J Fluoresc (2009) 19:249–255
DOI 10.1007/s10895-008-0410-6

ORIGINAL PAPER

Terbium Sensitized Luminescence for the Determination of Ketoprofen in Pharmaceutical Formulations

Salma M. Z. Al-Kindy · Zakiya Al-Harasi · Fakhr Eldin O. Suliman · Abdalla Al-Hamadi · Avin Pillay

Received: 16 June 2008 / Accepted: 11 August 2008 / Published online: 5 September 2008

Abstract This paper explores an ultra-sensitive luminescence method for the determination of Ketoprofen (KP) in pharmaceutical formulations. The technique is indirect and exploits the luminescence enhancement of terbium (Tb^{3+}) by complexation with KP (Tb^{3+}–KP), which was monitored at respective excitation and emission wavelengths of λ_{ex}=258 nm and λ_{em}=549 nm. The effect of varying the Tb^{3+} concentration and using multiple solvents was examined to determine optimal experimental conditions. Maximum sensitization was accomplished in the presence of methanol where the most favourable condition for the formation of the complex was recorded at a level of 1.0×10^{-5} M of Tb^{3+}. Under these optimum experimental conditions, linear calibration curve was obtained in the range of 2.8×10^{-7}–3.1×10^{-6} M with a detection limit of 8.7×10^{-8} M. The technique was validated with 'working' reference standards and produced relative standard deviations < 2% indicating that the reproducibility was highly acceptable. The proposed method was successfully applied to assays of KP in pharmaceutical formulations with average recoveries of 92–98%. The results were found to be in good agreement with those obtained by HPLC. The method is highly suited for general applications of this nature.

Keywords Ketoprofen · Terbium · Sensitized luminescence · HPLC · Drug formulations

S. M. Z. Al-Kindy (✉) · Z. Al-Harasi · F. E. O. Suliman · A. Al-Hamadi
Department of Chemistry, Sultan Qaboos University, College of Science, Box 36, Al-Khod 123, Muscat, Sultanate of Oman
e-mail: alkindy@squ.edu.om

A. Pillay
Department of Chemistry, The Petroleum Institute, Abu Dhabi Box 2533, UAE

Introduction

Ketoprofen (KP), (2-(3-benzoylphenyl) propionic acid, is a non-steroidal anti-inflammatory drug (NSAID) used for the treatment of inflammatory diseases and musculoskeletal injury. The drug is of use in relieving pain associated with rheumatic and non-rheumatic inflammatory disorders, vascular headaches, and dysmenorrheal. Ketoprofen and other NSAIDs have side effects that involve the gastrointestinal system, the irritation of the stomach, nausea and vomiting. All NSAIDs are useful in the inhibition of the enzyme cyclooxygenase (COX). COX is necessary in the formation of prostaglandins, which cause swelling and pain [1]. NSAIDS including aspirin, ibuprofen, indomethacin, ketoprofen and sulindac have been shown to prevent azoxymethane (AOM) induced aberrant crypt focus that are associated with colon cancer [1]. This beneficial effect is attributed to the blockage of COX-2 genes which is inappropriately turned on and stays on, in breast and other types of cancers. Toning down this kind of dysfunctional, uncontrolled inflammation can block critical steps in tumor development such as cell division, the growth of new blood vessels and the spread of the tumor to other areas of the body [2].

With ever increasing use and the number of formulations entering the market, there is always a need for simple, sensitive, accurate, rapid and reproducible analytical method for the estimation of KP in pure forms and in formulations.

Several analytical methods have been used for the determination of KP. These methods include spectrophotometry [3], capillary electrophoresis [4–7], chemiluminescence [8], gas chromatography-mass spectrometry (GC-MS) [9], capillary electro chromatography [10, 11], high performance liquid chromatography (HPLC) [12–16], HPLC-MS [17, 18] and micellar chromatography [19].

Fluorimetric methods are the methods of choice for the trace analysis because of their sensitivity and selectivity. Ketoprofen is weakly fluorescence in nature and hence limits its determination by fluorescence. However, this drug contains a carboxylic acid group which is known to form complexes with many metals such as Tb^{3+} and Eu^{3+}. Addition of these ions to the carboxylic acid solution leads to the formation of complexes that absorbs energy at the characteristic wavelength of the organic ligand and emits radiation at the characteristic wavelength of the lanthanide ions (Ln (III). Terbium-sensitized luminescence has been applied for the determination of benzoic acid and several derivatives such as anthranilic acid, salicylic acid, terephthalic acid and 1, 4, di-amino benzoic acid. [20–24]. On the other hand, lanthanide ions such as europium and terbium exhibit weak absorption coefficients and low fluorescence quantum yields. Lanthanide ions when chelated with ligands that have broad intense absorption bands lead to appreciable enhancement in the luminescence intensity of the system. This arises from the intramolecular energy transfer through the excited state of the ligand, which serves as an antenna chromophore, to the emitting level of the Ln (III) ion. The intramolecular energy transfer from the triplet state of the organic ligand to the lanthanide ion, depends on the structure of the ligand and the position of its triplet state, and could lead to a marked increase in the luminescence intensity [25]. This phenomenon is called the "antenna effect' and such complexes are considered to be light conversion molecular devices because they are able to transform light absorbed by the ligand into light emitted by the ions *via* an intramolecular energy transfer process.

