The application of kinetic methods in pharmaceutical analysis. Part 2. Chemiluminescence-based kinetic determination of drug

M. Ye. Blazheevskiy, N.Yu. Bondarenko

National University of pharmacy, 61168, Bluher Street, 4, Kharkov, Ukraine, e-mail: Blazejowski@ukr.net

Was sent: July 6, 2010 / reception to the publication: October 20, 2010

The articles are concerning to the application chemiluminescence-based kinetic determination of drug and biologically active substances is reviewed. The possibilities and limitation of modern chemiluminesce method in the pharmaceutical analysis are shown. The main advantages of chemiluminescent assay are simplicity, high sensitivity and expression

БЛАЖЕЄВСЬКИЙ М.Є., БОНДАРЕНКО Н.Ю. ЗАСТОСУВАННЯ КІНЕТИЧНИХ МЕТОДІВ У ФАРМАЦЕВТИЧНОМУ АНАЛІЗІ. ЧАСТИНА 2. КІНЕТИЧНІ МЕТОДИ ВИЗНАЧЕННЯ ЛІКАРСЬКИХ ЗАСОБІВ, ЗАСНОВАНІ НА ХЕМІЛЮМІНЕСЦЕНЦІЇ - Оглянуто праці, які стосуються застосування кінетичного методу хемілюмінесценції для визначення лікарських та біологічно активних речовин. Показані переваги та обмеження використання сучасних хемілюмінесцентних методів у фармацевтичному аналізі. Головними перевагами хемілюмінесцентного методу аналізу є простота, висока чутливість та експресність.

Ключові слова: хемілюмінесцентний метод аналізу, визначення ліків, фармацевтичний аналіз

Keywords: chemiluminescence-based kinetic method of analysis, determination of drug, pharmaceutical analysis

INTRODUCTION

The chemiluminescence (CL) process is probably the most markedly kinetic of the luminescent phenomena as factor that affect the emission intensity are a combination of luminescence and chemical reaction rate aspects. Thus, taking into account that CL measurements are dynamic in nature, because they are based on the detection of a transient light emission, all CL methods might be classified as kinetic methods.

As written in the first monograph [1] and recent review [2] CL reached analytical attention in the middle of 20th century when Erdey in 1957 studied the use of several substances (luminol or 5-aminophthalylhydrazide (H_2L); lophine and lucigenine or *bis*-*N*-methylacridinium nitrate (Lc)) as volumetric indicators and Ponomarenko in 1955 proposed the use of H_2L CL reaction as indicator to kinetic CL determination of inhibitors [3].

The analytical parameters most frequently employed in CL methods are CL intensity and the integrated area under all or part of the light emission – time curve. In both instances, one must rigorously control the interval between initiation of the reaction and acquisition of data. However, formation and decay rate of CL reactions have been found to provide better precision and selectivity that conventional parameters, which have been obtained by using flow-injection (FI), continuous addition of reagent (CAR) or stopped-flow (SF) mixing technique.

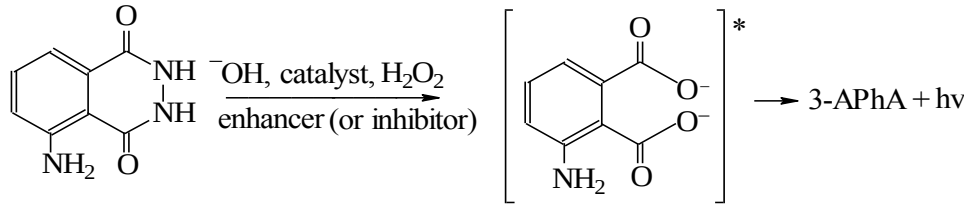
In contrast to spectrophotometry, the absence of strong background light levels in CL methods reduces noise signals and leads to improved detection limits (better sensitivity) and wide linear dynamic ranges. Moreover, the absence of the light excitation source leads to a low cost and simple operation of the instruments resulting in a simple, robust and cost-effective apparatus. Some shortcomings of the CL procedures are similar to other spectrometric systems as, e.g., limited selectivity due to the fact that usually a given CL reagent gives positive response to a group of similar compounds rather than just to a single analyte. Another drawback is the dependence of the CL emission on various environmental factors which must be controlled since the intensity of CL emission changes with time and this emission versus-time profile can vary widely in different CL systems [4,5]. The theme of CL as analytical tool was processed in a monograph [5] and the advantageous marriage between the continuous flow techniques and the CL in pharmaceutical analysis has been reviewed in a article [6].

