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FORMULATION AND EVALUATION OF TRANSDERMAL GEL OF KETOPROFEN WITH NATURAL GELLING AGENT FROM OCIMUM BASILICUM SEED AND PENETRATION ENHANCER IS MENTHOL

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ABSTRACT
According to present work is based on the Formulation and Evaluation of Transdermal Gel of Ketoprofen with Natural Gelling Agent From Ocimum Basilicum Seed Mucilage and Penetration Enhancer is Menthol for Treatment in Musculoskeletal Disorder such as rheumatoid arthritis, osteoarthritis, and spondylitis by using dispersion method. Gel were prepared by dispersing method where polymer such as OBM (Ocimum Basilicum Seed Mucilage) is dispersed over water for 2 hours till the polymer is soaked with water, after that other chemical ingredients are mixed and stirred well until a homogenous mass is obtained. The dispersion was then neutral. The OBM gel of ketoprofen were found to be homogenous with good drug loading. The pH of all the gel formulation was found within the neutral pH range which is compatibility with skin and viscosity of formulation was found to be feasible for topical drug delivery. Result of in-vitro drug release study shows that f4 formulation. It hasbetter diffusion of drug through egg membrane and hence further permeation studies carried out through HET-CAM test was used for the in-vitro assessment of skin irritation of the prepared gel sample. The compatibility study showed that the major peaks in FTIR spectra of the pure drug were found to be intact in their physical mixture. Hence there is no interaction between drug and OBM in their physical mixture. OBM can be effectively used as the polymerfor topical gel preparation. F4 formulation containing OBM may be effectively used as topicaltransdermal delivery for ketoprofen. Transdermal gel is one among the dosage form lying underthe category of controlled drug delivery, during which the aim is to deliver the drug through the skin within a predetermined and controlled rate. The transdermal Penetration and pharmacological efficiency of ketoprofen is superior because of it's intermediate log P value (3.12) Thus the present topic is undertaken for resolve limitations of conventional route of administration and improve patient compliance.

Keywords: Ketoprofen, NSAID, Penetration Enhancer(menthol), OBM (Natural gelling agent), Transdermal gel, Data analysis and release kinetics, compatibility study, dispersion method, Anti- inflammatory Activity.

INTRODUCTION:

Non-steroidal anti-inflammatory drugs (NSAIDs) like Diclofenac, Aceclofenac, Ibuprofen, Indomethacin etc. Find their clinical application as anti-inflammatory agents in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis and spondylitis. In general, NSAIDs provide only symptomatic relief from pain and inflammation. In this study, Ketoprofen which is one of the NSAID drugs, showing effective anti- inflammatory and analgesic properties is formulated into transdermal drug delivery system. Ketoprofen has been extensively studied for number of activities including anti-inflammatory,immunomodulatory. It belongs to NSAID class of agents but with a different mechanism of action, that is, the inhibition of COX-2, the key enzyme of prostaglandin synthesis.It has a good tolerability profile in a variety of painful conditions and is a non-selective and potent inhibitor of COX-2 which is the key enzyme of prostaglandin biosynthesis via the arachidonic acid pathway. It is of lipophilic nature and is formulated as a transdermal gel, so as to overcome its side effects when it is administered by the oral route like diarrhea, constipation, gastric irritation and avoid its hepatic first pass metabolism. Gels are superior formulation for several routes of administration. They are effective as liquid formulations in oral, topical, vaginal and rectal administration. Principle therapeutic effect of NSAIDs springs from their ability to inhibit prostaglandin production by inhibiting enzymatic activities within the prostaglandin synthesis. The primary enzyme is that the prostaglandin synthetase or carboxylic (fatty) acid cyclooxygenase. This enzyme converts arachidonic acid to the unstable intermediates PGG-2 and PGH-2. These aretwo types of cyclooxygenase. These are termed as COX-1 and COX-2. COX-1 is a constitutiveisoform found in stomach, blood vessels and kidney. These products differ from tissue to tissuedepending upon the actual PGH / PGG metabolizing enzymatic activities present. Arachidonic acid also can be converted via 12-lipoxygenase to 12-HPETE and 12-HETE or via the 5lipoxygenase pathway to a spread of leukotrienes. NSAIDs inhibit the cyclooxygenase enzyme and prostaglandins production. They do not suppress leukotriene formation. The dosage forms, whether a tablet, an injection or a patch, to deliver the right amount of medicine at the right time to the right target site becomes complicated if each medicine is to be delivered in an optimal and preferred manner to the individual patient. The medication may notbe absorbed if it is released too slowly or too rapidly, or the patient may suffer adverse effectsand as because it's desired effects may not last as long as it needed. These limitations are being overcome by transdermal drug delivery systems as they achieve several advantages over conventional dosage forms. Transdermal drug delivery is a route 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. Transdermal route of drug administration avoids discomfort associated with parental therapy and improves patient compliance. This route of administration also eliminates the side effects that are caused by the conventional drug forms and also provide controlled release of drugs directly into the bloodstream through the intact skin. Transdermal delivery can provide a number of advantages over the conventional method of drug administration like-enhanced efficacy, increased safety,greater convenience, improved patient compliance.

PENETRATION ENHANCERS

Definition:

The penetration enhancers are the substance which reversibly reduce the barrier resistance ofthe stratum corneum without damaging the viable cells.

Or

The agents which are capable of modifying the barrier to penetration presented by skin are called as "penetration enhancers''

Mechanism of action of penetration enhancer[4,8,11]:

Mainly the penetration enhancer cross into the skin and co-operate with the skin constituents and instigate at transitory and reversible increment in skin permeability by upsetting and fluidizing the lipid boundary of the skin. They expand medicines diffusivity through the skin proteins.

1. Penetration enhancers acts by one or great amount of following mechanism of actions,

2. Disruption of exceedingly requested structure of lipids of stratum corneum.

3. Interaction with intercellular proteins.
4. Increase the thermodynamic activity of the drug by acting as a cosolvent.
5. Increase the partition coefficient of the drug to promote its release from the vehicle intothe skin.
6. Promote penetration and establish drug reservoir in the stratum corneum.
7. Improves the apportioning of medication from the dissolvable into the stratumcorneum.

The former class generally comprises a long chain of the intercellular lipids, in addition to apolar head group that is capable of interacting with the lipid polar head group.