As part of our ongoing interest on method development on drug analysis [26–28], we report a novel method for the assay of ketoprofen in pharmaceutical formulations. The method is based on the luminescence enhancement and sensitization of terbium brought about by complexation with KP. The luminescence properties were investigated in various solvents. Factors affecting complexation such as the concentration of Tb^{3+} and the ratio of Tb^{3+} to KP was carefully investigated. The method was subsequently used to determine the concentration of KP in pharmaceutical samples. Our experimental results were validated by a well established HPLC method [29].

Experimental

Instrumentation

Time resolved luminescence studies were undertaken on a Perkin Elmer LS-55 luminescence spectrometer (Perkin Elmer, Beaconsfield UK) equipped with a xenon discharge flash lamp. Both the operation and data processing were controlled by the FL Win Lab Software. The excitation and emission wavelengths were set at 258 nm and 549 nm respectively. Gate and delay times of 1.5 ms and 0.03 ms, respectively, were used throughout. Absorption spectra were recorded on a diode array spectrophotometer (HP 8453, Hewlett Packard, Germany) using matching 1 cm quartz cells. HPLC experiments were carried out using a DIONEX instrument (Germany) equipped with a photodiode array detector (Dionex UVD 170S), and a P 580 high-precision pump. The injector is linked to a Rheodyne facility (Cotati USA) fitted with a 20 µl sample loop. The output of the detector was connected to a Pentium III computer system for data collection (DtK computer). The analytical column used for the separation was Waters Spherisorb, 5 µm particle ODS2 (250 mm×4.6 mm). 20 µl samples were injected onto the column. The mobile phase was acetonitrile: water: Phosphate buffer pH 3.5 (43:55:2 *v*/*v*), it was filtered through 0.45 µm pore PTFE membranes using a Millipore filtration system (Millipore, Milford, MA, USA), and degassed by vacuum prior to analysis. The flow rate was maintained at 1 ml/min. The detection wavelength was set at 233 nm.

Reagents and pharmaceuticals

Ketoprofen 99.4% pure was acquired from Sigma-Aldrich (St Louis Mo USA). Terbium (III) Chloride hexahydrate was obtained from Kanto (Tokyo, Japan). HPLC grade methanol was procured from Riedel-de Haën (Germany); and acetonitrile was obtained from (Chromasolv, for HPLC).

Pharmaceutical formulations: Oruvail-200 capsules ketoprofen BP (RhôNE-POULENC RORER, Dagenham, England), ketoprofen gel 2.5% (A. Menarini, Industrie Farmaceutiche Riunite S.r.l., Florence-Italy) and Profenid 100 mg (Aventis, France), were purchased from local retail outlets.

Preparation of standard solutions

A KP working standard solution (1.3×10^{-4} M) was freshly prepared by appropriate dilution of a stock solution with methanol. Likewise, a terbium (III) chloride stock standard solution (1×10^{-3} M) was independently prepared in methanol.

Preparation of drug samples

Three commercial products containing 100 mg KP coated tablet, 200 mg KP capsule and KP gel 2.5% were analyzed. The product (200 mg KP) contains excipients such as: lactose, corn starch, pregelatinized corn, starch, croscarmellose sodium, magnesium stearate and anhydrous colloidal silica, whereas the product (100 mg KP) contains sucrose. Ten

tablets of Profenid (100 mg KP) and five capsules of Oruvail 200 mg ketoprofen were separately weighed, and then the tablets were powdered and mixed. A portion of the powder known to contain an equivalent amount of one tablet was accurately weighed and sonicated with methanol for 30 min. It was then filtered into a volumetric flask and completed to the mark with methanol to make a stock solution. Working solutions of 3.9×10^{-4} M in methanol were prepared. Appropriate aliquots from the working solution were taken for the determination of KP in the samples. Complexation reaction between Tb and KP occurred instantly at room temperature and the luminescence intensity of the complex was measured within 5 min after mixing of TB with KP. For the ketoprofen gel preparation, an accurately weighed portion of the pharmaceutical gel corresponding to 4.9×10^{-5} moles of ketoprofen (about 0.5 g) was transferred into a 100 ml methanol in a beaker and sonicated for 30 min. It was then filtered into a 100 ml volumetric flask and completed to the mark with methanol to make a stock solution. Appropriate aliquots from these working solutions were taken for the determination of KP in the samples. For HPLC analysis, suitable solutions were prepared in the mobile phase.

