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Review on the Determination of the Pharmaceutical Compound Ketotifen fumarate

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Summary a review on different methods used for the determination of ketotifen fumarate in pure state and in its pharmaceutical preparations is given. These are categorized according to the type of method used.

Ketotifen fumarate, 4-(1-methylpiperidin-4-ylidene)-4H-benzo-4,9-dihydro-10H-benzo[4,5]cyclohepta-[1,2-b]thiophen-10-one hydrogen (E)-butenedioate[(1)] (Fig. 1), is an antihistamine that inhibits down regulation of beta receptors, which are often degraded by fat-burners such as Albuterol and Clenbuterol.

It can be used in combination with other drugs in order to keep feeling their fat-burning effects for longer periods of time without the need for periods of on and off cycling. Side effects can include drowsiness, irritability, nasal bleeding and dry mouth. Ketotifen increases appetite; therefore another side effect is typically weight gain. Ketotifen also (potentially) improves insulin sensitivity within muscle tissue.

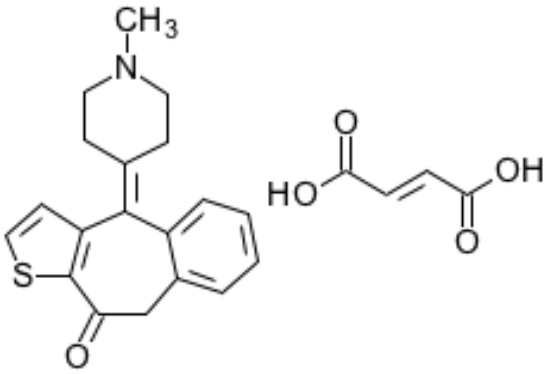

Fig. 1. The chemical structure of ketotifen fumarate

The antihistaminic drug, Ketotifen fumarate, was determined by several methods as Spectral, Chromatographic and Potentiometric methods, those methods are described below.

Spectral methods

Mohamed and Aboul-Enein[2] determined ketotifen fumarate in the powder form and in capsules by spectrophotometry at 300 nm (ε = 13,800) in acetate buffer solution. (pH 5). Beer's law was obeyed for 2 to 30 μg ml^{-1} and recoveries were 100.8 and 99.8% for powder and capsules, respectively.

Vachek[3] diluted an aqueous solution containing ~75 μg ketotifen fumarate to 4.5 ml with H_2O, mixed with 4 ml of aqueous 0.1% picric acid and extracted with 5 ml of $CHCl_3$ by shaking for 2 min. The absorbance of the extract was measured at 405 nm versus a reagent blank. The calibration graph was rectilinear for 5 to 25 μg ml^{-1} ketotifen fumarate in the extract. The method was used to analyze tablets.

Szczepaniak et al.[4] dissolved sample of ketotifen in 2 M HCl and the solution was shaken for 15 min with the ion exchanger Amberlyst 15 (H^+ form). The solution was then separated from the ion-exchanger and its absorbance was measured at 298 nm. Recoveries were 98.5 to 102.3% and the coefficient of variation was 2%.

Sane et al.[5] diluted aqueous sample solution of ticlopidine hydrochloride, buspirone hydrochloride or nefopam hydrochloride or methanolic sample solution of ketotifen fumarate with buffer solution and treated with aqueous 0.1% solution of bromophenol blue, bromothymol green, bromothymol blue or bromocresol purple. The drug dye complex was extracted into $CHCl_3$ and the absorbance of the extract was measured at the corresponding wavelength of maximum absorbance. Optimum reaction conditions (pH and volume of buffer solution, volume of dye, volume of $CHCl_3$ and λ_{max}, nm, recovery and coefficient of variation are tabulated for all four drugs. Details are given for the analysis of pharmaceuticals.

Sastry and Naidu[6] compared four spectrophotometric methods for the determination of ketotifen fumarate. The first was based on the formation of a coloured species via coupling of the diazotized sulphanilamide with the drug (λ_{max} = 520 nm). The second was based on oxidation with excess N-bromosuccinimide (NBS) and determination of the unconsumed NBS with decrease in the color intensity of celestine blue (λ_{max} = 540 nm). The third used reduction of Folin-Ciocalteau reagent (λ_{max} = 720 nm). The fourth was based on the formation of a chloroform-soluble, colored ion-association complex between the drug and Azocarmine G at pH 1.5 (λ_{max}

=540 nm). Beer's law was obeyed from 1-10, 2-12, 4-28 and 2.5-25 mg/l for the methods, respectively. The detection limits and RSD (n = 6) were 42-101 µg/l and 0.29-0.48%, respectively. The methods were validated by applying to pharmaceutical formulations; recoveries and RSD (n = 3) were 98.9-100.2% and ±1%, respectively.