GELS[1,3,12,13,14]:

The term gel originated in the late 1800's. Gels are swollen networks possessing both the cohesive properties of solids and the diffusive transport properties of liquids. Elastically they tend to be soft and somatically they are highly reactive. They are semisolids being either suspensions of small organic particles or large organic molecules interpenetrated liquid.with

It is the interaction between the units of colloidal phase, inorganic or organics, which sets up structural viscosity, immobilizing the liquid continuous phase. Thus, get exhibit characteristicsintermediate to liquids and solids.
When dispersed in an appropriate solvent, gelling agent merge or entangled to form three- dimensional colloidal network structures. This network limits fluid flow by entrapment and immobilization of the solvent molecules. The network structure is also responsible for a gel resistant to deformation and therefore its viscoelastic properties.
Gels are an excellent formulation for several routes of administration. They are useful as liquidformulations in oral, topical, ocular, vaginal and rectal administration. Gels can be clear formulations when all the particles completely dissolve in the dispersing medium. But this doesn't occur in all gels, and some are therefore turbid.

Methods of preparation of Gels[12,13,25]:

1. Dispersion method:

In this method polymer is dispersed over water for 2 hours till the polymer is soaked with water, after that other chemical ingredients are mixed and stirred well until a homogenous mass is obtained.

2. Cold method:

In this method all the ingredients are mixed together to form a homogenous mass, under low temperature at about 5^0C. In this polymer is mixed with penetration enhancer to form solution A, Drug is mixed with solvent to form a solution B. After that solution B is poured into solutionA slowly with complete stirring.

3. Chemical reaction:

In this preparation of sols by precipitation from solutions. E.g. Aluminium hydroxide gel precipitate by interaction in aqueous solution of an aluminium salt and sodium carbonate, increased concentration of reactants will produce a gel structure. Silica gel is another example and is produced by interaction of sodium silicate and acids in the aqueous solution.

4. Thermal effect:

As lower the temperature the solubility of most lyophilic colloids E.g. agar, gelatin, sodium oleate is reduced, so that if cooling a concentrated hot sol will often produce a gel. Similarly, to hydrogen bonding with water. Increasing the temperature of these sols will break the hydrogen bonding and the reduced solubility will produce gelatin.

5. Flocculation with salts and Non-solvents:

Gelatin is a popular collagen derivative primarily used in food, pharmaceutical, photographic and technical products. In foods, gelatin provides a melts-in-the-mouth function and do achieve thermo-reversible gel property. Gelatin is produced by adding just sufficient precipitate to produce the gel structure state but in sufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitants. Solutions of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amount of a nonsolvent such as petroleum ether. The addition of salts to moderately sols such as aluminium hydroxide, ferric hydroxide and bentonite produces gels.

Benefits of Natural gelling agent and Penetration enhancer:

- OBM has advantages over synthetic gelling agent as it was found to be Biocompatible &non-toxic because chemically it was found carbohydrate in nature and composed of polysaccharides.
- It has additional anti-inflammatory activity due to presence of quercetin flavonoid which inhibits the inflammatory cytokine (TNF-α).
- Menthol has penetration enhancer property it was found to be more potent as compared to synthetic penetration enhancer because sometimes synthetic penetration enhancer showed permanent damage of cell membrane.

So, in present study we used OBM as natural gelling agent and menthol as penetration enhancer.

MATERIALS AND METHOD:

List of Materials Used:

A) Drug:

Sr. No	Drug	Supplier
1.	Ketoprofen	Yarrow chem. products, Mumbai.

Table: List of Drug and supplier.

B) Excipients:

Sr. No.	Excipients	Supplier
1.	Xanthan gum	SBSPM' B. Pharmacy College,Ambajogai
2.	OBM powder	SBSPM' B. Pharmacy College,Ambajogai
3.	Menthol	SBSPM' B. Pharmacy College,Ambajogai
4.	Propylene glycol	SBSPM' B. Pharmacy College,Ambajogai
5.	Glycerin	SBSPM' B. Pharmacy College,Ambajogai
6.	Methanol	SBSPM' B. Pharmacy College,Ambajogai
7.	Benzyl alcohol	SBSPM' B. Pharmacy College,Ambajogai

Table : List of Excipients and suppliers.

C) Chemicals and Reagents:

Sr.No.	Chemicals and Reagents	Supplier
1.	Sodium hydroxide	SBSPM' B. Pharmacy College,Ambajogai
2.	Potassium dihydrogen phosphate	SBSPM' B. Pharmacy College,Ambajogai
3.	Acetone	SBSPM' B. Pharmacy College,Ambajogai
4.	Ethanol	SBSPM' B. Pharmacy College,Ambajogai

Table : List of Chemicals and suppliers

Method Used:

Dispersion Method :

In this method polymer is dispersed over water for 2 hours till the polymer is soaked with water, after that other chemical ingredients are mixed and stirred well until a homogenous mass is obtained.

Preparation of Transdermal Gel of Ketoprofen:

Procedure:

The required quantity of Ketoprofen was weighed accurately and dissolved in specified amountof methanol. To this solution specified quantity of Propylene glycol, Glycerin and Benzyl alcohol were added and dissolve. (Solution

A)

Different concentration of OBM and specified concentration of xanthan gum were dispersed insufficient amount of water, the mixtures were mixed uniformly by using magnetic stirrer. (Solution B)

Solution A and Solution B were mixed thoroughly.

Dispersions were allowed to hydrate for 30-60minutes.

Sr. No.	Ingredients	Role of Ingredients
1.	Ketoprofen	NSAID
2.	OBM	Gelling agent
3.	Xanthan gum	Stabilizer
4.	Menthol	Penetration enhancer
5.	Propylene glycol	Humectant
6.	Glycerin	Emollient
7.	Methanol	Solvent
8.	Benzyl alcohol	Preservative
9.	Distilled water	Vehicle

Table :Ingredients for Transdermal Gel Formulation.

Sr.no.	Ingredients(%w/v)	F1	F2	F3	F4
1.	Ketoprofen	1	1	1	1
2.	OBM	0.25	0.5	0.75	1
3.	Xanthan gum	1	1	1	1
4.	Menthol	5	5	5	5
5.	Propylene glycol	1	1	1	1
6.	Glycerin	3	3	3	3
7.	Methanol	1	1	1	1
8.	Benzyl alcohol	0.1	0.1	0.1	0.1
9.	Distilled water	Qs to 10%	Qs to 10%	Qs to 10%	Qs to 10%

Table : Composition for Transdermal Gel Formulations.

RESULTS AND DISCUSSION

Preformulation study:

Identification of Drug:

Organoleptic properties:

The drug was white in color, odorless and powder in nature meets specification mentioned in I.P.2014.