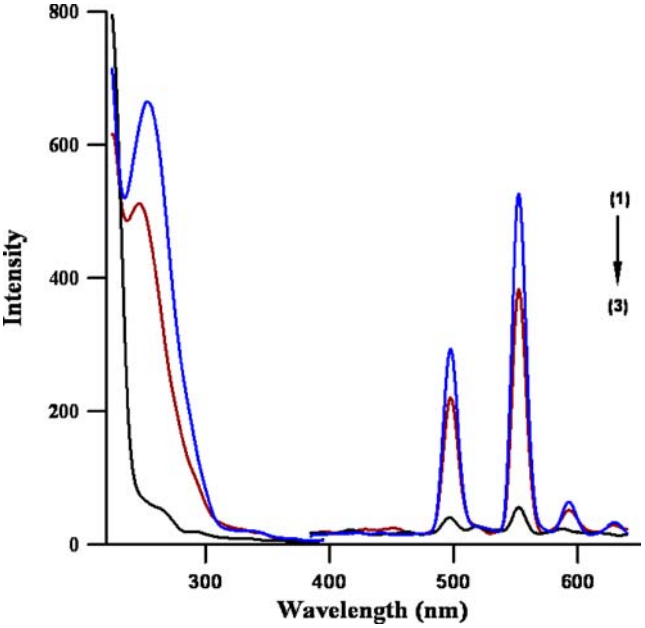


Fig. 1 Influence of [KP] on terbium sensitized luminescence. $[Tb^{3+}]=1\times10^{-5}$ M, $\lambda_{ex}=258$ nm. $\lambda_{em}=549$ nm. [KP]; (*1*) 1 ppm, (*2*) 0.8 ppm, (*3*) 0 ppm

Results and discussion

Spectral characteristics

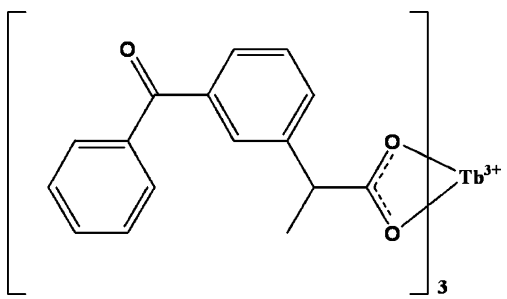
The fluorescence spectra of KP in methanol were investigated by measuring a KP solution (8×10^{-6} M) in methanol. A weak fluorescence signal of at $\lambda_{em}=353$ nm, with excitation at 293 nm was obtained. This fluorescence is ineffective for practical use in analytical studies at low concentrations of KP. To improve the analytical characteristics for the determination of KP in pharmaceutical formulations, the system of (KP–Tb^{3+}) in methanol was subsequently investigated, where KP was primed to sensitize the luminescence of terbium ion. The spectral characteristics of Tb (III) in methanol are shown in Fig. 1. A very weak signal was observed. However, the introduction of KP to this mixture resulted in an intense well known structured emission spectrum of Tb^{3+}. Clearly, the intensity of the emission line was greatly enhanced in the presence of KP as compared to Tb^{3+} alone. The luminescence enhancement of the Tb (III) ions upon complexation with KP is attributed to the efficient transfer of excitation energy from the KP moiety to the encapsulated Tb (III) ion, which can easily overcome the ion's intrinsically low extinction coefficient. The successful sensitization process requires the sensitizing moiety to be excited in the ultraviolet region since its triplet energy is sufficient to provide efficient energy transfer to the rare earth ion. The necessary criteria are adequately met by the KP chelate since it absorbs at 258 nm. It has been argued that the longest wavelength at which sensitized luminescence from Tb^{3+} can be excited is at 341 nm [30]. Further more, the intramolecular transfer efficiency depends on the energy transfer from the lowest triplet level (T) of the ligand to the resonance level of Tb^{3+} ion ($^5D_4$) located at 20,500 cm^{-1} and the back transfer from the resonance level of the ion to the triplet level of the ligand if the energy difference between the two levels is less than 1,500 cm^{-1} [31]. According to the phosphorescence spectrum of ketoprofen [32], the triplet state is expected to be located at 22,472 cm^{-1}, which would correspond to an energy difference of about 1,972 cm^{-1}. The emission spectrum of Tb–KP complex when excited by the π–π^* absorption band at 258 nm of the complex (Fig. 1) revealed the well known bands of terbium luminescence based on the $^5D_4$–$^7F_6$ (490 nm), $^5D_4$–$^7F_5$ (545 nm), $^5D_4$–$^7F_4$ (590 nm) and $^5D_4$–F_3 (620 nm). Among these transitions, the $^5D_4$–$^7F_5$, around 545 nm, is the strongest followed by the one at 490 nm. Therefore, in our study, the peak height at 550 nm was used to measure the luminescence intensity of the Tb–KP complex. Although this emission band partly overlaps with the second order scatter from the excitation wavelength, this is eliminated by the time resolved mode, which can be used in these systems since they have a relatively long luminescence lifetime. Moreover, the complex in methanol produced a large Stokes shift of 292 nm which was convenient as there is no overlap of the Tb^{3+} emission bands with the antenna

