Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL10, ISSUE 04, 2019

Preformulation Study of Ketoprofen for Transdermal Drug Delivery System

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ABSTRACT

PURPOSE: Preformulation study of ketoprofen for transdermal therapeutic systems.

METHODS: Identification of drug by organoleptic property, identification of drug by U.V. spectroscopy for determination of λ-max, identification of drug by fourier transform spectroscopy, solubility determination, partition coefficient, particle size, Melting Point, standard curve of Ketoprofen in methanol, standard curve of ketoprofen in phosphate buffer pH 7.4

RESULTS: The λ max of ketoprofen was found at 258 nm, which is comparatively same as given in I.P. This shows that the drug is pure. Results of qualitative solubility studies show that the ketoprofen is soluble in organic solvent and insoluble in water. So it is hydrophobic in nature. Quantitative solubility studies shown that ketoprofen is more soluble in methanol as compared to other solvents. The partition coefficient was found to be 3.47, which is suitable for transdermal drug delivery, the obtained value of partition coefficient of ketoprofen was more than 1 which showed that the ketoprofen is lipophilic in nature . The average particle size of ketoprofen was measured by microscopy method was found to be 2.2696 micrometer which is effective for better absorption through transdermal route. The melting point was observed at 90 ^{0}C, it shows the drug is crystalline & pure. The standard curve of ketoprofen was prepared in phosphate buffer 7.4 and in methanol, the r^2 values was obtained 0.9995 and 0.9941 respectively, which shows linearity of absorbance between the range of 2-14 ug /ml.

CONCLUSION: Oral therapy of Non-steroidal anti-inflammatory drugs is very effective, but the clinical use is often limited because of adverse effect such as irritation and ulceration of the gastrointestinal tract. Any drug for its permeation through skin should be potent, must be lipophilic as well as hydrophilic in nature, optimum partition coefficient etc, this prompted us to carryout the present study. The preformulation study for the ketoprofen was conducted. The preformulation study of ketoprofen showed satisfactorily results to select the drug for transdermal drug delivery system. Therefore, transdermal drug delivery has been considered to be an ideal route for administration of NSAIDs.

Key words: Transdermal, ketoprofen, NSAIDs and rheumatoid arthritis.

Novelty of work: Preformulation study of Ketoprofen was carried out by using different methods to determine properties of drug are suitable for transdermal drug delivery system.

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INTRODUCTION

Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrants evaluation in man. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. A through understanding of these properties may ultimately provide a rational for formulation design, or support the need for molecular modification[1]. The skin is too good barrier to permit the delivery of all but a few compounds and that transdermal transport is not even worth the consideration for new drugs of the biotechnology industry. This has however been disputed as today TDD is a well-accepted means of delivering many drugs to the systemic circulation in order to achieve a desired pharmacological outcome. Clearly, the clinical benefits, industrial interest, strong market and regulatory precedence show why TDD has become a successful and viable dosage form. The smallest drug molecule presently formulated in a patch is nicotine (162 Da) and the largest is oxybutinin (359 Da). Opening the transdermal route to large hydrophilic drugs is one of the major challenges in the field of TDD. Anatomically, the skin has many histologic layers but in general, it is described in terms of three major tissue layers: the epidermis, the dermis and the hypodermis. The outermost layer, the epidermis, is approximately 100 to 150 micrometers thick, has no blood flow and includes a layer within it known as the stratum corneum. Stratum corneum is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out[2].

Transdermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at controlled rate to systemic circulation. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body. If the drug is able to penetrate the stratum corneum, it can enter the blood stream thus stratum corneum is rate limiting step for permeation of transdermal preparation. Substances with both aqueous and lipid solubility characteristics are good candidates for diffusion through the stratum corneum, epidermis, and dermis (fig 1.1). The stratum corneum being keratinized tissue, behaves as a semipermeable artificial membrane, and drug molecules penetrate by passive diffusion[3].