Determination of melting point:

Name	M.P. Observed	M.P. Reported
Ketoprofen	94^0C	94^0C

Table: Melting point of Ketoprofen.

The melting point of Ketoprofen was found as 94^0C which complies with reported melting point range of standard Ketoprofen which indicates that the drug Ketoprofen was of pure quality.

Determination of solubility:

Sr. No.	Solvent	Solubility Profile
1.	Distilled Water	Insoluble
2.	Acetone	Soluble
3.	Alcohol	Soluble
4.	Benzene	Soluble
5.	chloroform	Soluble
6.	methanol	Soluble

Table : Solubility profile of Ketoprofen.

The solubility profile of Ketoprofen complies with reported solubility profile of standard Ketoprofen. It was showed in Table.

FTIR Analysis:

The FTIR Spectrum analysis of Ketoprofen reveals the presence of major functional groups it was showed in Figure and Table . The observed wavenumber was found to be within standard limits that indicates no any impurities present in drug sample.

Functional Groups	Observed frequency values (cm^{-1})	Standard frequency values (cm^{-1})
C=O (Amide)	1697.05	1680-1880
C=C(Stretching)	1653.97	1690-1640
C-H (Stretching)	2978	2500-3000
-C-O-(Stretching)	1073.04	1350-1000
-C-C-(Stretching)	964.82	800-1000
-OH (Stretching)	3745.83	3500-3100

Table : FTIR Spectrum Interpretation for Ketoprofen.

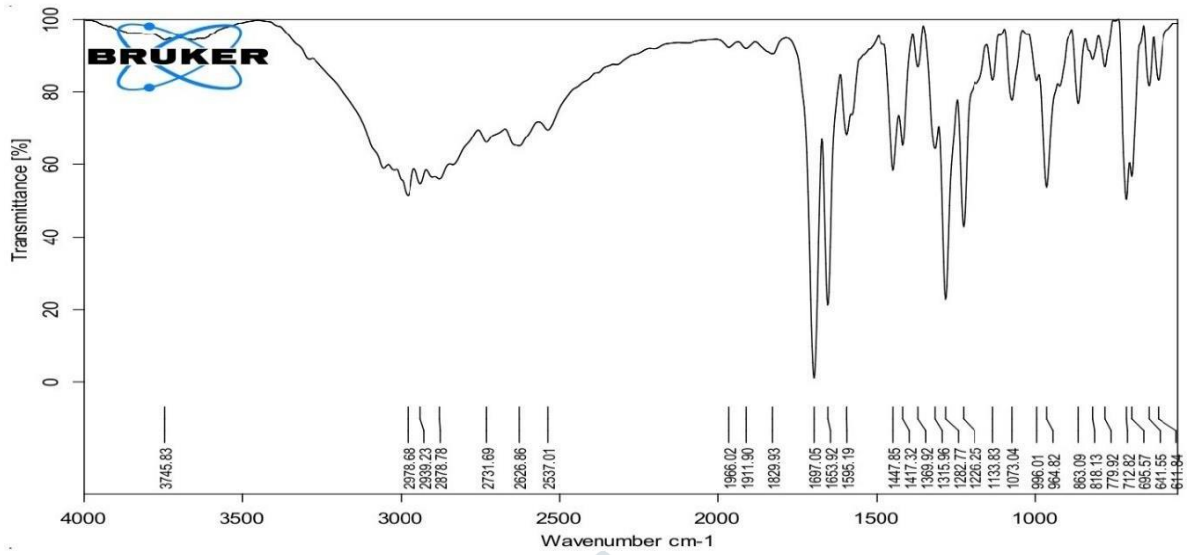

Figure: FTIR Spectrum for Pure Ketoprofen.

UV method for estimation of Ketoprofen:

Determination of λ max:

The UV absorption spectrum of Ketoprofen was determined in the phosphate buffer pH 7.4 as showed in fig. The maximum absorbance of Ketoprofen was observed at 260 nm.

Preparation of pH 7.4:

Preparation of pH 7.4: 2.38 gm of Disodium Hydrogen Phosphate, 0.19 gm of Potassium Dihydrogen Phosphate and 8 gm of Sodium Chloride were weighed accurately and it was diluted up to 1000 ml.[10]

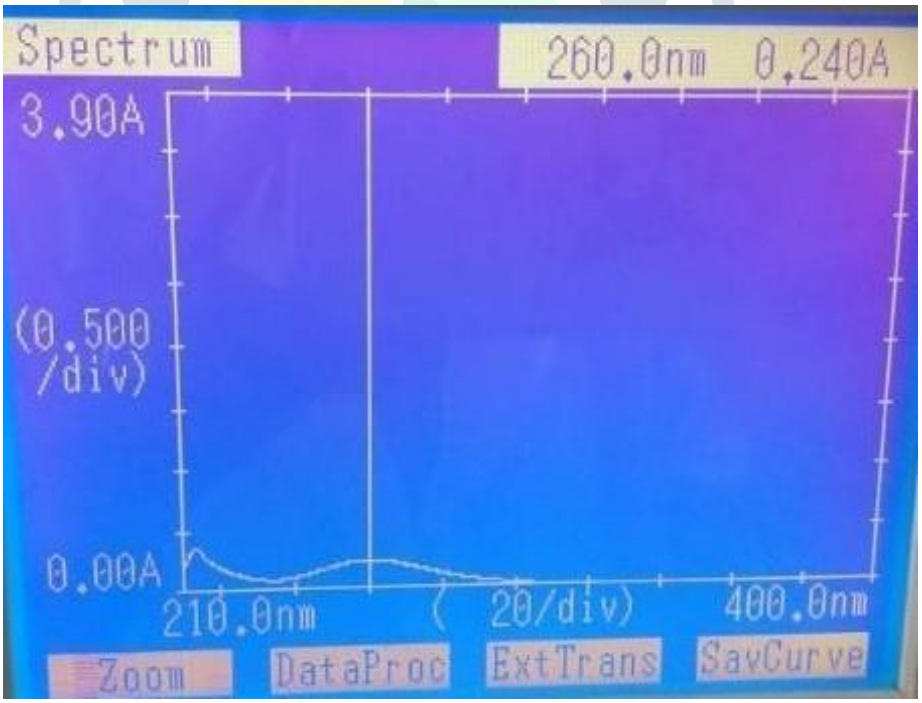

Fig. : Spectrum of Ketoprofen

Calibration curve of Ketoprofen in phosphate buffer pH 7.4:

Sr. No	Concentration (µg/ml)	Absorbance
1.	2	0.201
2.	4	0.307
3.	6	0.412
4.	8	0.511
5.	10	0.602
6.	12	0.727
7.	14	0.802
8.	16	0.917
9.	18	1.012
10.	20	1.129

Table: Calibration curve of Ketoprofen at 260 nm in phosphate buffer pH 7.4.

