

Analytical Methods for Determination of Ketoprofen Drug: A review

¹Jasim M. S. Jamur
jasimphduk@gmail.com

²Sumayha M. Abbas
sumayha.mu@gmail.com

³Zahra Mohammed Abbas
zahra.m.a@ihcoedu.uobaghdad.edu.iq

¹⁻³ Department of Chemistry, College of
Education for Pure Science \ Ibn Al-Haitham, University of Baghdad, Baghdad, Iraq.

Article history: Received 5 April 2022, Accepted 17 May 2022, Published in July 2022.

Doi: 10.30526/35.3.2842

Abstract

Ketoprofen has recently been proven to offer therapeutic potential in preventing cancers such as colorectal and lung tumors, as well as in treating neurological illnesses. The goal of this review is to show the methods that have been used for determining ketoprofen in pharmaceutical formulations. Precision product quality control is crucial to confirm the composition of the drugs in pharmaceutical use. Several analytical techniques, including chromatographic and spectroscopic methods, have been used for determining ketoprofen in different sample forms such as a tablet, capsule, ampoule, gel, and human plasma. The limit of detection of ketoprofen was 0.1 ng/ ml using liquid chromatography with tandem mass spectrometry, while it was 0.01- 0.30 µg/ ml using high performance liquid chromatography and 0.00004 - 0.436 µg/ ml, 0.82 µg/ ml, 1.0 µg/ ml, 10 µg/ ml and 208.5 - 237.6 µg/ ml using flow injection, electrokinetic chromatography, capillary electrophoresis, gas chromatography-flame ionisation detection and derivative infrared spectroscopy respectively.

Keywords: Analytical Methods, Ketoprofen, Non-steroidal anti-inflammatory drugs.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) and their metabolites are widely used in human medicine. Several methods for monitoring the most important members of this pharmacological class in different environmental samples were investigated due to the general problem of drug contamination and environmental risk assessment [1]. In medicine, NSAIDs are routinely used to treat rheumatoid arthritis and osteoarthritis [2].



The development of precise and reliable analytical methods for NSAID determination in a variety of samples is critical to employing NSAIDs safely in the pharmaceutical industry and medicinal therapies. These methods gather qualitative and quantitative data on the purity, pharmacokinetics, and pharmacodynamics of a drug, among other things. The metabolites formed as a result of this process can be far more harmful than the initial drug, necessitating drug environmental monitoring [3].

This review focuses on one of the anti-inflammatory drugs, ketoprofen, which is a highly effective medicine that has been utilized in a range of clinical trials and therapies. Ketoprofen is a distinct active ingredient in a multicomponent pharmaceutical form through routine pharmaceutical analysis using numerous chemical methods. Ketoprofen may be used to prevent and treat cancers such as colorectal and lung cancers, as well as neurological illnesses. Several ketoprofen formulations have also been used to treat a wide range of acute and chronic inflammatory diseases. Ketoprofen has been used to treat osteoarthritis, rheumatoid arthritis, menstrual cramps, and ankylosing spondylitis, among other disorders. Figure 1 shows the chemical structure of ketoprofen.

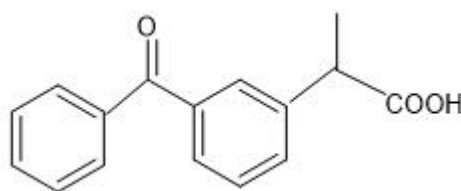


Figure 1. Ketoprofen's chemical structure

Simple, low-cost, and ecologically sound methods should be developed. As one of the important aspects of the analysis, sample preparation should be simple and quick. Because of the intricacy of the samples and the potential influence of interferences, selectivity should be emphasized as well.

2. Results and Discussion

Although a variety of analytical procedures have been used to determine ketoprofen, high-performance liquid chromatography (HPLC) is the most often used. The results of the method analysis are summarised in Table 1.

Table 1. Analytical methods for determining ketoprofen

Method	Sample form	Concentration range (µg/ml)	λ max (nm)	(r^2)	RSD (%)	LOD (µg/ml)	Recovery (%)	Ref. No.
Spectrophotometer	Tablet, Capsule, Gel	0.8-16	563	0.9983	0.0237	0.037		[2]
HPLC	Gel		233	0.9989	0.22-1.20	0.014	101.3	[4]
RP-HPLC	Human plasma	0.244-125	260	0.9999	< 2.0	0.122	98.86-99.27	[5]
HPLC and Flow injection	Gel, Ampoule	0.4-1.2, 7.5-75	261	0.9995-0.9999	0.44-1.27	0.303-0.436	99.18-100.4	[6]
UV-vis spectrophotometer	Tablet, Capsule	2.5-15	260	0.9980	< 2.0	0.780	99-101	[7]