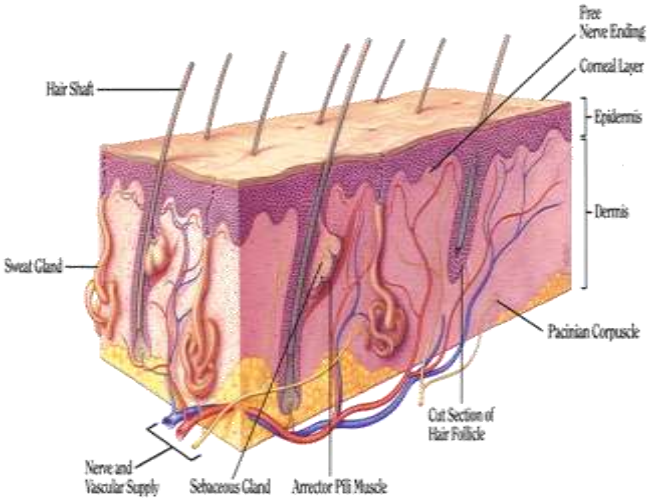

Fig 1.1 Cross-sectional view of human skin

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Advantages of Transdermal drug delivery system

- Provide for multiple daily doses with a single application.
- Provide a means to quickly terminate dosing.
- Provide improved systemic bioavailability of active ingredients.
- Sustains therapeutic drug levels.
- Permits self-administration.
- Non-invasive (no needles or injections).
- Bypasses the first pass metabolism, avoids inactivation of drugs by pH effects and enzymes present in GI tract, which otherwise happens on oral administration

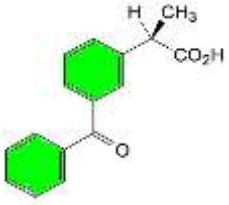
Disadvantages of Transdermal drug delivery system

- The drug must have desirable physico-chemical properties to penetrate the stratum corneum. The drug that requires high blood levels cannot be administered.
- Skin irritation or contact dermatitis due to use of drugs, excipients, enhancers and adhesives used.
- The adhesives may not adhere well to all types of skin[4].

Drug Profile of Ketoprofen

Ketoprofen is an effective non-steroidal anti-inflammatory drug, used as analgesic, anti-inflammatory and antipyretic and in the treatment of rheumatoid arthritis and osteoarthritis. Though rapidly absorbed following oral administration, it undergoes significant first-pass metabolism. Its half-life is about 1.8 ± 0.3hrs. These properties make ketoprofen as a model drug for exploring its application as transdermal drug delivery system. It is chemically, RS-2-(3-benzoyl phenyl) propionic acid (Table 1.1).

Table 1.1 Drug profile of ketoprofen[8]

S.NO.	Parameters	Properties
1.	Structural formula	
2.	Molecular formula	$C_{16}H_{14}O_3$
3.	Molecular weight	254.29
4.	Melting point	93 -96^{o}C
5.	Description	White or almost white crystalline powder odourless.

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6.	Solubility	Freely soluble in ethanol (95%), chloroform, ether, methanol and practically insoluble in water.
7.	Category	Analgesic and anti-inflammatory
8.	Storage	Stored in tight containers

i) Mechanism of action:

During inflammation, pain and fever, arachidonic acid is liberated from phospholipids fraction of cell membrane. Arachidonic acid is then converted by enzymes cyclooxygenase and lipoxygenase to prostaglandins, bradykinins, leukitrienes etc. These are the chemical mediators responsible for the pain, inflammation, and fever. Ketoprofen mainly acts by inhibiting the action of both enzymes cyclooxygenase and lipoxygenase.

ii) Absorption, fate and excretion:

Ketoprofen is rapidly absorbed after oral administration and maximal concentration in plasma is achieved within one to two hours (Table 1.2). Food reduces the rate and not the extent of absorption. The drug is extensively bound to plasma proteins and slightly longer half-lives are observed in elderly subjects. Ketoprofen is conjugated with glucuronic acid and the conjugate is excreted in urine. Patients with impaired renal function eliminate the drug more slowly.