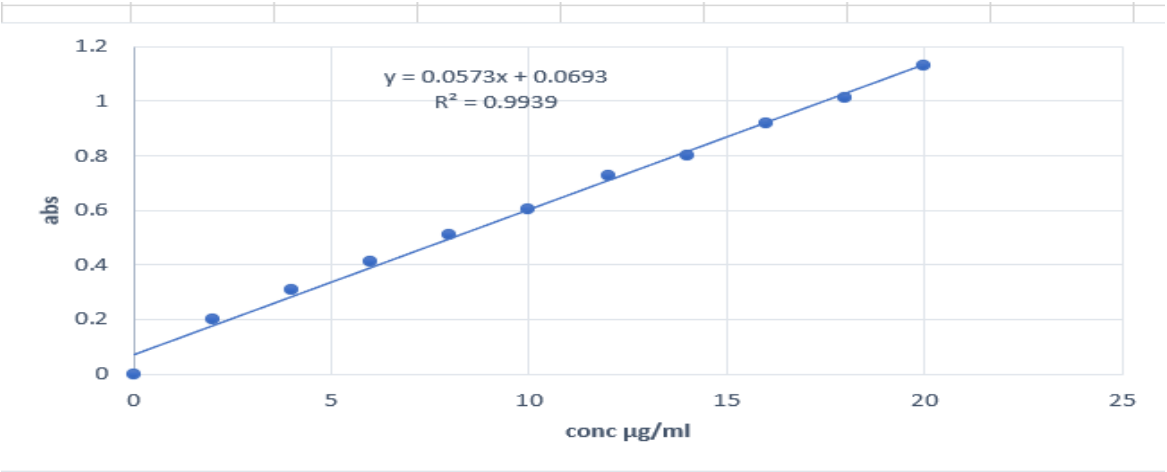

Fig. ; Calibration curve of Ketoprofen at 260 nm in phosphate buffer pH 7.4.

Calibration curve of Ketoprofen in phosphate buffer pH 7.4 was found to be linear in the concentration range 2-20 µg/ml. The slope(m), correlation coefficient(R^2) and intercept(Y) of the calibration curve was showed in fig. The drug concentration range obeys Beers-Lamberts law.

Identification of Gelling agents:

OBM

Phytochemical Tests:

The phytochemical screening of OBM reveals the presence of mucilage, alkaloids and flavonoids. The results found in phytochemical tests of OBM was showed in Table

Test Name	Observation	Inference
Mucilage Test	Red color	Mucilage Present
Mucilage Test	Powder swells	Mucilage Present
Dragendroffs Test	Orange-brown ppt	Alkaloids Present
Shinoda Test	Pink color	Flavonoids Present.

Table : Phytochemical Tests for OBM. Organoleptic

Properties:

OBM powder was found to be white, hygroscopic powder. It has characteristic odor.

Determination of Solubility:

The solubility profile of OBM complies with reported solubility profile of OBM. It was showedin Table

Sr.no.	Solvent	Solubility Profile
1.	Water	Soluble
2.	Ethanol	Insoluble
3.	Chloroform	Insoluble
4.	Acetone	Insoluble

Table :Solubility Profile for OBMSwelling Index

Determination:

The swelling index profile of OBM complies with reported swelling index profile of OBM. It was showed in Table.

Sr.no.	Observed value	Reported value
1.	11.3+0.03%	11.5%

Table :Swelling Index for OBFTIR Analysis:

The FTIR Spectrum analysis of OBM revealed that OBM contains -OH group with intermolecular hydrogen bonding as in polysaccharides with 1-4 glycosidic bonds. This was indicated that chemically OBM belongs to class of Carbohydrates. Besides that, it also shows presence of -OH(Stretching) and -COO- (asymmetric vibrations). It was showed in Figure 9.4.and Table no.9.8. The observed wavenumber was found to be within standard limits that indicates no any impurities present in OBM sample.

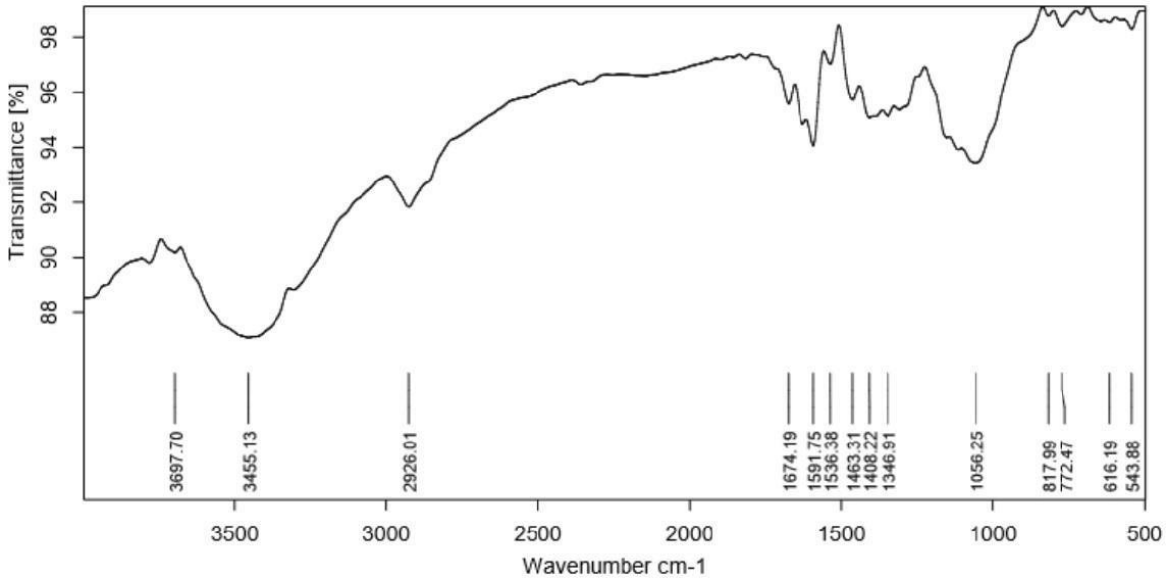

Figure : FTIR Spectrum for OBM.

Functional Groups	Observed frequency values (cm^{-1})	Standard frequency values (cm^{-1})
-OH (Stretching)	3455.13	3500-3100
C-H (Stretching)	2926.01	2500-3000
-COO- (Asymmetric vibrations)	1674.19	1680-1880

Table :FTIR Spectrum Interpretation for OBM.

