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The novel formulation design of O/W microemulsion of ketoprofen for improving transdermal absorption

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ABSTRACT: Two novel O/W microemulsions of ketoprofen for improving transdermal absorption were design. These formulations were prepared by constructing the pseudo-ternary phase diagrams using oleic acid, polysorbate-80, propylene glycol and water in different ratios and were gelled by incorporating cab-o-sil. Oleic acid was screened as the oil phase due to good solubilizing capacity and excellent skin permeation rate of ketoprofen. *In-vitro* diffusion study was carried out using artificial semipermeable membrane. Formulation-2 showed higher diffusion rate than the formulation-1. The formulation-2 consisted of 3% ketoprofen, 5% menthol, 31.61% oleic acid, 0.5% tocopheryl acetate, 23.71% polysorbate-80, 23.71% propylene glycol, 0.18% methyl paraben, 0.02% propyl paraben, 6% cab-o-sil, triethanolamine (qs), and 6.29% water. Formulation-1 consisted of 3% ketoprofen, 33.45% oleic acid, 0.5% tocopheryl acetate, 25.08% polysorbate-80, 25.08% propylene glycol, 0.18% methyl paraben, 0.02% propyl paraben, 6% cab-o-sil, triethanolamine (qs) and 6.69% water. Diffusion was increased when the formulation was incorporated with 5% menthol. The diffusion rate of ketoprofen from formulation was fast and rapid than marketed sample. Cab-o-sil was used for improving the viscosity and stability of the system. The percentage of drug release across the membrane from marketed product, formulation-1 and formulation-2 were found to be 64.65%, 84.64%, and 90.20% respectively in 8 hrs. Results obtained in evaluation physicochemical characteristics were satisfactorily.

Keywords: O/W microemulsion, ketoprofen, oleic acid, transdermal absorption

INTRODUCTION

Ketoprofen 2-(3-benzoylphenyl)-propionic acid, non-steroidal anti-inflammatory agent widely used for the treatment of rheumatoid arthritis and mild to moderate pain.[1] Oral therapy of ketoprofen is very effective, but the clinical use is often limited because of adverse effects such as irritation and ulceration of the gastrointestinal tract. This drug has a relatively short half-life (1–3 hr) in plasma and has the potential to be delivered topically.[2] In addition, it is an excellent drug for transdermal delivery amongst other NSAID.[3,4] Furthermore, topical administration via the dermal route can bypass disadvantages of the oral route. Therefore, transdermal drug delivery has been considered to be an ideal route for ketoprofen administration. The use of penetration enhancer is valuable and important for achieving therapeutic plasma levels for many drugs, but penetration enhancer causes extensive damage to skin along with large increase in transdermal penetration rate.[5,6,7,8] Hence, appropriate penetration rate and an acceptable level of irritation must both be jointly considered in the design of an optimum transdermal formulation. Menthol has a potential of enhancing percutaneous absorption of ketoprofen through rat skin.[9] Thus, transdermal delivery system of ketoprofen may provide better patient compliance over oral administration. Menthol is hydrophobic compound and need a co-solvent to help them dissolve in formulation.

Literature survey revealed different transdermal delivery systems of ketoprofen including gels,[10,11,12] creams,[13] ointments,[14,15] patches,[16,17] gelled self emulsifying delivery system,[18] and microemulsions.[19,20] Also, various vehicles including topical oleo-hydrogel preparation,[21] soya-lecithin formulation,[22] Iontophorectic delivery system,[23,24] and cyclohexanol derivatives using L-menthol[25] have already made been made to improve the skin penetration of ketoprofen. O/W microemulsion is the formulation, which is expected to be increase the solubility by dissolving poor water soluble compounds into an oil phase and to enhance bioavailability.[26]

In this research, attempts have made to design the two novel O/W microemulsions that enhance the transdermal absorption of ketoprofen by raising the solubility of poor water-soluble compound ketoprofen. First, isopropyl

myristate, isopropyl palmitate, ethyl oleate and oleic acid as an oil phase, polysorbate-80 and span-20 as a surfactant and caprylic capric of triglyceride, propylene glycol, isopropyl alcohol as co-surfactants were used to examine the kind of oil and the mixture ratio of surfactants that form a good O/W microemulsion. Also, menthol was evaluated as potential permeation enhancer for ketoprofen in microemulsion.