Kinetic spectrophotometer	Tablet, Capsule, Ampoule, Suspension, Suppository	1.0-8.0	605	0.9999	0.20-0.40	0.07	99.79-100.11	[8]
Flow injection	Capsule, Urine	0.0011-0.0681		0.9999	0.8	0.00045	90.0-105.0	[9]
Electrokinetic chromatography	Gel	100-2000	200	0.9969		0.82	96.56	[10]
UPLC-MS/MS	Human dermal microdialysis	0.5-500	255	0.9999	< 2.0	0.0001	87.68-88.25	[11]
HPLC	Blood, Urine	20-500	254		1.4-6.2	0.10		[12]
HPLC	Human plasma	0.001-0.5	254	> 0.9960	< 13.0	0.01	71.2-82.2	[13]
Derivative IR spectroscopy (normal and first)	Tablet	1000-4000		0.9930-0.9780	1.15-1.37	208.5-237.6		[14]
Capillary electrophoresis	Oral pharmaceutical preparation	1.0-2.5	254	0.9990		1.0	101	[15]
HPLC	Plasma, Urine	1-90		0.9974	≤ 7.75	0.02	95.5-97.63	[16]
LC-MS/MS	Human plasma	0.00005-2.5		0.997-0.998	4.0-7.0		97.5-102.8	[17]
GC-FID	Human serum	10-400				10	98-106.7	[18]
HPLC	Capsule	1-6	233	> 0.999	2.52-5.81	0.17	99.1-104.1	[19]
LC-APCI/MS	Tablet, Capsule	0.1-0.5		0.9993	1.8-3.4	0.001	99.5-102.2	[20]

Dvorak and colleagues developed HPLC method for measuring ketoprofen in pharmaceutical gels simultaneously using C₁₈ column (125 mm i.d.) and mobile phase of 40:58:2 (v/v/v) mixture of acetonitrile, water, and phosphate buffer pH 3.5. The complete analysis took less than 10 minutes with a flow rate of 1.0 ml/min [4].

Zafar et al. developed and validated the RP-HPLC technology for quantifying ketoprofen in human plasma. A 5 m (25 cm 4.6 mm) Discovery HS C₁₈ column was used with a mobile phase of methanol: water (70:30) pH 3.3. The measurements were obtained at 260 nm at a flow rate of 1 ml/min and the retention time was determined to be less than 10 minutes. The correlation coefficient (R²) was 0.9999 and RSD of less than 2%. Intraday accuracy was found to be 99.747%, 99.475%, 98.457% and 99.824% for 62.5 µg/mL, 15.625 µg/ml, 7.812 µg/ml, and 1.953 µg/ml respectively, while interday accuracy was found to be 99.104%, 99.091%, 98.96%, and 99.385% in plasma for days 1, 2, and 3 [5].

Basan and colleagues measured ketoprofen in ampules and gels at 261 nm. The LOD for ampules and gels were determined and found to be 0.303 and 0.436 g/ml, respectively. The mean S.D. values were 25.25 ± 0.27 in gels and 99.42 ± 0.44 in ampules. Gel and ampule recovery rates were 98.65–100.63 % and 99.1–101.5 % respectively [6].

Ketoprofen was determined in pharmaceutical formulations by Kormosh and co-workers using a simple spectrophotometric method. The procedure involves reacting ketoprofen with

the analytical reagent, then extracting the produced ion association in toluene and measuring it spectrophotometrically (its absorbance at 563 nm, = $7.6 \times 10^4 \text{ L mol}^{-1} \times \text{cm}^{-1}$). Ketoprofen had a LOD of 0.037 $\mu\text{g/ml}$ and a linear calibration plot from 0.8 to 16.0 $\mu\text{g/ml}$ [2].

A UV spectrophotometric method was used to analyze ketoprofen in its dose form, with 1M NaHCO_3 as the diluent. At 260 nm, ketoprofen had the highest absorption. It was shown to be linear ($r^2=0.998$) with low detection and quantification limits (0.78 $\mu\text{g/ml}$, 2.35 $\mu\text{g/ml}$) [7].

A simple kinetic method is used to identify ketoprofen in its purest form, medicines, and biological fluids. In the procedure, an electrophilic intermediate was generated, which then reacts with ketoprofen to produce a colored product. The absorbance was measured at 605 nm. The correlation was linear, with a LOD of 0.07 $\mu\text{g/ml}$. Tablets, gel, and suspension had percent recoveries of 100.11, 100.10, and 100.11, respectively, but suppositories, capsules, and ampoules all had percent recoveries of 100.0 [8].