Evaluation Parameters for Transdermal GelpH Determination:

pH of all prepared gel formulations(F1-F2) were evaluated for pH determination. It was foundin the range of 6.3 to 6.9 which was considered acceptable when compared with pH of marketed gel formulation to avoid the risk of irritation upon application to the skin. It was showed in Table.

Sr.no.	Formulations	Observed pH values
1.	F1	6.3+0.1
2.	F2	6.5+0.1
3.	F3	6.7+0.1
4.	F4	6.9+0.1
5.	Marketed Gel	6.9+0.1

Table :pH Determination of Transdermal Gels. (mean ±SD, n=3)

Viscosity Determination:

Viscosity of all prepared gel formulations (F1-F2) were evaluated for viscosity determination. It was found in the range of 13.1-19.1cp which was considered acceptable when compared withviscosity of marketed gel formulation. The viscosity of gel formulation shows consistency of gel formulation. Increase in gelling agent concentration increases the viscosity of the gel formulation. Among all prepared gel formulations F4 batch containing 1% of OBM as gellingagent shows greater viscosity i.e. 18.8cp it was greater than viscosity of F1, F2 And F3 batches.The results found in viscosity determination of all prepared gel formulations was showed in Table

Sr.no.	Formulations	Observed Viscosity(cp) values
1.	F1	11.4+0.1
2.	F2	13.1+0.1
3.	F3	16.5+0.1
4.	F4	18.8+0.1
5.	Marketed Gel	19.1+0.1

Table :Viscosity Determination of Transdermal Gels. (mean ±SD, n=3)

In-vitro diffusion study:

The all formulated transdermal gel batches (F1-F4) were evaluated for In-vitro diffusion studies in pH 7.4 Phosphate buffer across egg diffusion medium and found results were showed in Table no.9.11. Among all formulated transdermal gel formulations F4 batch (1% OBM) shows higher cumulative % drug release, it was found to be 98.51% within 6 hours as comparedto F1, F2 And F3 batches. The plot of % cumulative drug release from all formulated transdermal gel batches(F1-F4) across egg membrane vs time in minutes were showed in Figure.

Time in min	F1	F2	F3	F4
0	0	0	0	0
30	9.47± 0.02	11.22+0.18	15.2+0.02	18.3+0.01
60	17.54+0.023	20.87+0.01	21.75+0.02	25.6+0.02
120	28.77+0.03	31.05+0.02	33.85+0.01	42.8+0.01
180	47.89+0.02	50.35+0.01	51.05+0.02	59.77+0.01
240	54.03+0.01	70.3+0.01	72.28+0.017	78+0.011
300	70.1+0.02	78.59+0.01	81.15+0.01	88.18+0.01
360	85.78±0.01	89.4±0.01	92.11±0.02	98.51±0.01

Table : In-vitro diffusion study profile for Transdermal gel formulation (F1-F4) batches.(Mean+SD, n=3)

Figure : Plot of %CDR vs Time in min.

Data analysis of release kinetic:

The In-vitro drug release data was analyzed by using various kinetic models as Zero order, firstorder, Higuchi model and Korsmeyer-Peppas model in order to find out the mechanism of drug release. The model that gives higher regression coefficient value was considered as best fit model. The regression coefficient(R2) values for formulations F1-F4 was showed in Table

no. 9.12. The drug release kinetic study data obtained for all formulated transdermal gel batcheswere shown in Figure A, B, C, D.

Formulation batches	**Zero order release kinetic(R^2)**	**First order release kinetic(R^2)**	**Higuchi Model(R^2)**	**Korsmeyer -Peppas Model(R^2)**	**Korsmeyer -Peppas Model (n)**	**Best Fitted Model**
F1	**0.988**	0.717	0.932	0.579	1.24	Zero order
F2	**0.987**	0.645	0.943	0.556	1.24	Zero order
F3	**0.987**	0.655	0.948	0.498	1.17	Zero order
F4	**0.988**	0.619	0.970	0.460	1.14	Zero order

Table : Drug release kinetic study data for Transdermal gel formulation(F1-F4) batches.

%CDR

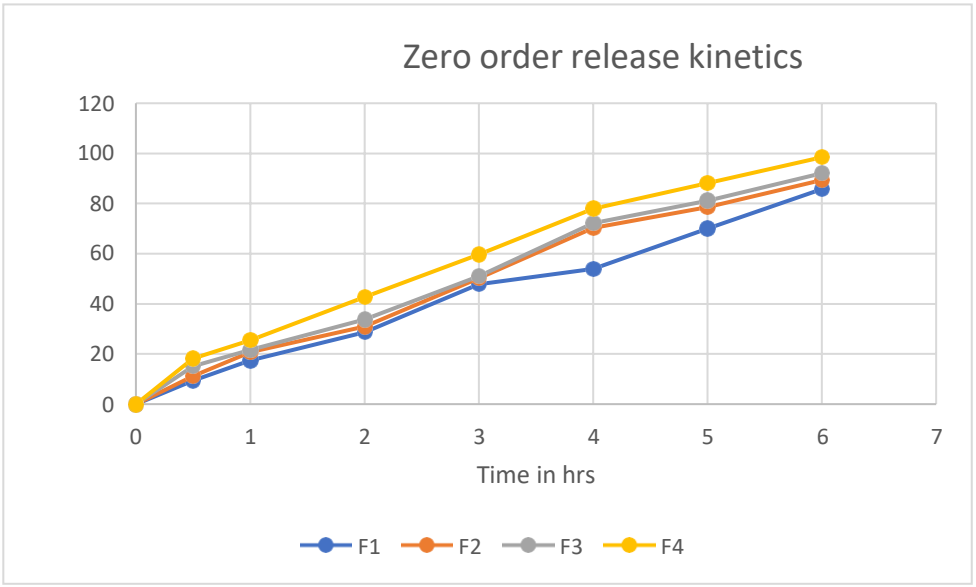

Figure A : Zero order release kinetics for Transdermal gel formulations(F1-F4) batches.

