**Menthol**	**Clove oil**
F1	-	-	-	-
F2	2	4		
F3	2		4	
F4	2			4
F5	2	2	2	
F6	2	2		2
F7	2		2	2

Percentage Elongation

A film strip (4 x 1cm) was cut on a glass plate with a sharp blade. The % elongation break is to be determined by observing the length just before the

breaking point with formula by pointer on the graph paper.

% Elongation = [Final length – Initial length] * 100/Initial length

Tensile Strength

The tensile strength of the patches was found by the apparatus and the design of instrument such that, it had one wooden frame that horizontally placed having fixed scale. On the top of frame two clips were attached to hold patches that under study. From two clips one clips fixed & other moved. Instrument also has pulley to hold weight a patch, weight applied to one end of pulley and other end attached to the fixed clip. During the test wooden platform not dislocate from the original place so platform was fixed carefully to avoid dislocation. Three patches were cut for study having 3.14 cm^2 sizes. Thickness and width of patches were noted at three sizes and calculated average value. Rate of stress changes was maintained constant with the addition of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation. Formula for tensile strength :

Tensile strength= F/a.b (1+L/l)

Where,

F is the force required to break; 'a' is width of film; 'b' thickness of film; L is length of the film; l is an elongation of film at break point.

***In-vitro* permeation studies** [14-18]

Franz diffusion cell (fabricated in our Lab.) with a diameter 3.7 cm was used in in-vitro release studies. A glass tube with both end open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. A transdermal patch sample was accurately placed on a semipermeable cellophane membrane to occupy a circle of 3.7 cm diameter. The loaded membrane was stretched over the lower open end of a glass tube of 3.7 cm diameter and made water tight by rubber band. The tube (donor compartment) was immersed in a beaker containing 100 ml of phosphate buffer pH 6.8 (receptor compartment) .The cell was immersed to a depth of 1 cm below the surface of buffer. The system temperature was maintained at 37°±1° and speed was maintained at 30 rpm throughout the experiment by magnetic stirrer. The samples 3 ml were withdrawn at different time intervals and analyzed without dilution or filtration for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Drug release kinetics

Drug release mechanism of drug through film investigated and analyzed with the following mathematical release models:

Stability studies[18,19]

As per ICH Guidelines of Accelerated stability studies were performed at the different storage condition $25^{O}C\pm2^{0}c$ temp., 60%±5% RH and $40^{O}C\pm2^{0}c$ temperature, 75%±5% RH, for 90 days on optimized formulation batches (FT5).The parameters studied for stability studies are thickness, drug content, moisture content and uptake, weight variation, folding endurance, Tensile strength, % elongation and swelling index.

Results and discussion

Physicochemical Evaluation

Table 4 and 5 shows the physicochemical evaluation like the Thickness, Folding endurance, Percentage moisture absorbed, Percentage moisture lost, Drug content uniformity.

Permeation studies and Permeation Kinetics

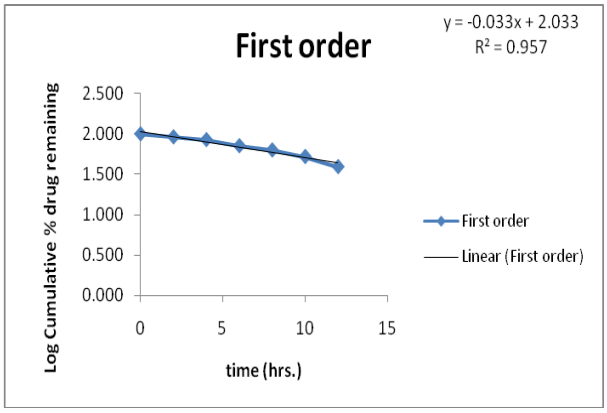
The drug permeation from the Patches is depends on the polymer type as well used concentration. In- Vitro (permeation) studies were performed with Franz cell in Phosphate Buffer Saline pH 7.4. In drug Permeation study the formulation F1 shows 50.41% at 12 hrs while F5 containing as the standard permeation enhancer shows maximum drug permeation 60.43 % at 24 hrs. The drug permeation data of F5 was plotted for Zero order, First order, Higuchi model and Korsmeyer-Peppas model to evaluate the permeation pattern of the dosage form. From these plots, kinetic values of the drug permeation were determined. Drug released from the matrix devices by diffusion studied with first order Model and result suggested that the drug permeation follow first order model.