chromophore absorption bands. The excitation spectra of Tb^{3+} revealed a strong band at 223 nm. Addition of KP resulted in a decrease of the band at 223 nm and formation of a new band at 258 nm (Fig. 1.) The luminescence enhancement of Tb in the presence of KP and the appearance of a new band in the excitation wavelength may be explained to be due to the complex formation between the drug and the terbium ion (Scheme 1). Similar results were previously reported for the luminescence sensitization of Tb (III) using Ibuprofen molecule [26].

The close agreement between the absorption spectrum of KP (λ=255 nm) and the excitation spectrum of Tb–KP complex (λ=258 nm; Fig. 2) clearly indicated that the excitation of the antenna chromophore may be the only photo physical pathway leading to the observable luminescence in the system [33]. The hypersensitive emission line of Tb^{3+} at 550 nm requires the investigation of different factors that affect the coordination environment. Hence the effects of varying the concentration of Tb^{3+}–KP, and using multiple solvents were investigated in order to optimize the luminescence intensity.

Effect of terbium (III) concentration

Since the sensitization occurs from complex formation between KP and Tb^{3+}, it is necessary to optimize the ratio of the concentration of the metal to the ligand that will result in maximum complexation and hence maximum intensity of the emission line of the terbium ion. The optimum concentration of terbium was determined by measuring the luminescence intensity of various molar ratios of Tb^{3+}:KP. This was achieved by maintaining a constant concentration of Tb at 1×10^{-5} M, and varying the concentration of KP by manipulating the molar ratio (KP: Tb^{3+}) between 0.5 and 5. The luminescence intensity increased with an increased concentration of KP and reached a maximum value at a ratio of 3:1 after which the intensity remained constant (Fig. 3). Hence the concentration of terbium in this study was maintained at three times that of KP.



Scheme 1 Structure of the Tb–KP complex

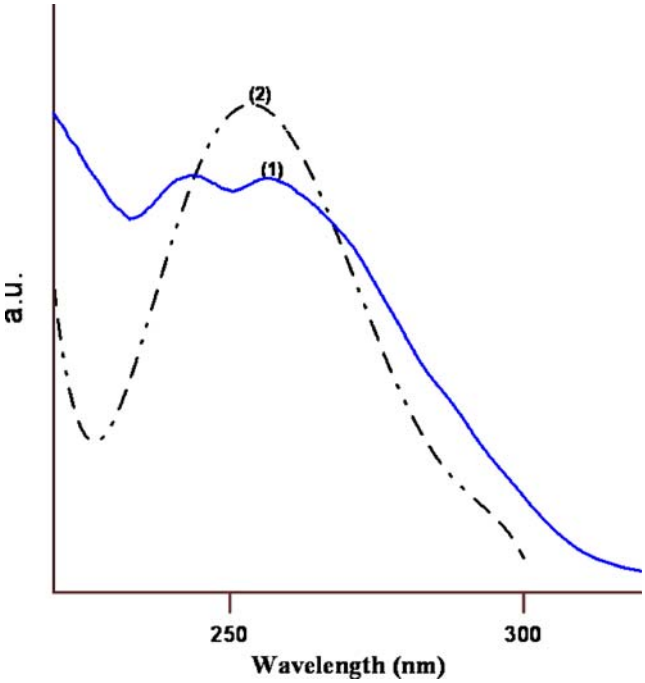


Fig. 2 Luminescence excitation spectra of: (*1*) Tb–KP complex in MeOH system, $[Tb^{3+}]=1\times10^{-5}$ M, $[KP]=5\times10^{-6}$ M, $\lambda_{em}=549$ nm (*2*) absorption spectrum of KP in MeOH, $[KP]=8\times10^{-6}$ M

The stoichiometry of the complex was corroborated using Job's plot of continuous variation. Equal concentrations of Tb^{3+} and KP (1.0×10^{-3} M) were used, and the molar ratio of Tb^{3+}:KP was varied. The luminescence intensity increased with an increase in the mole fraction of Tb^{3+}:KP and reached a maximum at a mole fraction of 0.25 (Fig. 4), indicating a stoichiometry of Tb^{3+}:KP of 1:3. The formation constant was calculated using numerical method described elsewhere [34]. A simple MATLAB computer program was developed to analyze the continuous variation data. Using this method, several models were fitted iteratively