A flow injection method is coupled with it sensitizing by Zhuang and Song to generate a fast chemiluminescence method to analyse ketoprofen. R^2 and LOD and R.S.D. were determined and found to be of 0.9999, $2.0 \times 10^{-8} \text{ mol/L}$ and 0.8 % respectively [9].

For the identification of ketoprofen in pharmaceutical preparations, a fused silica capillary was employed for separation at 200 nm with 15% (v/v) methanol. It takes roughly 13 minutes to complete a single separation. When comparing the results to those reported in the literature using the RP-HPLC method, no statistically significant differences were detected [10].

Ketoprofen in dialyses was determined using LC–MS/MS on a C_{18} column (100 mm \times 2.1mm i.d., 1.7 μm) with a mobile phase of 60:20:20 (v/v/v). 5 μl samples were injected and analyzed at a temperature of $22 \pm 0.5^\circ\text{C}$. At 1.07 minutes, ketoprofen eluted. At the transitions 253.00 > 209.00 ketoprofen response was optimized. Calibration curves showed a good linear correlation with correlation values > 0.999. The precision and accuracy were found to be between 99.97 and 104.67 %, with a mean recovery of ketoprofen of 88.03 ± 0.3 %. The LOD and LOQ were determined to be 0.1 and 0.5 ng/ml, respectively [11].

Rapid and easy analysis of ketoprofen in bodily fluids was developed using HPLC. This antirheumatic medication, as well as an internal standard, must be extracted selectively from acidified plasma and urine using ether. After the ether has evaporated, the residue is dissolved in methanol and examined using RP-HPLC [12].

HPLC was performed to quantify ketoprofen in human plasma using a C_{18} (100 4.6 mm) column with an acetonitrile/ potassium dihydrogen phosphate 0.01 M (40:60, v/v) mobile phase at pH 3.5. The flow rate was fixed to 5 ml/ min and a wavelength of 254 nm. It took less than 5 minutes to complete the analysis. The RSD was less than 13% at this level with the lowest LOD of 10 ng/ ml. After application of two topical ketoprofen formulations, human plasma samples were taken from healthy volunteers to measure relative bioavailability and demonstrate that ketoprofen applied topically has a low systemic bioavailability [13].

In the study by Azeez and co-workers, a simple first and normal derivative IR spectroscopy method was used for determining ketoprofen in pharmaceutical formulations. Ketoprofen has been quantified in the range of (1000 to 4000) $\mu\text{g/ml}$ using transmittance measurements for the normal and first derivative spectrums against concentrations with a relative error of +4.33% and 4.78%, respectively, and RSD 1.15% and 1.37%. The r^2 coefficients for both techniques were 0.993 and 0.978, respectively. The procedures were used to determine ketoprofen in various pharmaceutical samples, with a recovery rate of 97.691% [14].

The ketoprofen was determined in an oral pharmaceutical formulation by Blanco and co-workers using capillary electrophoresis method. All samples were examined during a stability study revealed that the ketoprofen content in the body did not alter considerably over time. The enantiomeric impurities was ranged from 0.1% to 0.4 % [15].

3. Conclusion

To determine the quality, safety, and efficacy of ketoprofen medications, as well as to monitor ketoprofen therapy, it is necessary to develop reliable, accurate, and efficient analytical methods. Therefore, the purpose of the current essay was to review the previous studies over the past few decades that have provided important information on determining ketoprofen. Different methods for determining ketoprofen are discussed in this review including chromatographic, spectroscopic and spectrometric methods. Although HPLC and UV spectroscopy was the most commonly used technologies for ketoprofen determination, LC-MS/MS showed great sensitivity with the lowest LOD (0.5 ng/ml). However, to develop and test new inventive ketoprogens, more study is required in this field based on green chemistry principles.

References

1. Gentili, A. Determination of non-steroidal anti-inflammatory drugs in environmental samples by chromatographic and electrophoretic techniques. *Analytical and Bioanalytical Chemistry*. **2007**,387(4),1185–202.
2. Kormosh, Z.; Hunka, I.; Basel, Y. Spectrophotometric determination of ketoprofen and its application in pharmaceutical analysis. *Acta Poloniae Pharmaceutica - Drug Research*. **2009**,66(1),3–9.
3. Dandić, A.; Rajkovača, K.; Jozanović, M.; Pukleš, I.; Széchenyi, A.; Budetić, M. et al. Review of characteristics and analytical methods for determination of indomethacin. *Reviews in Analytical Chemistry*. **2022**,41(1),34–62.
4. Dvořák, J.; Hájková, R.; Matysová, L.; Nováková, L.; Koupparis, MA.; Solich, P. Simultaneous HPLC determination of ketoprofen and its degradation products in the presence of preservatives in pharmaceuticals. *Journal of Pharmaceutical and Biomedical Analysis*. **2004**,36(3),625–9.
5. Zafar, F.; Shoaib ,MH.; Naz, A.; Yousuf, RI.; Ali, H. Determination of Ketoprofen in Human Plasma by RP-HPLC. *American Journal of Analytical Chemistry*. **2013**,04(05),252–7.