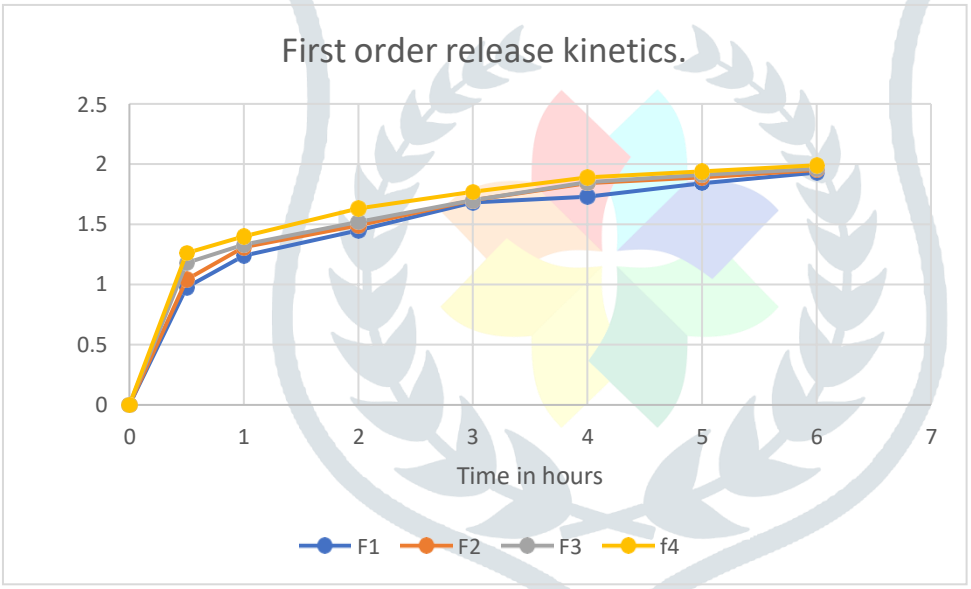

Figure B :First order release kinetics for Transdermal gel formulations(F1-F4) batches.

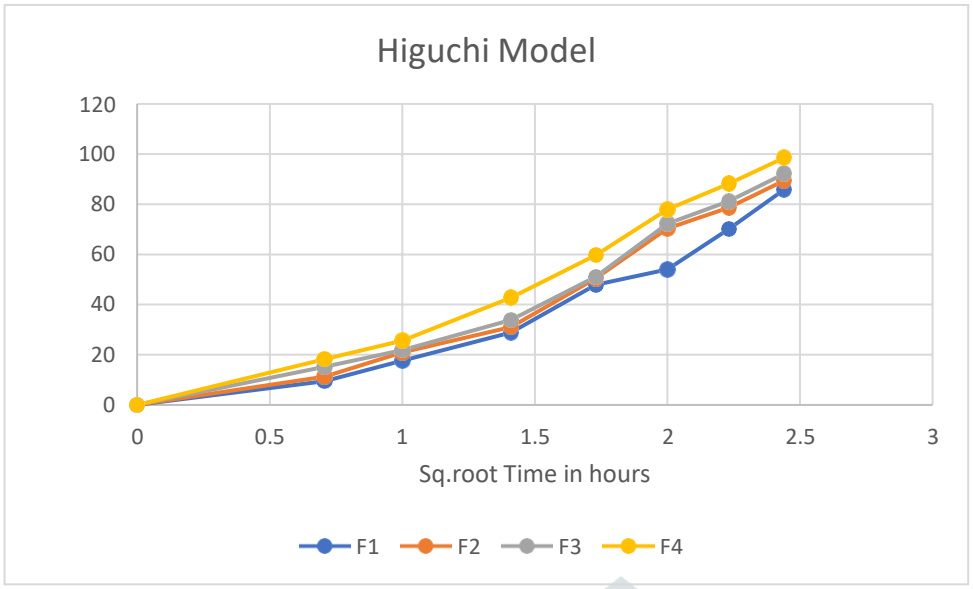

Figure C : Higuchi model for Transdermal gel formulations(F1-F4) batches

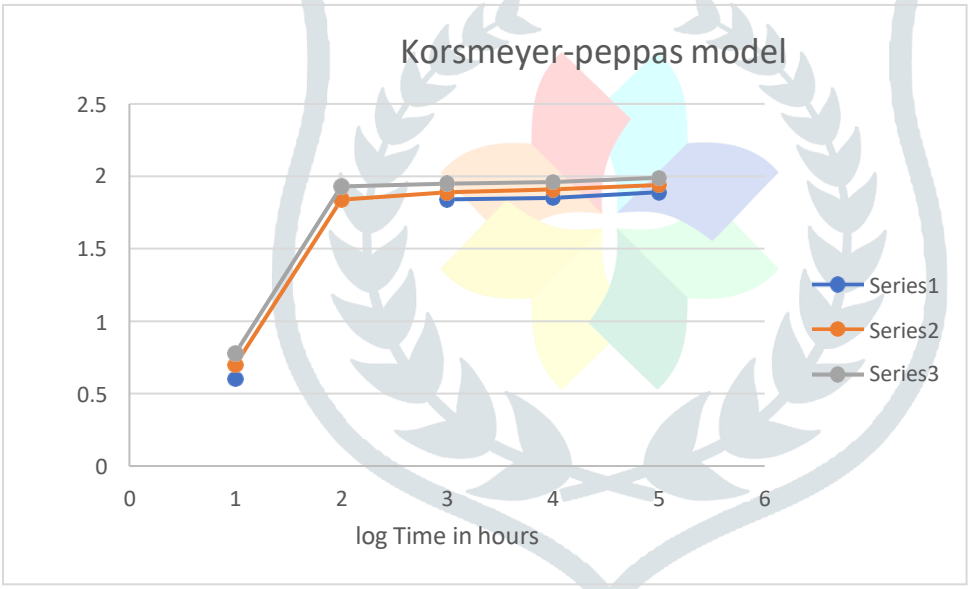

Figure D :Korsmeyer-Peppas model for Transdermal gel formulations(F1-F4) batches.

Statistical Analysis:

Student t- test:

The results obtained from Student t- test was showed in Table P- values less than 0.05indicated that model terms were statistically significant.

Student t- test.	P values obtained	Conclusion
F1 vs F2	0.029	Statistically significant.
F1 vs F3	0.0057	Statistically significant.
F1 vs F4	0.0013	Statistically significant.
F2 vs F3	0.014	Statistically significant.
F2 vs F4	0.0011	Statistically significant.
F3 vs F4	0.0019	Statistically significant.

Table :Statistical analysis.

From the study all above evaluation parameters we concluded that F4 batch showed pH and viscosity values similar to the marketed gel formulation values. Also, F4 batch shows higher
% drug release as compared to other formulated batches (F1, F2, F3). Therefore, we selected

F4 batch as an optimized batch and taken this for further evaluation studies.