MATERIALS AND METHODS

Ketoprofen BP was a generous gift sample from BEC Chemicals Pvt. Ltd. Mumbai. Oleic acid was procured from obtained from Shanghai Chemical Reagent Corporation (Shanghai, China). Polysorbate-80, propylene glycol, menthol, tocopheryl acetate, triethanolamine, methyl paraben, propyl paraben and cab-o-sil were purchased from Encube Ethicals Pvt. Ltd., Mumbai.

Selection of oils[27]

To find out the suitable oil, which can be used as oil phase in microemulsion, and provide excellent skin permeation rate of ketoprofen. The solubility of ketoprofen in various oils including isopropyl myristate, isopropyl palmitate, ethyl oleate and oleic acid was measured at 25°C. The solubility of isopropyl myristate, isopropyl palmitate, ethyl oleate and oleic acid in oily mixtures was also measured. About 10 gm of oil was accurately weighed in 25 mL glass beaker and 100 mg of ketoprofen was added into it, followed by stirring on magnetic stirrer at moderate speed to dissolve the drug. When drug was dissolved completely another 10 mg of ketoprofen was added and stirring was continued. Addition of drug was continued until the saturated solution is obtained. Finally, the total amount of drug consumed was determined by using UV-spectrophotometer at 260 nm. It was found that, oleic acid has consumed maximum amount of Ketoprofen and thus chosen as a vehicle for microemulsion oil phase.

Selection of surfactants and cosurfactants[28,29,30]

Since the non-ionic surfactants do not ionize at any great extent in the solution, they are greatly compatible with both anionic and cationic substances; various nonionic surfactants like polysorbate-80, span 20 and co-surfactants like caprylic capric of triglyceride, propylene glycol, and isopropyl alcohol were subjected to titration. Finally, polysorbate-80 and propylene glycol were selected as an ideal surfactant and co-surfactant for the system.

Construction of pseudo-phase ternary diagrams[31]

In order to find out the concentration range of components for the existence range of microemulsions, pseudo-ternary phase diagrams were constructed using water titration method at ambient temperature (25°C). Two pseudo-phase ternary diagrams were constructed with 1:1 and 2:1 weight ratios of polysorbate-80 to propylene glycol, respectively. For each phase diagram at specific surfactant/ co-surfactant weight ratio, the ratios of oleic acid to the mixture of surfactant and cosurfactant were varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. The mixtures of oil, surfactant and cosurfactant at certain weight ratios were diluted with H_2O drop wise, under moderate magnetic stirring. After being equilibrated, the mixtures were assessed visually and determined as being microemulsions, crude emulsions or gels.

Preparation of microemulsion and microemulsion-based hydrogel

Preparation of ketoprofen-loaded microemulsion

Ketoprofen was added to the mixtures of oil, surfactant, and cosurfactant with varying component ratio and then an appropriate amount of water was added to the mixture drop by drop and the microemulsion containing ketoprofen was obtained by stirring the mixtures at ambient temperature. Finally, pH was adjusted with triethanolamine in the range of 6.5 to 7.5. Same procedure was followed for formulation-2 with the addition of menthol.

Preparation of microemulsion-based gel

Polymers were soaked and stirred in microemulsion system for overnight. Cab-o-sil was selected as the gelling agent to prepare the microemulsion-based gel. Cab-o-sil was slowly mixed with microemulsion under stirring. After the complete dissolution of cab-o-sil in microemulsion, the clear microemulsion-based gel was obtained. To remove the entrapped air, formulation was heated on water bath at 60°C and then cooled at 8°C and centrifuged at 3000 RPM for 20 min. Similar procedure was followed for the formulation-2.

Physicochemical characteristics

Both the prepared microemulsions were subjected for the study of following characteristics.

Optical transparency

Optical transparency of the formulation was determined by inspecting the sample in clear and transparent container under the presence of good light against reflection into the eyes, and viewed against black and white illuminated background.