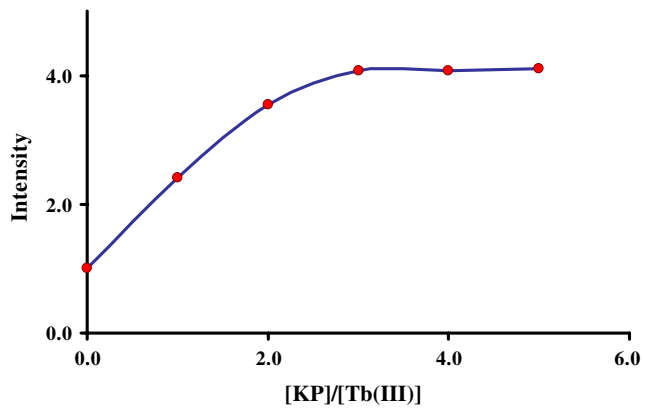


Fig. 3 Influence of [KP]:[Tb^{3+}] ratio on terbium sensitized luminescence. $[Tb]=1\times10^{-5}$ M, $\lambda_{ex}=258$ nm. $\lambda_{em}=549$ nm

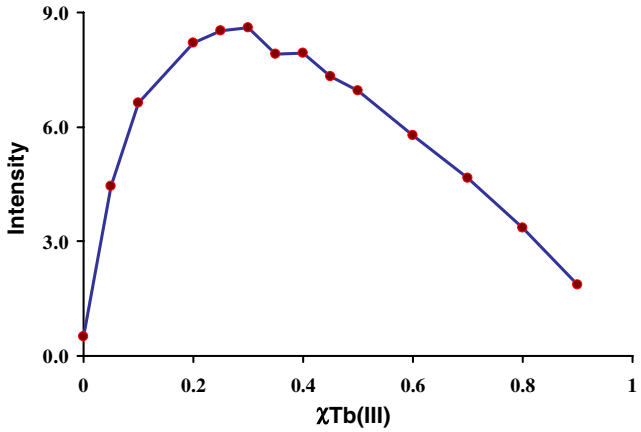


Fig. 4 Continuous variation method of the Tb (KP) complex in MeOH. [Tb]=[KP]=1.0×10^{-3} M, λ_{em}=549 nm, λ_{ex}=258 nm

to the experimental data by varying the stoichiometric ratio and the value of the formation constant. Using a least square method the stoichiometry of Tb^{3+}:KP of 1:3 was found to produce the lowest sum of square of errors. The formation constant obtained in this way was 1.1×10^{8}. According to the documented literature, a formation constant of similar order was previously reported by Hansen et al. [35] for unsubstituted benzoic acid derivatives.

Effect of solvent

It is a well known phenomenon that the type of solvent used influences the luminescence intensity of the molecule. Therefore an attempt was made to study the effect of the solvent on the luminescence intensity of the KP–Tb^{3+} complex. Figure 5 shows the effect of the solvent on the luminescence emission of the complex. It is clear that optimum conditions are obtained in methanol followed by ethanol, propanol, butanol and finally water. The dielectric constants (ε) of these solvents are: methanol 32.6, ethanol 24.5, propanol 20.3, butanol 17.1 and water 78.8. It was found that solvent polarity and dielectric constant are related to fluorescence enhancement. Similar results were previously reported by Dang et al. [36] and Qin et al. [37] for terbium and europium complexes, where maximum sensitization was observed in the presence of methanol. This behavior was attributed to the stronger coordination ability of methanol with terbium [36]. It has been reported that the difference in intensity of the hypersensitive transitions between the four alcoholic solutions indicates the different coordination behaviour of the alcohols with terbium metal. The emission intensity decreases with an increase in the alkyl chain in the alcohols [38]. The low sensitization in water may be due to the O–H oscillators of water molecules that are known to quench the excited state of the lanthanide ions by interaction with high-energy vibrations associated with O–H. Solvent molecules can usually replace coordinated water and avoid high frequency O–H bond vibration—thus greatly decreasing energy loss resulting through the coordination of water molecules, and increasing the fluorescence intensity of the emitting lanthanide ion. This suggests that the chemical environment plays an important role in determining the fluorescence intensity of the complexes; hence the choice of methanol was ideal in studying the luminescence of the Tb–KP complex. A red shift was observed in the excitation wavelength from 258 nm in methanol to 266 nm for the complex in ethanol, propanol and butanol and 276 nm in water (Fig. 5).