Table 1.2 Pharmacokinetic parameter of ketoprofen [2]

S.NO.	Parameters	Description
1.	Oral bioavailability :	100%
2.	Peak plasma concentration :	0.5 – 2 hrs
3.	Volume of distribution :	0.1 – 0.2 L/kg
4.	Clearance :	Plasma clearance about 1 – 2 ml/min/kg
5.	Dose	50 – 100 mg twice daily
6.	Half-life	2 hrs
7.	Protein binding	99%
8.	Onset	30 min

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iii) Adverse effects:
The adverse effects of ketoprofen are abdominal pain, changes in kidney function, constipation, diarrhea, fluid retention, headache, insomnia, nausea and nervousness.

iv) Contraindications:
- Allergy to aspirin or non steroidal anti-inflammatory drugs
- Bleeding or blood cell disorder
- History of ulcer disease
- Severe impairment of kidney function

v) Uses:
Ketoprofen is used for musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. Also used in treatment of migraine headaches and prophylaxis. It is used for postoperative pain, painful and inflammatory conditions such as acute gout or soft tissue disorders and to reduce fever. It is widely used in gynecological conditions which involve the management of dysmenorrheal following intra-uterine device (IUD) insertion and for uterine relaxation and analgesia in post-partum, non-nursing women. It is also indicated for the management of acute painful shoulder syndrome and rheumatoid arthritis. It is used as analgesic, anti-inflammatory and antipyretic actions[5,6,7].

Preparation of Phosphate buffer pH 7.4
Dissolved 2.38 gm of disodium hydrogen phosphate, 0.19 gm of potassium di-hydrogen phosphate and 8 gm of sodium chloride in sufficient distilled water to produce 1000 ml. The pH of the buffer was adjusted to 7.4[8].

EXPERIMENTAL DETAILS
Material:
- **Chemicals:** The list of material & suppliers name are shown in Table 1.3
- **Glassware:** Beaker, volumetric flask, glass rod, conical flask, funnel, pipette, measuring cylinder, separating funnel, slides, test tubes, capillary etc.
- **Equipment:** Table 1.4 enlists the equipments and suppliers name.

Table 1.3 Material and Supplier name

S. NO.	Material	Supplier Name
1.	Ketoprofen	Ranbaxy Lab Ltd
2.	Methanol	Merck
3.	Acetone	SDFCL
4.	Carbon tetra chloride	SDFCL

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5.	Chloroform	SDFCL
6.	Ethanol	Jigansu Huaxi International Ltd
7.	Potassium di hydrogen phosphate	Sunchem
8.	Di sodium hydrogen phosphate	Merck
9.	Sodium chloride	Merck
10.	n-octanol	Triza
11.	Liquid paraffin	SDFCL

Table 1.4 Equipments and Supplier Name

S.NO.	Equipments	Supplier name
1.	UV/VIS Double beam Spectrophotometer	Shimadzu 1601 – Double beam UV/VIS
2.	pH meter	MK VI
3.	Electronic Balance	Contech
4.	Optical Microscope	Labomed
5.	Melting point Apparatus	Rolex
6.	Dessicator	SD company
7.	Dona Balance	Dhona Instrument Ltd

Methods for Preformulation studies of Ketoprofen:

a) Identification of drug[9]

i) Identification of drug by organoleptic property: Ketoprofen was identified on the basis of color, crystallinity, taste and odor.

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ii) Identification of drug by U.V. spectroscopy for determination of λ-max: 100 mg of ketoprofen was dissolved in 100ml (75%) of methanol and, prepared solution of 0.001%w/v. suitable dilutions were made and finally scanned for maximum absorbance using double beam in the U.V. range from 230 to 360 nm. Average of triplicate readings was taken.

b) Solubility determination[10]

i) Qualitative: 10 mg of drug dissolved in 10 ml of solvent to detect the solubility of drug in the different solvents. The different solvents used for the solubility determination are methanol, ethanol, acetone, chloroform, hexane, octanol, pH 7.4 buffer, water etc.