Determination of pH

About 2 gm of formulation was dispersed in 20 mL of distilled water and pH was determined by using LabIndia pH meter standardized with standard buffers of pH 4 and pH 7.

Viscosity

The viscosity of the microemulsion was measured by a Brookfield viscometer by using spindle rotated at a speed of 0.5, 1, 2.5 and 5.0 rpm at 25°C. At each speed, the corresponding dial reading on the viscometer was noted. Then the spindle speed was successively lowered and the corresponding dial readings were noted.

Centrifugation
Microemulsion system were subjected to centrifugations (Remi Motor, Mumbai) at 10,000 rpm for a period of 10 min and examined for any change in phase separation.

Spreadability
The Spreadability of the microemulsion was determined by using an apparatus consist of two glass slides (20X 4 cm), one of them being fixed on to the wooden board and the other is moveable, tied to a string that passes over a pulley, carrying a pan for the weights. Height of the upper side and pulley was kept at the same level. About 2 gm of formulation was placed in between two glass slides. A heavy weight was allowed to rest on the upper slide for few minutes to expel the entrapped air between the slides and to provide a uniform film of the gel. The weight was removed and the top slide subjected to a pull of 20 gm. The time necessary for the top slide to travel pre-marked 10 cm distance was noted.

Drug contents
Preparation of Standard Calibration curve
Accurately weighed 100 mg of ketoprofen was dissolved in 0.01M phosphate buffer (pH 7.4) and volume was made up to 100 mL in volumetric flask to give a final concentration 100 µg/mL (stock solution). Aliquots of this solution were further diluted with same buffer to give solutions of different concentrations i.e. 2, 4, 6, 8, 10, 20, 30, 40 and 50- µg/mL. The absorbance of these solutions was measured at 260 nm using nm by UV-spectrophotometer (Milton Roy Sprectronic-1201) against blank solutions and calibration curve was performed.

Assay of formulation
An accurately weighed 0.2 g (equivalent 6 mg of drug) of three samples of formulation from top, middle and bottom of lami tube were transferred into three different 25 mL volumetric flask. A part of phosphate buffer (pH 7.4) was used to dissolve the sample and later the volume was made up to 25 mL with the same solvent. 1 mL aliquots from each flask was taken and diluted to 10 mL with phosphate buffer and absorbance was measured at 260 nm. The percentage drug content of all the three samples were found out from standard calibration curve. Same procedure was followed for another formulation.

***In- vitro* diffusion study**
In-vitro diffusion study of drug from both formulations was carried out using artificial semipermeable membrane. The receptor compartment was consist of 250-300 mL of 0.01M Phosphate buffer (pH 7.4) in 500 mL beaker and its temperature was maintained at 37 ±0.5°C and stirred at 300 rpm throughout the experiment. About 3 gm of 3% Ketoprofen microemulsion based gel was placed in artificial semipermeable membrane tied to the one end of open-ended glass cylinder that was then dipped into freshly prepared phosphate buffer on magnetic stirrer. Samples were taken from receptor mediums at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and replaced immediately with an equal volume of fresh phosphate buffer equilibrated at 37 ±0.5°C. All the samples were analyzed for ketoprofen content at 260 nm by UV-spectrophotometer. Same experiment was carried out for ketoprofen microemulsion containing 5% menthol and 2.5% marketed preparation of ketoprofen gel (Rhofinid gel®). Drug release after 8 hrs was determined for both formulations. Cumulative amount of drug release was calculated from standard calibration curve.

Skin irritation test
Irritation evoked by both formulations on rabbit's skin was visually judged after the end of experiments. The test was carried out on 8 healthy rabbits weighing 1.5 – 2.0 kg and age around 24 months. The dorsal surfaces of rabbits were cleaned and hairs were removed by shaving. The exposed skin was cleaned with rectified spirit. Both the formulations were applied by occlusive dressing technique to two different pairs of rabbits respectively. A pair of rabbits was applied with placebo microemulsion gel where as two rabbits were kept unapplied as control. Occlusive dressing was removed after 24 hours and the skin was examined for erythema and oedema.