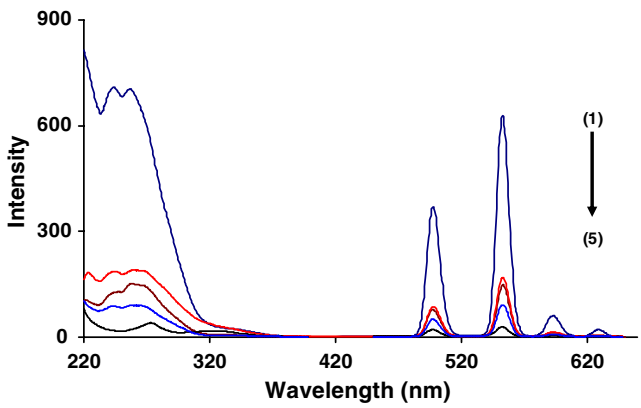


Fig. 5 Effect of type of solvent on terbium sensitized luminescence Excitation and Emission spectra. [KP]=3×10^{-5} M, [Tb] = 1×10^{-5} M, (*1*) methanol, (*2*) ethanol, (*3*) propanol, (*4*) butanol, (*5*) water

Table 1 Analysis of various commercially available dosage forms using the proposed procedure

Formulations	Claim amount	%Recovery±sd
Oruvail 200 (Dagenham, England)	196 mg	98.0±1.6
Gel 2.5% (Florence, Italy)	2.3%	92.±1.7
Profenid 100 (Aventis, France)	97 mg	97.0±1.7

Table 2 Results obtained by the proposed method and by HPLC-UV method

Sample	HPLC method	This method	T^a	F^b
Gel 2.5%	2.8±0.06%	2.3±0.04%	0.375	2.48
Profenid 100 mg	94±2.1	97±1.5	2.25	1.78

[a] t_{table}=2.447 (n1=3, n2=5, α=0.05)
[b] F_{table}=5.41 (n1=3, n2=5, α=0.05)

Verification of sensitisation by KP ligand

To verify that sensitization is brought about by the presence of the KP ligand, emission intensities in the presence of various concentrations of KP were measured while keeping the concentration of Tb^{3+} constant. An increase in the luminescence intensity was observed with an increase in the concentration of KP in the range studied. Figure 1 shows the sensitization of Tb^{3+} luminescence brought about by the presence of the KP ligand. The analytical performance of the proposed system was studied using the optimum conditions discussed above. A linear calibration was obtained with R^2= 0.9993. The calibration equation was: I=460.7C–7.70, where I is the emission intensity and C is the concentration. The detection limit (signal to noise ratio of 3) was 8.7×10^{-8} M. The reproducibility of the method was examined for standard solutions of KP and was found to be less than 0.9% (n=5).

Determination of KP in pharmaceutical preparations

The proposed method was applied to the determination of the concentration of KP in pharmaceutical formulations of different brands as shown in Table 1. Five samples were prepared as described above and were analyzed. The mean percent recovery was found to be in the range 92–98%. It is clear from this result that excellent recovery with no interference from excipients was obtained. The relative standard deviation was less than 2% (n=5) showing excellent precision.

Our technique was corroborated using HPLC-UV. Five independent determinations of ketoprofen in pharmaceutical formulations were undertaken using the proposed luminescence method and three determinations using HPLC-UV procedure as a reference method. The results are shown in Table 2. Both methods reported satisfactory recoveries and relative standard deviations compared with the 'certification' of the standard samples. The data in Table 1 clearly demonstrate that the method we developed is suitable for the determination of KP in pharmaceuticals without fear of interferences from the matrix. The results obtained by the two methods were tested by the Student's t-test and the F-test and produced comparable accuracy and precision.

Conclusions

A sensitive technique was developed for the assay of KP in pharmaceutical preparations. The proposed method (based on sensitized terbium time resolved luminescence) has the advantage of being simpler, more rapid, and suitable for automation. It was successful for a range of analyses conducted on appropriate solutions of varying concentration and solvent. The procedure was applied to the determination of KP in different tablets with excellent recoveries and reproducibility. It produced a minimum limit of detection for ketoprofen of 8.7×10^{-8} M. As a result, the proposed method represents a good analytical alternative for the determination of ketoprofen in pharmaceutical formulations. Future research involves monitoring of KP in biological systems.