In-vitro skin irritation study:HET-CAM Test

In the present work In-vitro skin irritation method (HET-CAM) were used to skin irritation study of optimized transdermal gel formulation batch (F4). The formulated transdermal gel formulation was found to be free from irritation. The result found in In-vitro skin irritation study was showed in Table and Figure.

Formulation Batch	**Parameters**	**Observation**	**Inference**
F4	Hemorrhage	No red blood dots around vessels.	No irritation
F4	Lysis	No disappearance of small blood vessels in CAM.	No irritation
F4	Coagulation	No dark spot, No denaturation of albumin.	No irritation

Table : In-vitro skin irritation study profile.

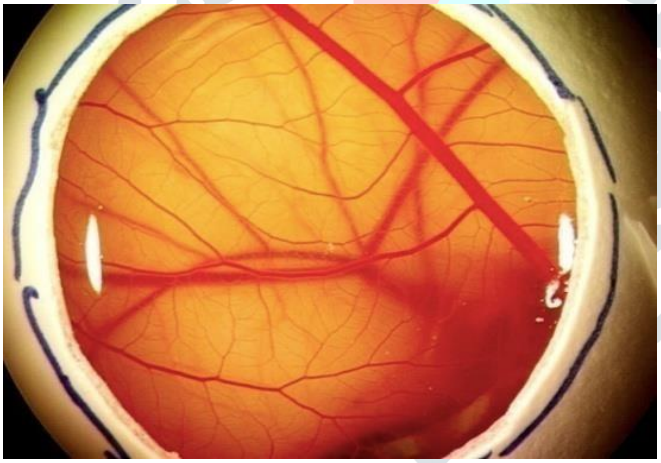

Figure : Skin irritation study.

Stability study:

The optimized transdermal gel formulation batch (F4) was kept for stability studies there was no significant change observed in appearance, pH, viscosity and drug diffusion at room temperature. The stability study revealed that the formulated transdermal gel formulation was

stable at room temperature for at least 15 days. The results found in stability studies wasshowed in Table.

Formulation batch	Day	Appearance	pH	Viscosity(cp)	%CDR
F4	1	Homogenous	6.9±0.1	18.8±0.1	98.33±0.01
F4	5	Homogenous	6.9±0.1	18.8±0.1	98.31±0.01
F4	10	Homogenous	6.9±0.1	18.8±0.1	98.22±0.01
F4	15	Homogenous	6.9±0.1	18.8±0.1	98.19±0.01

Table : Stability study. (mean ±SD, n=3)

CONCLUSION:

From the present study the following conclusions can be drawn:

The ketoprofen sample was successfully characterized for Melting point, Solubility.The natural gelling agent (OBM) was successfully isolated and characterized for Phytochemical tests, Solubility, Swelling index.The transdermal gels of Ketoprofen were successfully formulated using Dispersion method.The prepared transdermal gel formulations were evaluated for parameters as pH, Viscosity, In- vitro diffusion study, In-vitro skin irritation study, Stability study.Amongst all formulations, transdermal gel with 1% OBM as gelling agent i.e. F4 batch was better with respect to overall product qualities.When formulated transdermal gels were compared with marketed gel, its pH and viscosity wasfound to be acceptable.In-vitro drug diffusion study was performed in Phosphate buffer pH 7.4 for 6 hours. % cumulative drug release was found in a range of 85.78% to 98.51% from all the formulations at the end of 6 hours in a controlled manner. From in- vitro diffusion studies of transdermal gels were showed the drug release by Zero order release kinetic because it showed greater R^2 values as compared to R^2 values of other 3 models.The formulated transdermal gel showed no irritation after performing In-vitro skin irritation study by using HET-CAM.The optimized transdermal gel formulation batch (F4) was kept for stability studies there was no significant change observed in appearance, pH, viscosity and drug diffusion at room temperature. The stability study revealed that the formulated transdermal gel formulation wasstable at room temperature for at least 15 days.Thus, results of the present study clearly indicate that transdermal gel can be a good alternative to the conventional dosage form. However, further clinical studies were needed to access the utility of this formulation.

By considering all above points it was concluded that, the objectives of present research studywere achieved.

REFERENCES:

1. Chien YW, Novel Drug Delivery Systems. Marcel Dekker Inc. New York 1992, 2nd Edn:499.
2. Tortora Gerard J, Reynolds Grabowski Sandra, Principles of anatomy and physiology, Canada: John Wiley and Sons,2000,9th Edn: 140-151.
3. Jain NK, Controlled and Novel Drug Delivery Systems, CBS Publications, New Delhi 1997, 1st Edn:110-115.
4. Hsiesh D. Drug Permeation Enhancement Theory and Application: In Drug and the Pharmaceutical Sciences, New York, Marcel Dekker,1987,13.
5. Aulton ME. Pharmaceutics the science of dosage form design.2nd edition, Churchill Livingstone: Elsevier;2007,501-522.
6. Ranade VV, Hollinger AM. Drug delivery systems.2nd edition, CRS Press:2010,214.
7. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy.3rd edition, Varghese Publishing House, Mumbai:1991,502-508.
8. Ansel CH, Popovich GN, Allen VL. Pharmaceutical dosage forms and drug delivery system,9th edition, Lippincott Williams and Wilkins:2011,395,405,407.
9. Verma N, Deshwal S. Design and In-vitro Evaluation of Transdermal Patch containing Ketoprofen. World J.Pharm.Res.2014,3(3):3930-3944.
10. Vyas SP, Khar RK, Controlled Drug Delivery (Concepts and Advances), 2002, 1st Edn:411-444.
11. Cooper and Gunn, Disperse Systems In: Carter SJ editor, Tutorial Pharmacy, CBS Publishers and Distributors,2000:68-72.
12. Goyal S, Sharma P, Novel Anti-inflammatory Topical Gels containing Withania somnifera and Boswellia serrata. Int. J. Pharm. Bio. Arch.2011, 2(4):1087-1094.
13. Mehta R, Topical and Transdermal Drug Delivery: What a Pharmacists Needs to know,2004:146-221.
14. Darshan K, A Novel Approach: Transdermal Gel. Int.J. Pharm. Res. Rev, 2015, 4(10):41-50.
15. Gupta S, Organogels: A viable alternative for existing carrier system, Int. J. Clin. Pharm.2004: 1-4.
16. Zatz JL, Kushla GP, Liberman HA, Bankar GS, Pharmaceutical Dosage Form: Disperse System. Marcel Dekker Inc. New York, 2005, 2nd Edn:399-421.
17. Compounding Gelling Agents 1996[http:// pharmlabs.unc.edu/ labs/ gels/ agents.htm].
18. Shingade et al, Review on: Recent trend on Transdermal Drug Delivery System, Journal of Drug Delivery and Therapeutics, 2012,2(1): 66-75.
19. Langer R, Transdermal drug delivery: Past progress, current status and future prospects, Adv. Drug. Dev. Rev.2004,56: 557-558.
20. Keleb E, Sharma R, Transdermal Drug Delivery System-Design and Evaluation, Int.J. Adv. Pharm. Sci. 2010:201-211.
21. Loyd Allen. Transdermal skin as a part of drug delivery system. Int. J. Pharm.Comp.2010,13(5): 403-415.
22. Loyd VA, Ansel's Pharmaceutical Dosage Forms and Drug Delivery System, Philadelphia: Lippincott Williams and Willans, 9th Edn, 2011.
23. Ofner CM, Encyclopedia of Pharmaceutical Technology, *Informa Healthcare*,2007:1875-1890.
24. Indian Pharmacopeia. Government of India Ministry of Health and Family Welfare. Ghaziabad. The Indian Pharmacopoeia Commission. 2010; (2):717-719.
25. Bhoyar, Recent advances in novel drug delivery system through gels: a review, J. Pharm. Allied Health Sci.2012,2(2):21-39.
26. Adrian Williams C, Transdermal and Topical Drug Delivery, New York, Pharmaceutical Press,2003:30-33.
27. Darshan Kaur, A Novel Approach: Transdermal Gel, Int.J. Pharm. Res. Rev.2015,4(10):41-50.
28. Padma, Transdermal drug delivery system influencing factors, study methods and therapeutic application, Int.J. Pharm,2012,2(2):366-374.
29. Karande, Formulation and Evaluation of Celecoxib Gel, Journal of Drug Delivery and Therapeutics,2012,2(3):132-135.
30. Kaur LP, Development and Evaluation of topical gel of Minoxidil from different polymer bases in application of alopecia, Int. J. Pharm. Pharm. Sci.2010,2(3):43-47.
31. William L, Remington, The Science and Practice of Pharmacy, Mack Publisher, Easton PA, 20th Edn.
32. Gupta GD, Gaund RS, Release rate of Nimesulide from different gallants, Indian J Pharm Sci.1999,61:227-230.
33. Raymond CR, Paul JS. Handbook of Pharmaceutical Excipients,6th edition: Pharmaceutical