ii) Quantitative: Excess amount of the selected drug was taken and dissolved in a measured amount of above solvents separately in a glass beaker to get a saturated solution. The solution was shaken intermittently to assist the attainment of equilibrium with the undissolved drug particles. Then measured quantity of the filtered drug solution was withdrawn after 24hrs and successively diluted with respective solvents and the concentration was measured spectrophotometrically. Average of triplicate readings was taken.

c) Partition coefficient[10]

A drug solution of 1mg/ml was prepared in n-octanol. 25ml of this solution was taken in a separating funnel and shaken with an equal volume of phosphate buffer of pH 7.4 (aqueous phase) for 10 minutes and allowed to stand for two hrs. Then aqueous phase and organic phase were collected separately and centrifuged at 2000 rpm. Both the phases were analyzed for the drug concentration using U.V. spectrophotometer. Partition coefficient was calculated by taking the ratio of the drug concentration in n-octanol to drug concentration in aqueous phase. Triplicate readings were taken.

$$P_{o/w} = C_{oil}/C_{water}$$

d) Particle size[10]

i) Calibration of eyepiece: Use standard stage micrometer to calibrate the eyepiece micrometer and calculate for the least count (1 eye piece division)

Least count = No. of stage division/No. of eye piece div x 10.

ii) Mounting of the sample: Transfer a small portion of the given sample on clean slide and disperse it uniformly and place the slide on the stage of microscope.

iii) Measurement of particle size: Focus the slide in low magnification (10x). Observe the particles than shift to high power (45x) and focus the slide. Measure the size of each particle in terms of eyepiece divisions. A total of 100 particles should be considered. Tabulate the particles in terms of division of eyepiece and no. of particles (frequency) obtained above. Classify the diameter into size ranges and average frequency of particles in terms of no. distribution.

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e) Melting point determination[10]

Melting point of the drug was determined by taking a small amount of the drug in a capillary tube closed at one end and was placed in Thiel's melting point apparatus and the temperature at which the drug melts was noted. Average of triplicate readings was taken.

f) Standard graph of ketoprofen in methanol[11]

100mg of ketoprofen was accurately weighed and dissolved in methanol in a 100 ml volumetric flask and the volume was made upto the mark using methanol. The above prepared solution of ketoprofen was subsequently diluted with methanol to get 2, 4, 6, 8, 10, 12 µg per ml of the final solution. Then the absorbance was measured by spectrophotometer at 258nm using methanol as blank. Average of triplicate readings was taken.

g) Standard graph of ketoprofen in phosphate buffer pH 7.4[11]

100mg of ketoprofen was accurately weighed and dissolved in phosphate buffer solution pH 7.4 in a 100 ml volumetric flask and the volume was made up to the mark using same solvent. The above prepared solution of ketoprofen was subsequently diluted with phosphate buffer solution pH 7.4 to get 2, 4, 6, 8, 10, 12 µg per ml of the final solution. Then the absorbance was measured by spectrophotometer at 261nm. Average of triplicate readings was taken.

RESULT

Preformulation studies

a) Identification of drug:

i) Identification of drug by organoleptic properties: Result obtained from organoleptic properties of was ketoprofen shown in Table 1.5.

Table 1.5 Organoleptic properties of Ketoprofen

S.No.	Parameter	Description
i)	Color	White or almost white
ii)	Crystallinity	Crystalline powder
iii)	Taste	Bitter
iv)	Odor	Almost odorless

ii) Identification of drug by ultraviolet spectroscopy: The λ-max of ketoprofen was obtained by using double beam ultra violet spectroscopy in the range of 230-360 nm. The maximum peak was observed at 258 nm shown in fig. 1.2, which is same as reported in I.P. This shows that the drug is pure.