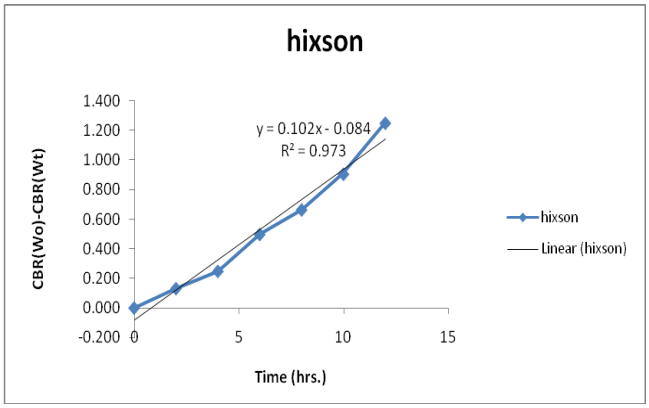
Drug release kinetic modeling of optimized formula

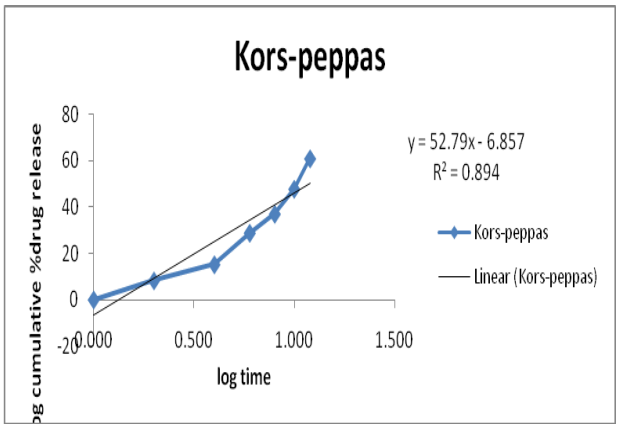
On comparison of kinetic modeling and release profile data it was evident that Transdermal Patch containing *Commiphora mukul extract* was found to release the drug in accordance to Hixson kinetics, the regression coefficient was not found to be exactly near to 1, which could be due to influence of some other factors.

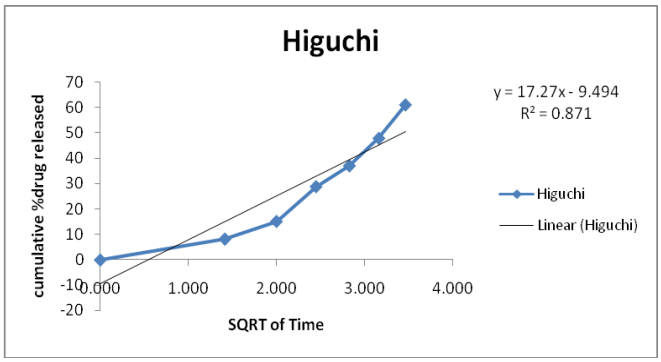
Stability Study

Stability is the essential factor for quality, safety and efficacy of product. The drug product is with insufficient stability result in altering of their physical as well as chemical characteristics. The selected formulations namely F5 was subjected for stability studies as per ICH guidelines and observed for all evaluation parameters at a temperature of $25^{0}C$ and 60% RH, $40^{0}C$ and 75% RH, at an interval of three month. There were no physical changes in flexibility and physicochemical evaluation parameter was slightly changed









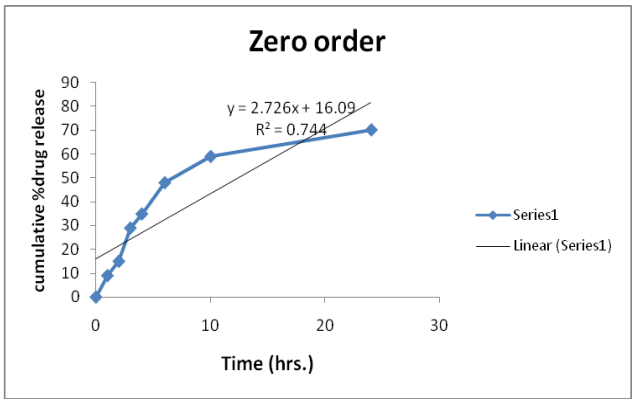


Figure 1: Kinetic Model for *Commiphora mukul* TDDS formulation F5

Conclusions

TDDS are the ideal delivery system for drugs that undergo hepatic first pass metabolism. In the present study, an attempt was made to prepare, characterize and evaluate of transdermal matrix patches of *Commiphora mukul* plant extract. Based on results of various evaluation parameters like thickness, strength, elongation, better compatibility and stability the transdermal matrix patches was successfully designed and developed by trial and error method. Formulations were prepared by employing combination of HPMCK_{15}M, PVP$K_{30,}$ and EC in various ratios.