press:2006,64-785.
34. www.drugbank/drugs/DBO1009.
35. en.wikipedia.org/wiki/Ketoprofen.
36. Mohsin J. Formulation and Evaluation of Herbal Gel Formulation J. Pharm.Res.Edu,2017,1(2):201-224.
37. Baratam S, Preparation and Characterization of Sustained Release Dosage Form of Ketoprofen using Natural Gums. Int. J. Pharm. Investigations 2020,10(1):54-58.
38. Reddy M, Formulation and Evaluation of Sustained Release Tablets of Repaglinide using Hydrophilic Natural and Synthetic Polymers, Int. J. Pharm.Sci.Res.2018,9(7):2914-2920.
39. Ramchandani U, Sangameswaran Formulation and Evaluation of Topical Gel of Ketoprofen Using Different Polymer. Int.J. Pharm.Bio. sarchive.2013,4(2):323-326.
40. Satyabrata, Kumar. Formulation and Evaluation of Diclofenac Transdermal Gel. J. Adv. Pharm. Edu & Res.2013,3(3):248-259.
41. Rasool A, Khan S. Development and Evaluation of Ibuprofen Transdermal Gel Formulations. J. Pharm Res.2010,9(4):355-363.
42. Patel Z, Shah R. Formulation and Development of Ketoprofen Nanoemulsion As A Carrier for Topical Delivery. World J.Pharm.Sci.2016,5(7):786-802.
43. Pathan I, Ambekar R. Formulation and evaluation of Ketoprofen loaded chitosan nanogel for pain management: Ex-vivo and In-vivo study. Ars.Pharm:2019,60(2):101-108.
44. Mishra K, Bhanja S. Development and Evaluation of Nanoemulsion Gel for Transdermal Delivery of Ketoprofen, Int.J.Pharm.Sci.2019,56(2):10-21.
45. Soumen P, Puranik S. Formulation and Evaluation of Ketoprofen loaded Nanoparticulate Gel for Topical Delivery, Int. J. Pharm.Res. Human2018, 1(3):250-260.
46. Ozguney, Guneri. Transdermal delivery of Diclofenac sodium through rat skin from various formulations, App.Pharm. Sci.Tech,2006,7(4):11-16.
47. Thakare VM. Formulation and Characterization of Ketoprofen Topical Gel, Int. J. Current. Pharm. Clin. Res.2014,4(10):35-42.
48. Patil MP, Nikumbh KV Formulation development in vitro and in vivo evaluation of microemulsion based gel loaded with Ketoprofen, J Drug Delivery,2015,22(4):509-515.
49. Sang Cheol chin, H. Won Jun. Anti-inflammatory activity of Ketoprofen gel on Carrageenan Induced Paw Edema in Rats, J. Pharm.Sci.1990,79(11):974-977.
50. Patel RK. Comparison of Ketoprofen, piroxicam and diclofenac gel in the treatment of soft tissue injury in general practice, Clinical therapeutics,1996,18(33):497-507.
51. Gbaj AM, Sadawe AA. Comparing the Physicochemical and Pharmaceutical Properties of Brand name and Generic Ketoprofen Gel Products, Current Trends in Pharmacologicaland Clinical Trials,2019,2(2):1-7.
52. Mohammed A. Topical ketoprofen nanogel: artificial neural network optimization, clustered bootstrap validation and in-vivo activity evaluation based on longitudinal dose response modeling, J. Drug Delivery,2016,23(9):3294-3306.
53. Bempong DK Development and validation of a stability indicating HPLC assay for KPF topical penetrating gel, J. Chromatogram A,2005,1073(2):341-346.
54. Sowjanya P, Kumar R. Formulation and In-vitro Evaluation of Transdermal Gel containing Ketoprofen Silver Nanoparticles, Indo American Journal of Pharmaceutical Sciences,2018,5(5):4625-4631.
55. Bhanja S, Das AK. Formulation and Evaluation of Diclofenac Transdermal Gel, J. Adv. Pharm. Edu. Res.2013,3(3):248-252.
56. Mahaparale S, Gaikwad A. Formulation and Evaluation a Novel Non-Steroidal Anti- inflammatory Zaltoprofen Gel, World J. Pharm. Pharm. Sci.2016, 5(7):3127-3135.