Sastry and. Naidu[7] extracted an equivalent to 3.4 mg ketotifen or 3.2 mg terfenadine with $CHCl_3$ (4x5 ml) from tablet powder or syrup. The combined extracts were evaporated to dryness, treated with 3 ml 10% citric acid in acetic anhydride and heated on a water bath for 15 min. A 0.5 ml of the cooled solution was diluted to 25 ml with methanol then, fluorescence measurements were made after 5 min and before 3 h, excitation was at 428.2 and 425 nm, and measuring at 468 and 465.2 nm for ketotifen and terfenadine, respectively. Beer's law was obeyed for 0.064-0.400 µg/ml ketotifen and 0.062-0.400 µg/ml terfenadine, the recoveries were >98%. Common excipients, diluents and synthetic colors did not interfere.

For AAS, El-Kousy and Bebawy treated sample solution containing ketotifen, loratadine or pizotifen with 6 ml 56.25% NH_4SCN and 13% $CoCl_2$ solution, diluted to 15 ml with citrate buffer solution of pH 2.0, and extracted with 2 x 10 ml CH_2Cl_2, $CHCl_3$ or benzene, respectively. The combined extracts were shaken with 2x10 ml 0.1 M HCl, the combined acid extracts were diluted to 25 ml with 0.1 M HCl, and the absorbance was measured at 240.7 nm by using Co hollow-cathode lamp in an air/acetylene flame. Calibration graphs were linear up to 95, 93 and 74 µg/ml, with determination limits (LOQ) of 14.1, 12.6 and 12.6 µg/ml, and detection limits (DL) of 2, 2 and 1 µg/ml, respectively. For spectrophotometry, a mixture of 2 ml 0.01 M ammonium molybdate in aqueous 1% NH_3, 8 ml 5 M HCl and 6 ml each of 10% NH_4SCN solution and 10% ascorbic acid solution was set aside for 15 min, the sample solution is added, and the mixture is diluted to 25 ml with H_2O, set aside for 15 min, and extracted with 10 ml CH_2Cl_2. The absorbance of the extract was measured at 469.5 nm versus a reagent blank. Calibration graphs were linear up to 37.5, 22.5 and 25 µg/ml, with LOQ of 11.2, 7.9 and 7.9 µg/ml, and DL of 0.3 µg/ml, respectively. Alternatively, the sample solution is treated with 4 (for ketotifen or loratadine) or 5 ml (for pizotifen) of 0.3% 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) solution in acetonitrile and diluted to 10 ml with acetonitrile, and the absorbance is measured at 588 nm vs. a reagent blank. The calibration graphs were linear up to 80 µg/ml with

LOQ 12.6 µg/ml and detection limit 1 µg/ml. Sample-preparation procedures are given for ketotifen and pizotifen in tablets and syrup and loratadine in tablets. Recoveries of the pure compounds and known additions to the cited preparations were quantitative.[8]

Chromatographic methods

Hoogewijs and Massart[9] compared two ion-pair extraction techniques with classical extraction for basic drugs, e.g., ketotifen, oxomemazine, diphenhydramine, ephedrine, chlorpheniramine and metoclopramide, from their pharmaceutical preparations. Phosphate buffer solution (pH 10) and $CHCl_3$ were used for the classical extraction. Sodium octylsulphate (0.05 M) in phosphate buffer solution (pH 3) and $CHCl_3$ were used for the first ion-pair extraction, and bis-(2-ethylhexyl) hydrogen phosphate (1 mM) in $CHCl_3$ and phosphate buffer solution (pH 5.5) for the second ion-pair. The extracts were thus analyzed by HPLC on a column (25 cm x 4 mm) packed with LiChrosorb-CN (10 µm) with various mobile phases, chiefly hexane-CH_2Cl_2-acetonitrile-propylamine (at various ratios) and 254-nm detection. Phosphate buffer solution yielded the best recovery in each instance. Full chromatographic conditions were tabulated.