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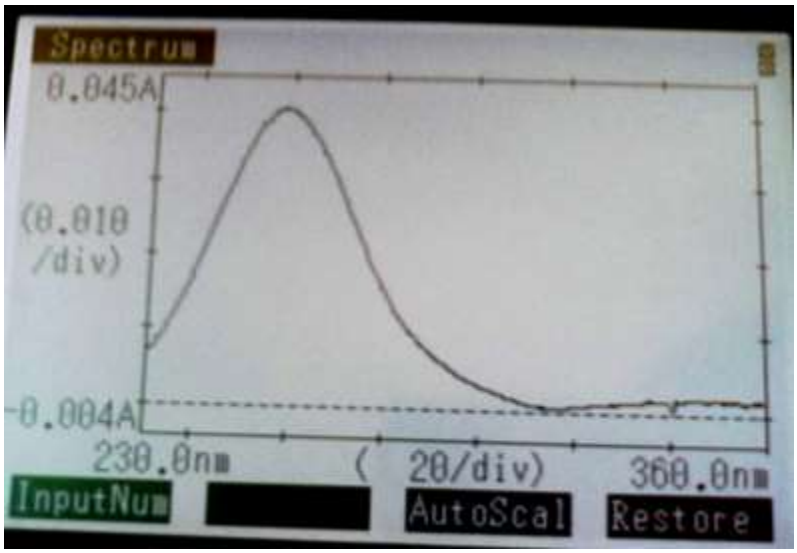

Fig 1.2 λ-max of ketoprofen

b) Solubility determination: It was found that ketoprofen was soluble in most of the organic solvent and insoluble in water is shown in Table 1.6, so it is hydrophobic in nature. Quantitative solubility studies showed that Ketoprofen is more soluble in methanol as compared to other solvents.

Table 1.6 Solubility of ketoprofen

S.No.	Parameter	Description
i)	Qualitative	Insoluble in water. Freely soluble in ethanol (95 %), methanol, chloroform, acetone, pH 7.4 buffer, carbon tetra chloride.
ii) a) b) c) d) e)	Quantitative Water Phosphate buffer pH 7.4 Chloroform Acetone	 2.72 mg in 5ml water. 41.79 mg in 5ml phosphate buffer P^H 7.4 79.32 mg in 5 ml chloroform 455 mg in 5 ml acetone 630 mg in 5 ml ethanol

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f)	Ethanol	649 mg in 5 ml methanol
g)	Methanol Carbon tetra-chloride	53.55 mg in carbon tetra chloride

c) Partition co-efficient: The partition coefficient of ketoprofen in n-octanol/pbs 7.4 was found to be 3.47 i.e. more than 1 which showed that the ketoprofen is lipophilic in nature. The obtained value of partition coefficient is suitable for transdermal drug delivery. .

d) Particle size: The least count was calculated i.e. 1.351 micrometer. The particle size of the ketoprofen was found to be 2.2696 micrometer is given in Table 1.7 & fig.1.3. Particle size under this range provides better absorption of drug via transdermal route.

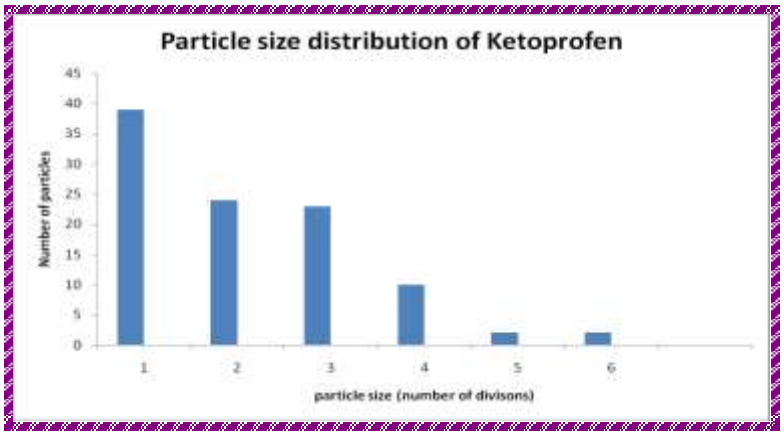

Fig 1.3 Particle size distribution of ketoprofen

Table 1.7 Particle size of ketoprofen

S. No.	Size range	Mid Point (d)	No. of Particles (n)	n*d
1.	0-1	0.5	39	19.5
2.	1-2	1.5	24	36
3.	2-3	2.5	23	57.5
4.	3-4	3.5	10	35
5.	4-5	4.5	2	9

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6.	5-6	5.5	2	11
			Σ =100	Σ =168

e) Melting Point: The melting point of ketoprofen was obtained by Thiels melting point apparatus. The melting point was observed from 90^0C which is approximately same as I.P.1996; it shows the drug is crystalline & pure.

f) Standard curve of Ketoprofen in methanol: The standard curve of Ketoprofen was prepared in methanol shown in Table 1.8 & fig 1.4. The r^2 values were obtained 0.9941 which shows linearity of absorbance between the range of 2-14 ug /ml.