Stability studies
Accelerated stability studies
One sample of both the formulations of microemulsion-based gels was charged at 40°C and 75% relative humidity for 1, 2 and 3 months, respectively. After completion of time, samples were drawn and analyzed for physical parameters and drug contents.

Freeze-thaw studies
This was somewhat critical process than former, as it requires close observation by formulator/analyst. In this method microemulsion-based gels samples were cycled at 50^0 C and 8°C periodically and the samples were analyzed for their physical properties and drug content at the completion of first, third and fifth cycle.

RESULTS AND DISCUSSION
Different oils, surfactants and co-surfactants were screened to select ideal components of microemulsions with good solubility and excellent skin penetration of ketoprofen. The solubility of ketoprofen was highest in oleic acid, followed by ethyl oleate, isopropyl myristate, and isopropyl palmitate. Therefore, oleic acid was chose as oil phase for microemulsion. The results of solubility study have shown in **Table 1**. However, the oily mixtures of oleic acid, polysorbate-80 and propylene glycol led to increased in drug solubility. After extensive screening for physical characteristics and appearance, final ratios of surfactants- cosurfactants were decided. The data of selection of surfactants and cosurfactants is given in **Table 2**.

The aim of the construction of pseudo-ternary phase diagrams was to find out the existence range of microemulsions. The pseudo-ternary phase diagrams with various weight ratios of polysorbate-80 to propylene glycol have shown in **Fig. 1**. The translucent

microemulsion regions for both systems are presented in phase diagrams. No distinct conversion from oil-in-water (o/w) to water-in-oil (w/o) microemulsion was observed for both. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual observation. The phase study revealed that the maximum proportions of oil were incorporated in microemulsion systems when the surfactant-to-cosurfactant ratio (km) was 1:1 and 1:2. Therefore, formulation-1 (without menthol) and formulation-2 (with menthol) containing surfactants -cosurfactants in the ratio of 1:1 and 2:1, respectively were prepared. Cab-o-sil in the formulation was used for improving the viscosity and stability of microemulsion, whereas menthol was used for enhancing penetration. The compositions of microemulsions are given in **Table 3**.

Both the microemulsions were subjected to the study of physicochemical characteristics. Both the formulations were optically clear, transparent and elegant in appearance. The pH of both the formulations was found to be between 6.50 and 7.50, respectively. It was clear from the physicochemical data of both the systems that the developed formulations had high viscosities (127920 cps & 129480 cps). From the viscosity study, it can be concluded that the systems are of the o/w type. When formulations are subjecting to the centrifugation at 10,000 rpm for 10 min, they did not cause phase separation. Prepared microemulsion gels were free flowing and possess better spreadability. The data of the physicochemical characteristics of developed microemulsions is given in **Table 4.**

In the preparation of microemulsions, HPMC, HPC and Carbopol polymers did not cause gel formation. HPMC formed a sticky layer at the bottom of the container with microemulsion floating at the top at all the concentrations tried. HPC polymer did not dissolve in the microemulsion system and remain settled at the bottom of the container. Carbopol-940 produced cloudy mucilage and therefore failed to give the desired attribute the clarity. There was no gel formation with these polymers at all the concentrations tried may be due to high concentration of oily phase, surfactant and cosurfactant present in the formulation. Xanthan gum produced gels at only 2.5-3.5% w/w concentration following cold method. At this low concentration also the gels were stiff and very sticky. Aerosil fails to achieve gelling viscosity at all concentrations (5-8% w/w). Cab-o-sil produced o/w type of microemulsion-based gel. However, with higher proportion of surfactant/cosurfactant at 2: 1 ratio cab-o sil fails to achieve viscosity of gel. At 5% w/w concentration of cab-o-sil, there was incomplete gel formation and at 8% w/w concentration the gels formed were little stiff. At 6% w/w concentration of cab-o-sil, the consistency of the microemulsions was appropriate. Among the methods tried for degassing, centrifugation method found to be the most effective and quick.