Jelinek et al.[10] separated the enantiomers of ketotifen and its intermediate satisfactorily in a PTFE tube (37 cm x 0.5 mm). The leading electrolyte is 5 mM-Na acetate containing hydroxyethylcellulose 4000, adjusted to pH 5.5 with acetic acid and modified with 3 to 5 mM β-cyclodextrin or 1 mM heptakis-(2,6-di-o-methyl)-β-cyclodextrin, and 10 mM β-alanine as terminating electrolyte. A cationic current of 150 µA for 9 min was used, and conductivity (50 µA) detection. The electrolyte system was appropriate for 0.86 to 3.42 µg injected. The extent of chiral isotachophoretic separation by the choice of cyclodextrin was strongly influenced.

To determine ketotifen fumarate, Sieradzki et al.[11] incubated a 1 ml sample with β-glucuronidase at 37°C and pH 5.2 for 18 h and the mixture is then, treated with 1 ml of 1 M NaOH and extracted with benzene. The extract is evaporated to dryness, the residue is dissolved in 0.05 ml of methanol, and a 2 µl portion is injected on to a glass column (1.5 m x 4 mm) packed with 3% of SE-30 on Diatomite CQ (100 to 120 mesh) and operated at 243°C with Ar (90 ml min^{-1}) as carrier gas and ECD. The separation takes ~8 min. Calibration is linear with 5 to 50 ng ml^{-1} of ketotifen fumarate, and the peak heights are measured. The recovery is ~91% and the coefficient

of variation was 3.6% (n = 6) when determining 25 ng ml^{-1} of ketotifen fumarate in rabbit serum.

Zarapkar et al.[12] dissolved powdered tablets equivalent to 1 mg of ketotifen hydrogen fumarate in mobile phase, mixed with 5 ml of niacinamide (internal standard) solution and diluted to 50 ml with mobile phase. A 20 µl of solution was analyzed by HPLC on a column (15 cm x 3.9 mm) of ODS (5 µm) with aqueous. 10% acetonitrile (1 ml min^{-1}) was used as mobile phase and detection at 220 nm. Calibration graphs were rectilinear up to 35.8 µg ml^{-1} of ketotifen hydrogen fumarate. Coefficients of variation were 2.0 to 2.8% and recoveries were 98.07%

Extraction of powdered tablets equivalent to 110 mg ketotifen fumarate was done by Sanghavi et al.[13] with 5 ml methanol, filtered and diluted to 10 ml with methanol. After the dilution, 10 µl were applied to 60F254 precoated HPTLC plates. The plates were developed for 50 min with ethyl acetate/methanol/liquid NH_3 (150:15:1) as mobile phase. Detection was by densitometric scanning at 301 nm. The calibration graph was linear for 3.8-20 ng/µl with a detection limit 0.1 ng/µl. The recovery was 99.9±0.3% and the RSD was 1.98% for content uniformity. There was no interference from excipients or diluents.

Han and Xu[14] dissolved the outer layers of ten tablets in aqueous 60% methanol and the solution was filtered. 20 µl of the resulting solution was analyzed for salbutamol sulphate and ketotifen fumarate on a 10 µm Spherisorb SiO_2 column (25 cm x 4.6 mm) with methanol/H_2O/acetic acid (100:150:1) as mobile phase (1.5 ml/min) and detection at 276 nm. The calibration graphs were linear from 0.0384-0.192 and 0.0112-0.056 g/l for salbutamol sulphate and ketotifen fumarate, respectively. Recoveries were 99.8-100.2% with RSD of 0.47-1.09%. Excipients and co-existing components did not interfere. The influence of the methanol and acetic acid concentrations, and column packing, on chromatographic retention was studied.

A case discussing the need for validated analytical methods and procedures used in support of pharmaceutical quality control and for the validation of manufacturing process is reported[15]. Also it describes briefly the installation and operational qualifications, and the analytical validation documentation required for a validated HPLC method. Details as an illustrative example, discuss the validation elements of the robotic controlled HPLC analysis of ketotifen 1 mg capsules and

tizanidine hydrochloride 1 mg tablets, and provide comparative content uniformity data of the products performed by robotic and two manual methods.