References

1. Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, Pereira MA (1999) Termination of piroxicam treatment and the occurrence of azoxymethane-induced colon cancer in rats. Cancer Lett 147:187–197 doi:10.1016/S0304-3835(99)00296-7
2. Baek SJ, Kim KS, Nixon JB, Wilson LC, Eling TE (2001) Cyclooxygenase inhibitors regulate the expression of a TGF-beta superfamily member that has proapoptotic and antitumorigenic activities. Mol Pharmacol 59:901–908
3. Aboul-Enein HY, Dal AGl, Tuncel M (2003) A validated method development for ketoprofen by a flow-injection analysis with UV-detection and its application to pharmaceutical formulations. Farmaco 58:419–422
4. Blanco M, Coello J, Iturriaga H, Maspoch S, Perez-Maseda C (1998) Chiral and nonchiral determination of ketoprofen in pharmaceuticals by capillary zone electrophoresis. J Chromatogr A 799:301–307 doi:10.1016/S0021-9673(97)01040-6
5. Wolbach JP, Lloyd DK, Wainer IW (2001) Approaches to quantitative structure—enantioselectivity relationship modeling of chiral separations using capillary electrophoresis. J Chromatogr A 914:299–314 doi:10.1016/S0021-9673(01)00580-5
6. Glówka FK, Karaźnieuricz M (2004) High performance capillary electrophoresis for determination of the enantiomers of 2-arylpropionic acid derivatives in human serum. Pharmacokinetic studies of ketoprofen enantiomers following administration of standard and sustained release tablets. J Pharm Biomed Anal 35:807–816
7. Sadecka J, Cakrt M (2005) Effect of non-ionic surfactants on isotachophoretic separations of 2-arylpropionic acids. J Chromatogr A 1084:152–159 doi:10.1016/j.chroma.2004.08.139
8. Zhuang Y, Song H (2007) Sensitive determination of ketoprofen using flow injection with chemiluminescence detection. J Pharm Biomed Anal 44:824–828 doi:10.1016/j.jpba.2007.03.014
9. Lin WC, Chen HC, Ding WH (2005) Determination of pharmaceuticals residues in waters by solid phase extraction and large volume on-line derivatisation with gas chromatography-mass spectrometry. J Chromatogr A 1065:279–285 doi:10.1016/j.chroma.2004.12.081
10. Hoegger D, Freitag R (2001) Acrylamide-based monoliths as robust stationary phases for capillary electrochromatography. J Chromatogr A 914:211–222 doi:10.1016/S0021-9673(00)01119-5
11. Pai Y, Liu C (2002) Capillary electrochromatographic separation of non-steroidal anti-inflammatory drugs with a histidine bonded phase. Electrophoresis 22:518–525
12. Pradosa P, Fukushima T, Santa T, Homma H, Tsunoda M, Al-Kindy SM et al (1997) 4-N,N-Dimethylaminosulfonyl-7-*N*-(2-aminoethyl)aminobenzofurazan as a new precolumn fluorescence derivatization reagent for carboxylic acids (fatty acids and drugs containing a carboxyl moiety) in liquid chromatography. Anal Chim Acta 344:227–232 doi:10.1016/S0003-2670(97)00020-2
13. Al-Kindy SM, Santa T, Fukushima T, Homma H, Imai K (1997) 1-(5-Dimethylamino-1-naphthalenesulphonyl)-(*S*)-3-aminopyrrolidine (DNS-Apy) as a fluorescence chiral labelling reagent for carboxylic