From the present study, the following conclusion can be drawn:

The used polymers (HPMCK_{15}M, PVPK30, and EC in various ratios) employed to design transdermal patches in different proportion.

PEG 400 and Dibutyl phthalate can be successfully utilized as a plasticizer and penetration enhancer tween 80, Oleic acid, Camphor and DMSO were used successfully.

The optimized TDDS formulation containing *Commiphora mukul* and 2:2: 2 ratios of oleic acid, camphor & menthol were found to F5.

From the formulated patches, formulation F5 showed highest permeation through cellophane

membrane .All the formulation shows good folding endurance and other physicochemical property. Stability study performed on optimized formulation .

No major changes showed in the parameters during study period, thus it could be concluded that formulation was stable

Table 3. Physicochemical Evaluation data of F5 Transdermal Patches

Formulation Code	Thickness (mm)	Weight variation (mg)	% Drug Content	Folding endurance	Tensile strength Kg/mm^2
F1	0.30±0.06	0.159±0. 01	97.82±2. 02	57.7±12.02	3.31±0.81
F2	0.32±0.004	0.151±0. 005	98.15±2.42	058±02.04	2.79±0.80
F3	0.29±0.02	0.150±0. 021	97.41±2.17	59±08.20	3.02±0.70
F4	0.31±0.09	0.159±0. 011	99.71±1.43	58±14.13	3.41±1.80
F5	0.31±0.31	0.153±0. 027	99.12±5.02	57±20.03	3.45 ±1.24
F6	0.31±0.013	0.158±0. 014	98.91±1.42	58±11.42	2.94±1.84
F7	32±0.003	0.157±0. 015	98.16±2. 02	57±59.41	3.16 ±1.78

Table 4.Physicochemical Evaluation data of F5 Transdermal Patches

Formulation Code	% Elongation	% Moisture Content	% Moisture uptake	Swelling index
F1	33.23±2.51	2.68±0.35	4.37±4.03	25.31±1.28
F2	33.10±2.12	2.53±0.77	4.25±2.7	24.71±0.52
F3	34.65±2.61	2.79±1.29	5.24±1.22	24.49±1.12
F4	35.71±4.12	2.81±1.82	5.16±0.85	24.51±0.74
F5	36.84±3.71	3.36±2.68	5.31±1.15	24.10±0.25
F6	3502±4.19	3.53±0.98	4.35±1.06	25.10±1.37
F7	32.98±4.18	3.27±0.97	4.49±1.05	24.22±1.26

Figure 2 In-*vitro* Drug Permeation *Commiphora mukul* of F1 to F7

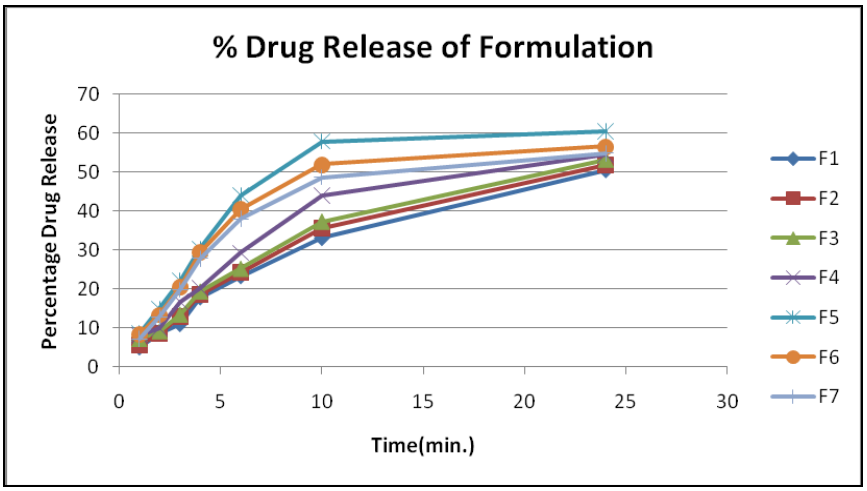


Table 5 *In-vitro* Drug Permeation of *Commiphora mukul* Kinetics

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
1	5.01	5.53	7.1	8.03	8.43	8.21	7.25
2	8.53	8.49	09.12	09.89	14.89	13.22	12.89
3	10.99	12.81	13.35	16.77	22.07	20.45	19.86
4	17.81	18.52	19.26	20.24	30.24	29.36	27.86
6	23.23	24.21	25.12	29.23	44.02	40.44	38.02
10	33.03	35.56	37.21	43.88	57.78	51.81	48.71
24	50.41	51.77	53.12	54.43	60.43	56.51	54.87