Nnane et al.[16] analyzed ketotifen in aqueous solutions and in silicon oil suspensions on a 5 µm Bondapak C_{18} column (30 cm x 3.9 mm) equipped with a 10 µm pellicular ODS guard column (5 cm x 2 mm). A1 mM phosphate buffer of pH 7.4/methanol/acetonitrile/ trimethyl-amine (29.8:45:25:0.2) as a mobile phase (1 ml/min) and detection at 299 nm. 250 µl Silicon oil suspensions were spiked with 20 µl imipramine (20 mg/ml; internal standard, IS) was mixed with 250 µl 0.05 M HCl and centrifuged at 3000 rpm for 5 min. Portions (100 µl) of the aqueous solution were diluted 10-folds with HPLC mobile phase. The recovery of ketotifen and IS was > 80%. The limit of detection was 2.5 µg/ml with a coefficient of variation 1.56 and RSD 4.8% within-day of analysis.

Tzvetanov et al. [17] heated samples (1 ml) with 0.5 ml β-glucuronidase/sulfatase reagent of pH 5.2 for 18 h at 37°C. The solution was diluted with 4 ml H_2O and mixed with 0.5 ml 0.1 M NaOH and 50 µl pizotifen (140 ng/ml in methanol, internal standard, IS). The mixture was applied to a 0.5 g Bond Elut CN-E cartridge, the cartridge was washed with 4 ml H_2O and 1 ml propan-2-ol/H_2O (1:2) and ketotifen and IS were eluted with methanol (5 x 0.5 ml). The combined elutes were evaporated in a current of N_2 at 37°C and the residue was dissolved in 50 µl methanol. A 1 µl portion was analyzed by GC on a fused-silica column (15 m x 0.25 mm) coated with HP-5 MS (0.25 µm), operated with temperature programming from 100-250°C, (program details given), with He as carrier gas (0.9 ml/min) and 70 eV EIMS detection operated in selected-ion monitoring mode at m/z 309 and 295, respectively, for ketotifen and IS. The calibration graph was linear for 0.5-10 ng/ml of ketotifen in plasma, with a detection limit 10 pg/ml. Over the calibration range, the intra-assay RSD (n = 7) were 2.18-3.25% and inter-assay RSD (n = 2) were 1.49-3.78%. The average recovery of ketotifen over the calibration range was 81%. No interfering peaks were observed.

Quinones et al.[18] proposed a quantitative retention-activity relationship (QRAR) models based on the retention data of 33 antihistamines including ketotifen in a biopartitioning micellar chromatography (BMC) system using a Brij 35 mobile phase for describing pharmacokinetic parameters such as half-life and volume of distribution, or the pharmacodynamic parameters, therapeutic plasma levels, lethal

doses and drug-receptor dissociation constant. The predictive ability of these models is statistically validated. These results are compared to traditional quantitative structure-activity relationship (QSAR) models using lipophilicity data. The adequacy of the QRAR models can be explained taking into account the fact that the retention of compounds in BMC depends on their hydrophobic, electronic and steric characteristics which are of great importance in pharmacokinetic and pharmacodynamic behaviour.

Misztal and Paw[19] investigated the selectivity of the separation of five antihistamines by TLC on silica gel 60 F254 and on aluminium oxide 60 F254 with a variety of mobile phases in horizontal chambers. The best separation selectivity and retention differences for the drugs on the two types of plate were obtained with the mobile phases, chloroform-ethyl acetate (1:1 (v/v)), ethyl acetate, and butan-2-one-toluene, (7:3 (v/v)). The plates were visualized by illumination at λ 254 nm and by reaction with different reagents. The greatest detection sensitivity 0.06 µg for cetirizine, 0.1 µg for chloropyramine, and 0.2 µg for antazoline, doxylamine, and ketotifen was obtained by spraying with potassium iodoplatinate.

Chen et al.[20] developed a sensitive and specific liquid chromato-graphy/tandem mass spectrometry (LC/MS/MS) method for the investigation of the pharmacokinetics of ketotifen and its major metabolite, ketotifen N-glucuronide, in human plasma. The plasma samples were treated by liquid-liquid extraction and analyzed using LC/MS/MS with an electrospray ionization interface. Diphenhydramine was used as the internal standard. The method had a lower limit of quantitation 10 pg/ml ketotifen which offered increased sensitivity, selectivity and speed of analysis, compared with existing methods. The intra- and inter-day precision was measured to be below 8.2% and accuracy between -2.4% and 3.4% for all QC samples. Incubation of the plasma samples with β-glucuronidase allowed the quantization of ketotifen N-glucuronide. This quantization method was successfully applied to a pharmacokinetic study of ketotifen and its major metabolite after oral administration of 2 mg ketotifen fumarate to 16 healthy volunteers.