6. Basan, H.; Eda, S.; Ozl, C.; Ertas, N, G G. Quantitative determination of ketoprofen in gels and ampules by using flow-injection UV spectrophotometry and HPLC. **2005**,39,606–11.
7. Hassan, AA.; Shantier, SW.; Gad-kariem, EA. Method and validation of UV-visible spectrophotometric method for estimation of ketoprofen in capsule and tablet dosage. *Indo American Journal of Pharmaceutical Research*. **2019**,9(01),1865–70.
8. Eid, M.; Talaat, W. Kinetic Spectrophotometric Method For The Determination of Ketoprofen in Pharmaceuticals and Biological Fluids. *Structure*. **2006**,2(4),405–12.
9. Zhuang, Y,.;Song, H. Sensitive determination of ketoprofen using flow injection with chemiluminescence detection. *Journal of Pharmaceutical and Biomedical Analysis*. **2007**;44(3 SPEC. ISS.):824–8.
10. Šafra, J.; Pospíšilová, M. Separation and determination of ketoprofen, methylparaben and propylparaben in pharmaceutical preparation by micellar electrokinetic chromatography. *Journal of Pharmaceutical and Biomedical Analysis*. **2008**,48(2),452–5.
11. Tettey-Amlalo RNO, Kanfer I. Rapid UPLC-MS/MS method for the determination of ketoprofen in human dermal microdialysis samples. *Journal of Pharmaceutical and Biomedical Analysis*. **2009**,50(4),580–6.
12. Farinotti, R.; Mahuzier. G. High-performance liquid chromatographic determination of ketoprofen in blood and urine. *Journal of Pharmaceutical Sciences*. **1979**,68(4),484–5.
13. Allegrini A, Nuzzo L, Zucchelli M, Scaringi AT, Felaco S, Giangreco D, Pavone D, Toniato E, Mezzetti A, Martinotti S, Comuzio S, Di Grigoli M. Fast HPLC method for the determination of ketoprofen in human plasma using a monolithic column and its application to a comparative bioavailability study in man. *Drug Research*. **2009**,59(3):135–140.
14. Azeez AM, Fakhre NA. Determination of ketoprofen in tablet dosage forms by derivative IR spectroscopy. *Egyptian Journal of Chemistry*. **2022**;65(1):215–9.
15. Blanco M, González JM, Torras E, Valverde I. Enantiomeric purity determination of ketoprofen by capillary electrophoresis: Development and validation of the method. *Analytical and Bioanalytical Chemistry*. **2003**;375(1):157–63.
16. Shafique A, Alothman ZA, Akram S, Akram S, Saad Sohail C, Mushtaq M. An expedient and rapid High-Performance Liquid Chromatographic method for the kinetic study of Ketoprofen. *Journal of King Saud University - Science* [Internet]. **2020**;32(3):2212–8. Available from: <https://doi.org/10.1016/j.jksus.2020.02.033>
17. Eichhold TH, Bailey RE, Tanguay SL, Steven H H. Determination of (R)- and (S)-ketoprofen in human plasma by liquid chromatography/tandem mass spectrometry following automated solid-phase extraction in the 96-well format. *Journal of Mass Spectrometry*. **2000**;35(4):504–11.
18. Hložek T, Bursová M, Čabala R. Fast ibuprofen, ketoprofen and naproxen simultaneous determination in human serum for clinical toxicology by GC-FID. *Clinical Biochemistry*. **2014**;47(15):109–11.

19. Koppala S, Ranga Reddy V, Anireddy JS. Development and Validation of a Novel Stability-Indicating RP-HPLC Method for the Simultaneous Determination of Related Substances of Ketoprofen and Omeprazole in Combined Capsule Dosage Form. *Journal of Chromatographic Science*. **2016**;54(5):765–75.
20. Abdel-Hamid ME, Novotny L, Hamza H. Determination of diclofenac sodium, flufenamic acid, indomethacin and ketoprofen by LC-APCI-MS. *Journal of Pharmaceutical and Biomedical Analysis*. **2001**;24(4):587–94.