The drug content in each sample was determined by using standard calibration curve (see **Fig. 2**). The mean percent drug contents in formulation-1 and formulation-2 was found to be 99.37% w/w and 98.63% w/w, respectively. The results of drug contents are given in **Table 5**. From *In-vitro* diffusion study, it is clear that penetration is significantly increases with addition of menthol. The addition of 5% menthol to the microemulsion further increased the skin permeation rate of ketoprofen. The drug diffusion rate of developed formulations was superior to the marketed formulation (See **Fig. 3**).

Result of skin irritation test in albino rabbits shows no skin irritation or inflammation in both formulations. In accelerated stability studies, results obtained shows that the formulations maintain the drug content in the prescribed limit (95-106 % w/w) for the period of 3 months. After 3 months, the drug content in formulation-1 and formulation-2 was found to be 97.72% w/w and 96.72 % w/w, respectively. In addition, there was no change observed in the physical properties (for the results, see **Table 4**).

In freeze-thaw study, after completion of fifth cycle, samples were analyzed for physical properties and drug content. The physical properties were not varied to the greater extent, which shows that formulations are stable and the content of ketoprofen in formulation-1 and formulation-2 was found to be 97.08 and 96.18 % w/w, respectively. Thus, from the above results it is clear that, both the formulations can maintain the efficacy when stored for longer period, even at the fluctuations of temperature. The details of cycling are presented in **Table 6**.

CONCLUSION

Two novel O/W microemulsions containing ketoprofen were designed for improving transdermal absorption. The components and their concentration range for the formation of microemulsion were decided constructing pseudo-ternary phase diagrams. Their concentrations were optimized after the evaluation of their effect on skin permeation of the drug. Both the developed formulations were free flowing, translucent and spontaneously formed. When microemulsions were gelled, they found to have uniform viscosity, spreadability, elegant appearance and did not produce skin irritation. Drug content at top, middle and bottom of the formulations revealed the percentage of drug close to 100%. The results of physicochemical characteristics are satisfactorily. Both the formulations are superior to marketed formulation in the respect of drug permeation across the membrane.

Table 1
Solubility of ketoprofen in various oils at 25^{O} C

Oils	Solubility (mg/10g of oil)
Isopropyl myristate	190
Isopropyl palmitate	170
Ethyl Oleate	210
Oleic Acid	280

Table 2
Selection of surfactant and co-surfactants for optimization

Surfactant: co-surfactant	Concentration ratio	Appearance
Polysorbate-80: Caprylic capric of triglyceride	1:1	Cloudy
	2:1	Clear
Polysorbate-80: Propylene glycol	1:1	Clear
	2:1	Clear
Polysorbate-80: Isopropyl alcohol	1:1	Slight cloudy
	2:1	Clear
Span 20: Caprylic capric of triglyceride	1:1	Cloudy
	2:1	Cloudy
Span 20: Propylene glycol	1:1	Clear
	2:1	Cloudy
Span 20: Isopropyl alcohol	1:1	Slight cloudy
	2:1	Cloudy

Table 3
Composition of selected microemulsion formulations

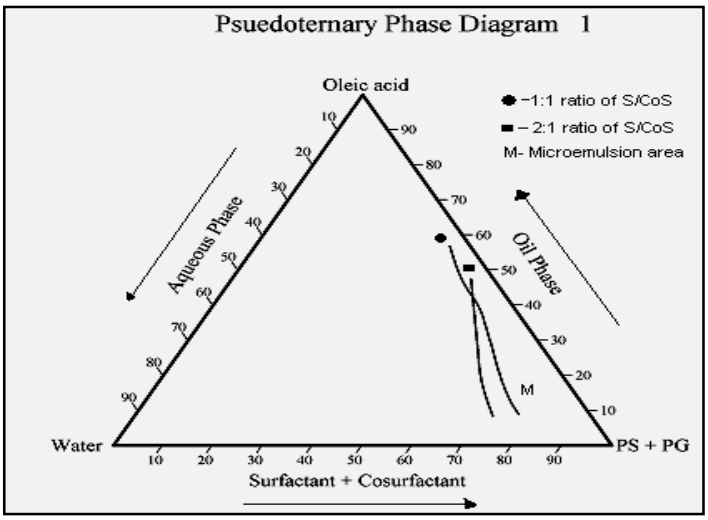
Ingredient	% Contents	
	Formulation-1	Formulation-2
Ketoprofen	3.00	3.00
Oleic Acid	33.45	31.61
Tocopheryl acetate	0.50	0.50
Polysorbate-80	25.08	23.71
Propylene glycol	25.08	23.71
Methyl paraben	0.18	0.18
Propyl paraben	0.02	0.02
Cab-o-sil	6.00	6.00
Water	6.69	6.27
Triethanolamine	Sufficient	Sufficient
Menthol	--	5.00