Chen and Qu[21] established a method for determination of ketotifen fumarate in compound metamizol sodium tablets. HPLC method was carried on a column of KR100-5SII (2.6 mm x 150 mm) with the mobile phase of ethanol-0.01% H_3PO4 solution-ethylenediamine (50:50:0.02), at the flow rate of 0.2 ml/min and the detection

at 302 nm. Ketotifen fumarate revealed linearity over the range of 0.6-30 µg/ml. The average recovery was 100.5% (RSD = 1.2%, n = 5). This method is simple, rapid, accurate, and successfully used to assay metamizol sodium tablets.

Analytical validation of a new liquid chromatographic-mass spectrometric (LC-MS) method for determination of total amount of ketotifen (unchanged and conjugated) in human plasma is presented. Pizotifen was used as an internal standard. An enzyme hydrolysis of conjugated ketotifen was conducted with a combination of β-glucuronidase and aryl sulfatase. After enzyme hydrolysis, a liquid-liquid extraction was performed as a cleaning step. The quantitative determination was obtained using selected ion monitoring (SIM) LC-MS. Chromatographic condition was a combination of reverse phase gradient system and a switching column technique. A satisfactory hydrolysis, acceptable accuracy, improved precision in the linear range from 0.5 to 20.0 ng/ml plasma, absolute recovery of 98.04% for ketotifen and 95.13% for pizotifen and stability for 7 months at -20°C have been achieved[22].

Van Gyseghem et al.[23] made generic orthogonal chromatographic systems which might be helpful tools as potential starting points in the development of methods to separate impurities and the active substance in drugs with unknown impurity profiles. The orthogonality of 38 chromatographic systems was evaluated from weighed-average-linkage dendrograms and color maps, both based on the correlation coefficients between the retention factors on the different systems. On each chromatographic system, 68 drug substances were injected as mixtures of three or four components to increase the throughput. The peaks were identified and resolved with a peak purity algorithm, orthogonal projection approach (OPA). The visualization techniques applied allowed a simple evaluation of orthogonal and groups of similar systems.

Electrometric methods

For the determination of ketotifen hydrogen fumarate, Bersier et al.[24] treated a single Zatiden tablet with 10 ml 1 N H_2SO_4 for 10 min in an ultrasonic bath then, the mixture was centrifuged. The supernatant solution was filtered and a 2 ml portion of the filtrate was mixed with 1 N H_2SO_4 (15 ml). After, deaeration for 10 min, the solution was subjected to differential pulse polarography. The peak height of the reduction wave (-815 mV versus SCE) was rectilinear from 6 to 30 µg ml^{-1} of

ketotifen hydrogen fumarate and the coefficient of variation (n = 11) was 3.7%. Ketotifen in "Positan" (Polfa-Poznan) samples was determined (without preliminary separation of excipients) by absorptive stripping voltammetry in 0.1 M KCl with a pre-concentration time of 60 s; the coefficient of variation was 3%. For the determination of ketotifen in urine, sample was subjected to solid-phase extraction with C_{18} silica and the analyte was eluted with KCl, methanol and H_2O. The methanol was evaporated from the eluate and the solution was diluted with 0.2 M KCl before adsorptive stripping voltammetry. The detection limit was 2.5 nM, ketotifen hydrogen fumarate.

A differential pulse polarographic method for determination of ketotifen fumarate was carried out by Mohamed and Aboul-Enein[(2)] at room temperature at 50 mV pulse amplitude with a peak potential on the dropping mercury electrode of -1.06 V vs. Ag/AgCl as reference electrode. Calibration graphs were rectilinear from 5 to 70 µg ml^{-1} with recoveries of 99.3 and 101.2% for powder and capsules, respectively.