Table 1.8 Data for standard curve of ketoprofen in methanol

S.NO.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.068
3.	4	0.185
4.	6	0.319
5.	8	0.467
6.	10	0.599
7.	12	0.743
8.	14	0.879

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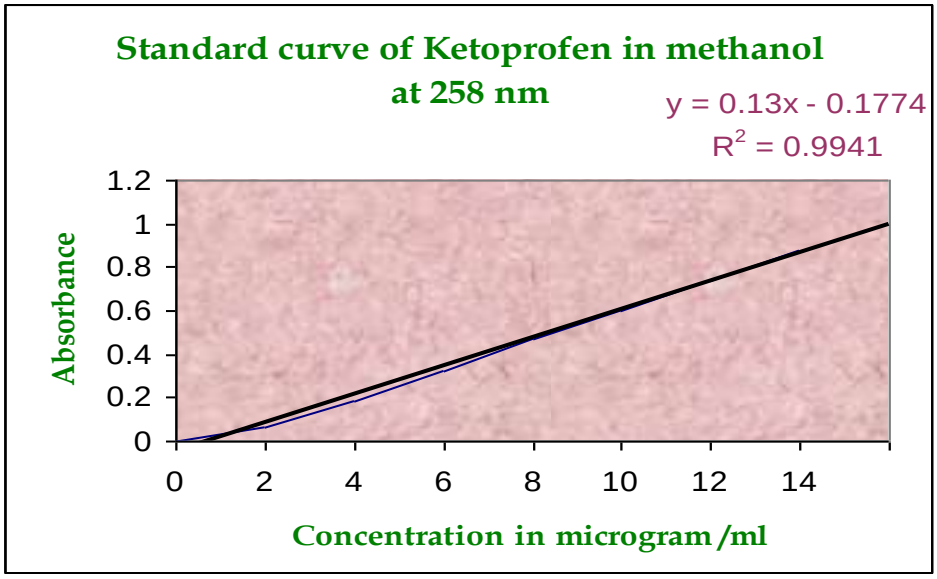

Fig 1.4 Standard curve of Ketoprofen in methanol

g) Standard curve of ketoprofen in phosphate buffer 7.4: The standard curve of Ketoprofen was prepared in phosphate buffer 7.4 shown in Table 1.9 & fig 1.5. The r^2 values were obtained 0.9995 which shows linearity of absorbance between the range of 2-12 µg /ml.

Table 1.9 Data for standard curve of ketoprofen in phosphate buffer pH 7.4

S.NO.	Concentration (µg /ml)	Absorbance
1.	0	0
2.	2	0.190
3.	4	0.377
4.	6	0.536
5.	8	0.721
6.	10	0.885
7.	12	1.072

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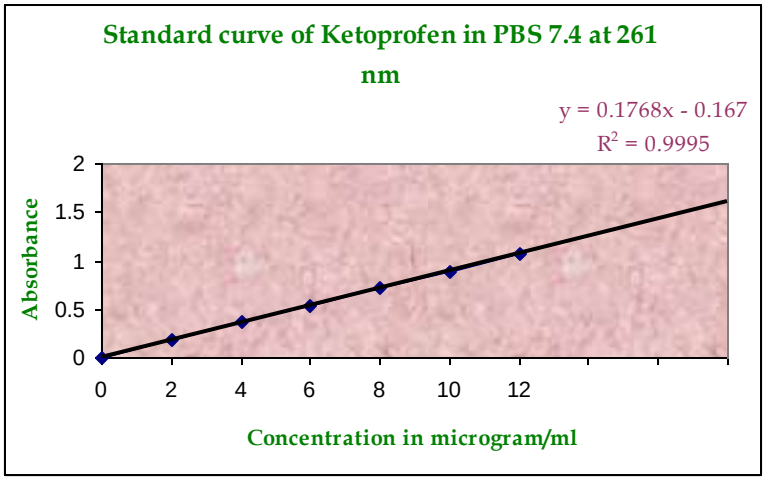

Fig 1.5 Standard curve of Ketoprofen in phosphate buffer pH 7.