Table 4
Characterization and evaluation of microemulsion formulations

Parameters	Initial	Freeze thaw 5th cycle	Accelerated stability studies		
			1 Month	2 Month	3 Month
Formulation-1					
pH	7.36	6.59+	7.18	7.01	6.86
Viscosity in cps	127920	113880	124800	118560	117000
Phase separation	No	No	No	No	No
Spreadability	Better	Better	Better	Better	Better
% Drug content	99.37	97.08	98.79	98.10	97.72
Formulation-2					
pH	7.21	6.59	7.18	7.01	6.86
Viscosity in cps	129480	112320	126360	123240	115440
Phase separation	No	No	No	No	No
Spreadability	Better	Better	Better	Better	Better
% Drug content	98.63	96.18	97.76	97.04	96.72

Table 5
Assay of microemulsion formulations

Sample	Top	Middle	Bottom	Mean
Formulation-1				
Absorbance	1.173	1.178	1.169	1.173
Concentration (µg/mL)	23.93	24.04	23.85	23.93
Drug content (% w/v)	99.37	100.16	99.36	99.37
Formulation-2				
Absorbance	1.159	1.163	1.158	1.160
Concentration (µg/mL)	23.65	23.73	23.63	23.67
Drug content (% w/v)	98.55	98.89	98.46	98.63



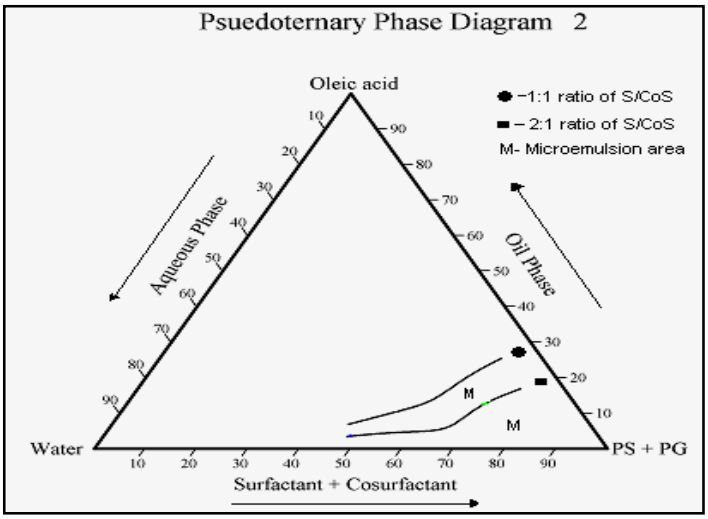


Fig. 1. The pseudo-ternary phase diagrams for oil-surfactant-water system at the 1:1, and 2:1 weight ratio of polysorbate-80 to propylene glycol

Table 6
Freeze thaw study calendar

Date	Temperature cycle	Time
13/12/08	50.0 °C	10.00 am
	Sunday	
15/12/08	8.0 °C	10.00 am
16/12/08	50.0 °C	10.00 am
17/12/08	8.0 °C	10.00 am
18/12/08	50.0 °C	10.00 am
19/12/08	8.0 °C	10.00 am
20/12/08	50.0 °C	10.00 am
	Sunday	
22/12/08	8.0°C	10.00 am
23/12/08	50.0 °C	10.00 am
24/12/08	8.0 °C	10.00 am
25/12/08	Completion of five cycles	10.00 am