Hopkala and Drozd[(25)] prepared a ketotifen ion-pair complex by mixing 10 ml 0.01 M ketotifen hydrogen fumarate in aqueous solution with 10 ml 0.01 M potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate in ethanol. The ethanol was evaporated and the precipitate filtered, washed with H_2O, dried and ground to fine powder. A 10 mg portion of the obtained precipitate was added to a solution of 170 mg PVC in THF with 2-nitrophenyloctylether, 2-nitrophenyldodecylether, bis-(2-ethylhexyl)sebacate or 1-isopropyl-4-nitrobenzene as plasticizers. The homogeneous mixture was poured into a 3.1 cm glass ring and the THF allowed to evaporate slowly to form a membrane. 8 mm discs were cut from the membranes and glued to the front end of a PVC electrode body containing an inner Ag/AgCl junction with 0.01 M solution of ketotifen hydrogen fumarate in 0.001 M NaCl as inner electrolyte. EMF measurements for electrodes made using the four different plasticizers were obtained using SCE as a reference electrode and calibration graphs of potential versus the logarithm of the ketotifen hydrogen fumarate concentration were obtained. Potentiometric titrations of ketotifen hydrogen fumarate were carried out using membrane containing isopropyl-4-nitrobenzene. A 10 ml portion of solution containing 4-17 mg ketotifen hydrogen fumarate was added to 5 ml 0.01 M NaCl and 35 ml H_2O before titration against 0.01 M sodium tetraphenylborate solution. A similar method was used for ketotifen tablets, finely powdered tablets equivalent to 4.26 mg ketotifen hydrogen fumarate being

added to 5 ml 0.01 M NaCl and 35 ml H_2O before extraction and titration as above. Recoveries and RSD for each test are tabulated, results being equivalent to those obtained using UV spectrometry.

Tsukamoto and Kusu[26] used ion-transfer voltammetry at a nitro-benzene/water interface to study the ion-transfer reaction and the adsorption of histamine and anti-histamine drugs, such as dl-chlorpheniramine, clemastine, diphen-hydramine, cyproheptadine, meclizine, promethazine, ketotifen, and terfenadine. Ion-transfer voltammograms showed that all anti-histamine drugs gave an anodic wave at a potential less positive than that of histamine. Electrocapillary curves showed that the anti-histamine drugs were adsorbed on the interface with great facility. They assessed the effects of the ionization of these drugs on the ion-transfer reaction and adsorption by ion-transfer voltammograms and electrocapillary curves, respectively. Based on these results, the half-wave potentials for the drugs at pH 4 were plotted against the calculated log KD values obtained by using PALLSA (CompuDrug International). The half-wave potentials had a strong correlation with the calculated log KD values. They concluded that the half-wave potentials determined by the present method would be a more reliable parameter of hydrophobicity for neutral and ionic forms of drugs when dealing with structure-activity relationships of drugs compared to experimental log P values obtained by the conventional methods.

Tabrizivand, Sabzi and Farhadi[27] made a new type of carbon paste electrode (CPE) using ketotifen fumarate ($C_{23}H_{23}NO_5S$) and hexacyanoferrate. For this purpose, ketotifen fumarate was dissolved in acidic solution (pH 1) and hexacyanoferrate was added by agitation, resulting in ketotifen–hexacyanoferrate (Ket–HCF) precipitate. The obtained precipitate was separated and introduced into carbon paste. The electrochemical behavior of Ket–HCF CPE was studied by cyclic voltammetry. A modified electrode shows one pair of peaks with surface-confined characteristics, with a 0.1 M phosphate buffer as supporting electrolyte. The effects of pH, alkali metal cations and anions of supporting electrolytes on the electrochemical characteristics of modified electrodes were studied. The diffusion coefficients of hydrated $Keto^+$ in film (D), the transfer coefficient (α), and the transfer rate constant for electrons (ks) were determined.

Ciesielski et al.[28] presented a method for the determination of ketotifen involving its reaction with iodine in an alkaline medium. In coulometric titration using biamperometric end-point detection 0.25-2 μmol (77–618 μg) of ketotifen was successfully determined. The elaborated method was applied to the determination of ketotifen in drugs.

A chemometric study has been conducted on a published data set consisting of the retention times of 83 substances, from five pharmacological families, on eight HPLC systems. Principal-component analysis, clustering and sequential projection pursuit were applied. In this way, it was investigated to which extent the combination of chromatography and chemometrics allows one to make conclusions about pharmacological activities of (candidate) drugs and what the contribution is of the different HPLC systems is considered[29].

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