acid enantiomers. Biomed Chromatogr 11:137–142 doi:10.1002/(SICI)1099-0801(199705)11:3<137::AID-BMC648>3.0.CO;2-T
14. Bempong DK, Bhattacharyya L (2005) Development and validation of a stability-indicating high-performance liquid chromatographic assay for ketoprofen topical penetrating gel. J Chromatogr A 1073:341–346 doi:10.1016/j.chroma.2004.12.061
15. Dvoˇr'ak J, H'ajkov'a R, Matysov'a L, Nov'akov'a L, Koupparis MA, Solich P (2004) Simultaneous HPLC determination of ketoprofen and its degradation products in the presence of preservatives in pharmaceuticals. J Pham Biom Anal 36:625–629 doi:10.1016/j.jpba.2004.07.018
16. Fukushima T, Santa T, Homma H, Al-Kindy SM, Imai K (1997) Enantiomeric separation and detection of 2-arylpropionic acids derivatized with [(*N*, *N*-Dimethylamino)sulfonyl] benzofurazan reagents on a modified cellulose stationary phase by high-performance liquid chromatography. Anal Chem 69:1793–1799 doi:10.1021/ac961105g
17. Abdel-Hamid ME, Novotny L, Hamza H (2001) Determination of diclofenac sodium, flufenamic acid, indomethacin and ketoprofen by LC-APCI-MS. J Pham Biom Anal 24:587–594 doi:10.1016/S0731-7085(00)00444-1
18. Panusa A, Multari G, Incarnato G, Gagliardi L (2007) High-performance liquid chromatography analysis of anti-inflammatory pharmaceuticals with ultraviolet and electrospray-mass spectrometry detection in suspected counterfeit homeopathic medicinal products. J Pham Biom Anal 43:1221–1227 doi:10.1016/j.jpba.2006.10.012
19. Mart'ınez-Algaba C, Escuder-Gilabert L, Sagrado S, Villanueva-Camañas RM, Medina-Hernández MJ (2001) Comparison between sodium dodecylsulphate and cetyltrimethylammonium bromide as mobile phases in the micellar liquid chromatography determination of non-steroidal anti-inflammatory drugs in pharmaceuticals. J Pham Biom Anal 36:393–399 doi:10.1016/j.jpba.2004.06.011
20. Arnoud N, Georges J (2003) Investigation of the luminescence properties of terbium—anthranilate complexes and applications to the determination of anthranilic acid derivatives in aqueous solutions. Anal Chim Acta 476:149–157 doi:10.1016/S0003-2670(02)01357-0
21. Panadero S, Gómez-Hens A, Pérez-Bendito D (1996) Kinetic determination of salicylic acid, diflunisal and their mixture based on lanthanide-sensitized luminescence. Anal Chim Acta 329:135–149 doi:10.1016/0003-2670(96)00144-4
22. Agüilar-Caballos MP, Gòmez-Henz A, Pèrez-Bendito D (1999) Simultaneous determination of benzoic acid and saccharin in soft drinks by using lanthanide-sensitized luminescence. Analyst (Lond.) 124:1079–1085 doi:10.1039/a902402f
23. Caro de la Torre MA, Gömez-Henz A (2000) Evaluation of the terbium (III)-sensitized luminescence with benzenecarboxylic acids. Determination of terephthalic acid in drink samples. Anal Chim Acta 407:53–60 doi:10.1016/S0003-2670(99)00824-7
24. Panadero S, Gömez-Henz A, Përez-Bendito D (1998) Use of time-resolved lanthanide-sensitized luminescence for the kinetic determination of *p*-aminobenzoic acid. Talanta 45:829–834 doi:10.1016/S0039-9140(97)00169-0
25. Lis S (1993) Analytical applications of lanthanide luminescence in solution. Chem Anal Warsz 38:443–454
26. Al-Kindy SM, Suliman FO (2007) Determination of ibuprofen in pharmaceutical formulations using terbium sensitized luminescence. Lumin 22:294–301 doi:10.1002/bio.962
27. Al-Kindy SM, Suliman FO, Al-Wishahi AA, Al-Lawati HAJ, Aoudia M (2007) Determination of piroxicam in pharmaceutical formulations and urine samples using europium-sensitized luminescence. J Lumin 127:291–296 doi:10.1016/j.jlumin.2006.12.005
28. Al-Kindy SM, Suliman FO, Al-Wishahi AA (2004) A sequential injection method for the determination of piroxicam in pharmaceutical formulations using europium sensitized fluorescence. Talanta 64:1343–1350 doi:10.1016/j.talanta.2004.04.014
29. The European Pharmacoepia fourth Ed, Council of Europe, Strasbourg France, 2003, pp3065–3066
30. Steemers FJ, Verboom W, Renihoudt DN, Vander EB, Verhoeven JW (1995) New sensitizer-modified calixarenes enabling near-UV excitation of complexed luminescent lanthanide ions. J Am Chem Soc 117:9408–9414 doi:10.1021/ja00142a004
31. Wei-Na Wu, Tang N, Yan L (2008) Rare earth complexes with a novel ligand *N*-(naphthalene-2-yl)-*N*-phenyl-2-(quinolin-8-yloxy) acetamide: Preparation and spectroscopic studies. Spectro Chimic Acta A. doi:10.1016/j.saa.2008.05.001
32. Lhiaubet V, Gutierrez F, Penaud-Berruyer F, Amouyal E, Jean-Pierre Daudley R, Poteau Chouini-Lalanne N, Paillous N (2000) spectroscopic and theoretical studies of the excited states of fenofibric acid and ketoprofen in relation with their photosensitizing properties. New J Chem 24:403–410
33. Werts MHV, Hofstraat JH, Geurts FAJ, Verhoeven JW (1997) Fluorescein and eosin as sensitizing chromophores in near-infrared luminescent ytterbium (III), neodymium (III) and erbium (III) chelates. Chem Phys Lett 276:196–201 doi:10.1016/S0009-2614(97)00800-2
34. Suliman FO, Al-Lawati HAJ, Al-Kindy SM, Nour IE, Salama SB (2003) A sequential injection spectrophotometric method for the determination of penicillamine in pharmaceutical products by complexation with iron (III) in acidic media. Talanta 61:221–231 doi:10.1016/S0039-9140(03)00250-9
35. Hansen Y, Jianping E, Qun YU (1988) Luminescence properties of benzoic acid terbium complexes. J Lumin 42:29–34 doi:10.1016/0022-2313(88)90062-2
36. Dang F, Li Y, Liu W (2007) The new fluorescence enhancement system Tb-*N*-(2-pyridinyl) ketoacetamide-Et_3N-Zn and its application. Spectro Chimic Acta A 66:676–680 doi:10.1016/j.saa.2006.04.010
37. Qin W, Zhang Y, Liu W, Tan M (2003) Synthesis and infrared and fluorescence spectral properties of luminescent terbium and europium complexes with open chain–chain carboxylate crown ethers. Spectro Chimic Acta A 59:3085–3092 doi:10.1016/S1386-1425(03)00112-4
38. Ansari AA, Singh N, Khan AF, Singh SP, Iftikhar K (2007) Solvent effect on optical properties of hydrated lanthanide tris–acetylacetone. J Lumin 127:446–452 doi:10.1016/j.jlumin. 2007.02.057