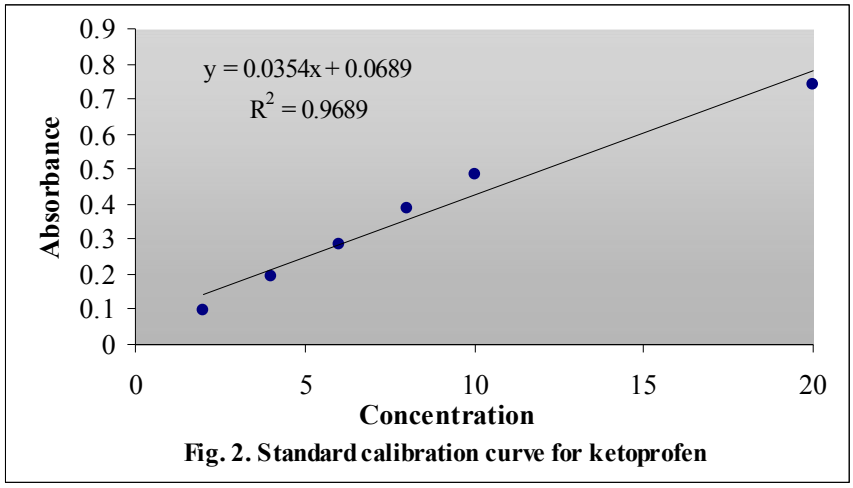


Fig. 2. Standard calibration curve for ketoprofen

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REFERENCES

1. Lacy CF, Armstrong, LL, Ingrim NB, Lance LL; Drug Information Handbook, sixth ed. Lexi-Comp Inc., Cleveland, 1998.
2. Jamali F, Brocks DR; Clinical pharmacokinetics of ketoprofen and its enantiomers. Clin. Pharmacokinet. 1990,19:197–217.
3. Cordero JA, Alarcon, L, Escribano E, Obach R, Domenech J; A comparative study of the transdermal penetration of a series of nonsteroidal anti-inflammatory drugs. J. Pharm. Sci. 1997, 86:503–508.
4. Vincent, CM, Laugel C, Marty JP; In vitro topical delivery of non-steroidal anti-inflammatory drugs through human skin. Arzneim.-Forsch, 1999, 49:509–513.
5. Kabayashi D, Matsuzawa T, Sugibayashi K, Morimoto Y, Kimura M; Analysis of the combined effect of l-menthol and ethanol as skin permeation enhancers base on a two-layer skin model. Pharm. Res. 1994, 11:96–102.
6. Degim IT, Uslu A, Hadgraft J, Atay T, Akay C, Cevheroglu S; The effect of azone and capsaicin on the permeation of naproxen through human skin. Int. J. Pharm. 1999, 179:21–25.
7. Peltola S, Saarinen-Savolainen P, Kiesvaara J, Suhonen TM, Urtti A; Microemulsions for topical

delivery of estradiol. Int. J. Pharm. 2003, 254:99–104.