In the present review the methods are classified according to the kind of the CL process to direct and indirect CL assays. In the direct methods the CL is emitted due to direct interaction between the analyte and CL reagent (usually a redox reaction) whereas in the indirect methods the analyte merely influences an indicator CL reaction and plays the role of an inhibitor or sensitizer; typical indicator reactions utilized in this indirect assays are based on the oxidation of H_2L, Lc, 9-cyano-10-methylacridinium (9-CMA), lophine, sulphite or peroxyoxalates.

H_2L is so far the most frequently used CL reagent. The CL emission of luminol is based on its oxidation by hydrogen peroxide, peroxy acid, hexa-

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

cyanoferrate(III), persulphate, permanganate, *N*-bromosuccinimide (or *N*-chlorosuccinimide), periodate, dichromate, dichlorocyanurate or trichlorocyanuric acid, chlorate and electrogenerated hypobromite in alkaline medium. According to the well-known mechanism the supposed emitter is excited 3-aminophthalate anion (3-APhA) whose maximum emission occurs at 425 nm [5]. The relevance of the H_2L as analytical CL reagent does not rely on the emission efficiency but on possibilities that many different species can influence the mechanism and the kinetics of the indicator reaction (Scheme 1).



Scheme 1. Chemiluminescence oxidation of luminol by hydrogen peroxide in the present of analytes

The analyte can act as enhancer, inhibitor or catalyst whose concentration may influence the intensity or amount of emitted light. For example enzymes such as peroxidases or oxidases are able to catalyze the oxidation of substrates generating activated oxygen species (e.g. superoxide radical) reacting with H_2L with CL emission.

Some catalysts such as Cu(II) [7], Co(II) and Fe(III)/Fe(II) were implemented into the H_2L /oxidant system to improve sensitivity of the indirect assay. Thus Cu(II) was used as a catalyst in the determination of methimazole and carbimazole [8]; these drugs formed complex species with Cu(II) and thus inhibited Cu(II)-catalysed H_2L –hydrogen peroxide reaction; with increasing concentration of analyte equilibrium concentration of Cu(II) diminished and this resulted in the decrease of CL intensity.

A simple and sensitive method has been proposed for the amikacin sulphate determination. It is based on the inhibition of the CL emission generated from the oxidation of H_2L in alkaline medium by H_2O_2 catalyzed by Cu(II), due to the interaction caused by amikacin, which forms a robust complex with the catalyst. The optimization of the experimental and instrumental variables affecting this CL inhibition effect has been carried out using statistical models, based on the application of two-level full factorial and Box–Behnken designs. The performance characteristics of the proposed method have been established, showing that the method is efficient to determine amikacin sulphate in the linear range of 9,89−20 mg/l with a detection limit of 2,97 mg/l. It has been successfully applied to the amikacin sulphate determination in pharmaceutical formulations [9].

A new FI-CL-method is proposed for the determination of thiamine, based upon its enhancing effect on the CL reaction of H_2L with hydrogen peroxide in alkaline solution. The method allows the determination of thiamine within 0,05–8 μg/ml range with a detection limit (3σ) of 0,01 μg/ml. The relative standard deviation is 1,4% (n=11, 0,5 μg/ml thiamine) and the sample throughput is about 90 samples h^{-1}. The method was successfully applied to the determination of thiamine in pharmaceutical preparations [10].

A CL method for the determination of isoniazid is described. The method is based on the CL generated during the oxidation of H_2L by sodium dichloroisocyanurate (SDCC) and trichloroisocyanuric acid (TCCA) in alkaline medium. It was found that isoniazid greatly enhances this CL intensity when present in the H_2L solution. Based on this observation, a new flow-injection CL method for the determination of isoniazid has been proposed in this paper. The detection limits were 2 and 3 ng/ml isoniazid for the SDCC-H_2L and TCCA-H_2L CL systems, respectively. The relative CL intensity was linear with the isoniazid concentration in the range of 4–100 and 100–200 ng/ml for the SDCC- H_2L CL system, and 6–200 and 200–1000 ng/ml for the TCCA-H_2L CL system. The results obtained for the assay of pharmaceutical preparations compared well with those obtained by the official methods and demonstrated good accuracy and precision [11].