DISCUSSION

The transdermal drug delivery is one of the promising routes of drug delivery system, since it by passes the first pass metabolism, avoids inactivation of drugs by pH effects and, provides a continuous mode of administration at rates approaching zero order similar to that provided by an intravenous infusion, increase the half life of the drug and improves patient compliance. Any drug for its permeation through skin should be potent, must be lipophilic as well as hydrophilic in nature, optimum partition coefficient etc, this prompted us to carryout the present study. The preformulation study for the drug was conducted. The λ-max of ketoprofen was found at 258 nm, which is comparatively same as given in I.P. This shows that the drug is pure. By the determination of organoleptic properties, it was observed that the ketoprofen is a white colored, crystalline powder, bitter in taste and odorless drug. Results of qualitative solubility studies show that the ketoprofen is soluble in organic solvent and insoluble in water. So it is hydrophobic in nature. Quantitative solubility studies shown that ketoprofen is more soluble in methanol as compared to other solvents. The partition coefficient was found to be 3.47, which is suitable for transdermal drug delivery, the obtained value of partition coefficient of ketoprofen was more than 1 which showed that the ketoprofen is lipophilic in nature . The average particle size of ketoprofen was measured by microscopy and found to be 2.2696 micrometer. The melting point was observed at 90^0C and this range is nearly same as reported in I.P., it shows the drug is crystalline & pure. The standard curve of ketoprofen was prepared in methanol and in phosphate buffer 7.4, the r^2 values were obtained 0.9941 and 0.9995 respectively, which shows linearity of absorbance between the ranges of 2-14 µg/ml. This preformulation study of ketoprofen showed satisfactorily results to select the drug for transdermal drug delivery system.

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REFERENCE

1. Saini TR, Gupta MM. Preformulation parameters characterization to design, development & formulation of vancomycin hydrochloride tablets for pseudomembrane colitis. IJPRD, 2009; 1 (9); 1-7.
2. Amlalo RNOT. In vitro release of ketoprofen from proprietary and extemporaneously manufactured gels. Rhodes University, Grahamstown, 2005, 1-222.
3. Jain, NK, Controlled and novel drug delivery. 1st ed. CBS publishers & distributors; 1997, 100-127.
4. Vyas, SP; Khar, RK., Controlled drug delivery concepts and advances. 1st ed. Published by vallabh prakashan, Delhi, 410-446. 2002.
5. Tripathi, KD.; Essentials of medical pharmacology. 5th ed. Published by jaypee brother's medical publisher's pvt. Ltd., New Delhi, 167-184. 2003
6. Dennis MJ, French PC, Crome P, Babiker M, Shillingford J & Hopkins R. Pharmacokinetic profile of controlled release Ketoprofen in elderly patients. Br. J. Clin. Pharmacol, 1985 6; 567-573.
7. Merk. Ketoprofen drug information provided by lexi-com. The Merck manuals online medical library, 2010.
8. Indian Pharmacopoeia. Government of India ministry of health and family welfare. The Controller of Publication, Delhi; (1996), Vol. 2; A-147.
9. Indian Pharmacopoeia. Government of India ministry of health and family welfare. The Controller of Publication, Delhi; 1996.1; 424-425.
10. Lachman, L.; Lieberman, HA.; Kanig, JL., The theory and practice of industrial pharmacy.3rd ed. Varghese publishing house; 1990, 171-195.
11. Tipwichai, S. Development of ketoprofen patch for transdermal drug delivery systems. FAPA Congress, Bangkok, 2005, 1-81.