8. Chang JS, Wu PC, Huang YB, Tsai YH; In vitro evaluation of meloxicam permeation using response surface methodology. J. Food Drug Anal. 2006, 14:236–241.
9. Wu PC, Chang JS, Huang YB, Chai CY, Tsai YH; Evaluation of percutaneous absorption and skin irritation of ketoprofen through rat skin: in vitro and in vivo study. Int. J. Pharm. 2001a, 222:225–235.
10. Noda K, Nakagawa A, Yamagata T, Ide H; Anti-inflammatory and analgesic gel composition. US Patent 4, 12 July 1983, 393,076.
11. Chi SC, Jun HW; Anti-inflammatory activity of ketoprofen gel on carrageenan-induced paw edema in rats. J. Pharm. Sci. 1990, 79:974–977
12. Yaw-Bin Huang, Ren-Jiunn Wang, Jui-Sheng Chang, Yi-Hung Tsai, Pao-Chu Wu; Evaluation of ketoprofen formulations via penetration rate and irritation in vivo study, Int. J. Pharm., 2007, 339:47–51
13. Itoh Y, Kato H, Matsumura K, Nishikawa T, Hisano A, Yamada T, Kishinaka E; Anti-inflammatory and antipyretic cream. US Patent 4, 13 August 1985, 534,980.
14. Henmi T, Fujii M, Kikuchi K, Yamanobe N, Matsumoto M; Application of an oily gel formed by hydrogenated soybean phospholipids as a percutaneous absorption-type ointment base. Chem. Pharm. Bull. 1994m, 42:651–655.
15. Gurol Z, Hekimoglu S, Demirdamar R, Sumnu M; Percutaneous absorption of ketoprofen. In vitro release and percutaneous absorption of ketoprofen from different ointment bases. Pharm. Acta Helv. 1996, 71:205–212.
16. Yim DS, Jang IJ, Shin SG, Yoo JH, Eun HC; Pharmacokinetic and skin irritation of transdermal ketoprofen. Kor. J. Clin. Pharmacol. Ther. 1994, 2:21–27.
17. Valenta C, Almasi-Szabo I; In vitro diffusion studies of ketoprofen transdermal therapeutic systems. Drug Dev. Ind. Pharm. 1995, 21:1799–1805.
18. Patil P, Joshi P; Effect of formulation variable on preparation and evaluation of gelled self-emulsifying drug delivery system of ketoprofen, AAPS Pharm. Sci. Tech. 2004, 5, 3:42
19. Yun– Seok Rhee, Jung-Gyo Choi; Transdermal delivery of ketoprofen using microemulsions. Int. J. Pharm. 2001, 228:61-170.
20. Podlogar F, Beˇster M, Gaˇsperlin M; The effect of internal structure of selected water-Tween 40®-Imwitor 308®-IPM microemulsions on ketoprofene release. Int. J Pharm. 2005, 302:68–77
21. Rhee GJ, Woo JS, Hwang SJ, Lee YW, Lee CH; Topical oleo-hydrogel preparation of ketoprofen with enhanced skin permeability. Drug Dev. Ind. Pharm. 1999, 25:717–726
22. Valenta C, Wanka M, Heidlas J; Evaluation of novel soya-lecithin formulation for dermal use containing ketoprofen as a model drug. J. Control. Release. 2000, 63:165– 173.
23. Panus PC, Campbell J, Kulkarni SB, Herrick RT, Ravis WR, Banga AK; Transdermal iontophoretic delivery of ketoprofen through human cadaver skin and in humans. J. Control. Release. 1997, 44:113–121.
24. Tashiro, Y., Kato, Y., Hayakawa, E., Ito, K., 2000. Iontophoretic transdermal delivery of ketoprofen: Novel method for the evaluation of plasma drug concentration in cutaneous vein. Biol. Pharm. Bull. 23, 632–636.
25. Obata Y, Sato H, Li CJ, Takayama K, Higashiyama K, Nagai T, Isowa K; Effect of synthesized cyclo-hexanol derivatives using L-menthol as a lead compound on the percutaneous absorption of ketoprofen. Int. J. Pharm. 2000, 198:191–200.
26. Panayiotis PC, Review lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm. Res. 1995, 12:1561–1572.
27. Huabing chen, Xueling Chang; Micro emulsion–based hydrogel formulation of ibuprofen for topical delivery, International Journal of Pharmaceutics, 2006, 315:52 -58.
28. Natesan S, Ghosal S; Formulation and physicochemical characterization of micro emulsion system using Isopropyl myristate, medium– chain glycerides, polysorbate–80 and water, Chem. Pharm. Bull. 2005, 53, 12:1530-1535.
29. Li Ping, Ghosh A; Effect of combined use of nonionic surfactant on formulation of oil–in-water microemulsion, Int. J. Pharm. 2005, 288:27-34.
30. Richard D. O'Brien; Fats and Oils, Formulating and processing for application, 2nd Edn. 276.
31. Nandi I, Bari Mohd, Joshi H; Study of Isopropyl myristate micro emulsion system containing cyclodextrin to improve solubility of 2 model, Hydrophobic drugs, AAPS Pharm. Sci. Tech. 2003, 4,1.