Table 6: R2 value of optimized formulation F5

Model Name	Zero order	Fist order	Higuchi model	Hixson	Cross peppas	Best fit model
R2 value of F5 for *Commiphora mukul* extract	0.744	0.957	0.871	0.973	0.894	Hixson kinetics model

Reference

1. Quaye Osbourne, Cramer Precious, Ofosuhene Mark, Okine Laud K N, and Nyarko Alexander K. Acute and Subchronic Toxicity Studies of Aqueous Extract of *Desmodium adscendens* (Sw) DC. (2017); Journal of Evidence-Based Complementary & Alternative Medicine; 22(4): 753-759.
2. Saleem Uzma, Amin Sadia, Ahmad Bashir, Azeem Haroon, Anwar Fareeha, Mary Sunita. Acute oral toxicity evaluation of aqueous ethanolic extract of *Saccharum munja* Roxb. roots in albino mice as per OECD 425 TG. (2017); Toxicology reports; 1-20.
3. Upadhyay Prabhat, Shukla Rashmi, Mishra Sunil Kumar. Acute and sub-acute toxicity study of hydro-alcoholic leaves extract of *Reinwardtia indica* in rats. (2019); Biomedicine & Pharmacotherapy; 111: 36–41.
4. Al-Yahya M.A., Rafatullah S., Mossa J.S., Ageel A.M., Al-Said M.S., Tariq M., et al. (1990) "Gastric antisecretory, antiulcer and cytoprotective properties of ethanolic extract of *Alpinia galanga* Willd in rats" Phytotherapy research 4(3): 112-114.
5. An N., Zou Z., Tian V, Luo X, Yang S, Xu LET., et al. (2008) "Diarylheptanoids from the rhizomes of *Alpinia officinarum* and their anticancer activity" Fitoterapia 79: 27–31.
6. Bendjeddou D., Lalaoui K., Satta D. (2003) "Immunostimulating activity of the hot water-soluble polysaccharide extracts of *Anacyclus pyrethrum*, *Alpinia galanga* and *Citrullus colocynthis*" Journal of Ethnopharmacology 88: 155-160.
7. Kokate C.K., Purohit A.P. and Gokhale S.B. (2005). *A Text-book of Pharmacognosy*, 31st edition, Nirli Prakashan, 37, 48-52, 57.
8. Roopa Pai S. and Kusum Devi V. "Indomethacin Liposomes for Transdermal Delivery Formulation, Characterization, Stability and In vitro *Evaluation*".*International Journal of Pharmaceutical Sciences and Nanotechnology* Volume 1,Issue 4,January-March 2009 p317 – 326.
9. P. Anitha et. al, Ethosomes - A noninvasive vesicular carrier for transdermal drug delivery, Anitha *et al.*, Int. J. Rev. Life. Sci., 1(1), 2011, 17-24
10. K Pavan Kumar *et al*, Ethosomes-A Priority in Transdermal Drug Delivery, International Journal of Advances in Pharmaceutical Sciences,1 (2010) 111-121
11. Jain S, Tiwary AK, Sapra B, Jain NK.,Formulation and Evaluation of Ethosomes for Transdermal Delivery of Indomethacin, *AAPS PharmSciTech*. 2007, 8(4): Article 11
12. A. K. Barupal *et al*, Preparation and Characterization of Ethosomes for Topical delivery of Aceclofenac, Indian J Pharm Sci. 2010 Sep-Oct; 72(5): 582–586.
13. Jain S, Tiwary AK, Sapra B, Jain NK.,Formulation and Evaluation of Ethosomes for Transdermal Delivery of Indomethacin, AAPS PharmSciTech. 2007, 8(4): Article11.
14. A.K. Barupal *et al*, Preparation and Characterization of Ethosomes for Topical delivery of Aceclofenac, Indian J Pharm Sci. 2010 Sep-Oct; 72(5): 582–586.
15. Kavitha K., More MR., Design and evaluation of transderrmal films of Lornoxicam: Int. J. Pharma & Bio Sci, 2011, 2(2), 54-62.
16. Kavitha K., More MR., Design and evaluation of transderrmal films of Lornoxicam Int. J. Pharma & Bio Sci, 2011, 2(2), 54-62
17. Patel DM., Kavitha K., Formulation & Evaluation aspects of transdermal drug delivery system, Int. J. Pharma Sci. Rev. Res. 2011, 6(2), 83-90
18. Suchika Sharma, Geeta Aggarwal, Sanju Dhawan. Design and evaluation of Olanzapine transdermal patches containing vegetable oils as permeation enhancers. Scho. Res. Lib. 2010; 2(6):84-98