A sensitive CL method to determine the antipsychotic risperidone (RSP) is proposed, based on the catalytic effect of risperidone on the CL reaction between H_2L and hydrogen peroxide in flow system. The increment of CL intensity was correlated with risperidone concentration in the range of 10 pg/ml to 1.0 ng/ml with a relative standard deviation of less than 5,0% (n = 5); and a limit of detection of 4 pg/ml (3σ). At a flow rate of 2,0 ml/min, the flow injection CL method exhibited both high sensitivity and excellent selectivity giving a throughput of 120 samples per hour. The proposed method was applied successfully to the determination of risperidone in pharmaceutical preparations [12].

The effect of pH on inhibition and enhancement of $H_2L - H_2O_2 - Co^{2+}$ CL by 18 phenolic compounds

and 20 aminoacids was studied. It was found that most of the tested compounds showed an inhibiting effect at lower pH and an enhancing effect at higher pH. At a midrange pH, for some phenolic compounds with two ortho-position-OH, both an inhibiting and an enhancing peak were simultaneously observed. UV-visible spectra of the tested phenolic compounds at different pH values were studied. The mechanism for CL inhibition and enhancement was proposed. It is likely that the competition of the -OH or the $-NH_2$ group and other reducing groups in the molecules with H_2L for O_2*- led to the CL inhibition. A reaction of -COO(-) and quinone or ketone formed by phenolic compounds at higher pH via deprotonation with O_2*- also resulted in the CL enhancement [13].

A rapid and sensitive CL method for the quantitation of oxymetazoline hydrochloride in pharmaceutical formulations has been developed. Oxymetazoline hydrochloride inhibits strongly the chemiluminescence from the oxidation of H_2L in alkaline medium. Based on this effect, a simple method is proposed for the determination of this imidazoline derivative by flow injection analysis employing chemiluminescence detection. The optimization of the experimental and instrumental variables such as, selection of the oxidant, concentration of reagents, flow rates, injection volume, etc., has been carried out using the proposed flow injection manifold. The performance characteristics have been established, showing a wide linear response in the range of 1,88–200 ng/ml and a detection limit of 1,21 ng/ml. This is the first chemiluminescent method for the determination of oxymetazoline which has been satisfactorily applied to the analysis of the drug in intranasal pharmaceutical formulations [14].

A metal cation forming an metalporphyrin or metalphthalocyanine complex may act as a CL catalyst as demonstrated with Co(II) in the CL assay of diethylstilbestrol [15]. The catalytic effect of Co(II) was also used in the CL determination of vitamin B_{12} (cobalamin) [16] after releasing Co(II) from the vitamin molecule by acidifying the analyte solution. In the current article, chemiluminescence from the vitamin B_{12} and luminol reaction was studied under alkaline conditions to develop a sensitive analytical method for vitamin B_{12} using the carbonate enhancement effect. The method was successfully applied to the determination of vitamin B_{12} in vitamin B_{12} tablets, multivitamin capsules, and vitamin B_{12} injections. The limit of detection was 5 pg/ml, and the linear range was 10 pg/ml to 1 μg/ml with a regression coefficient of r = 0,999. Extraction of vitamin B_{12} was carried out, and the observed recovery was 97–99,2% with a relative standard deviation in the range of 0,30–1,09%. The results obtained were compared with those of the flame atomic absorption spectrometry method. [17]

The selectivity of CL analysis can be improved by using of solvent extraction in micellar aqueous–organic systems. A good example is the CL determination of chlorpromazine hydrochloride [18], which is based on the dichloromethane solvent extraction of ion-pair complex of tetrachloroaurate(III) with chlorpromazinium cation and H_2L CL detection in a reversed micellar medium formed by the cationic surfactant cetyltrimethylammonium bromide in a dichloromethane–cyclohexane–aqueous carbonate buffer system. The ion-pair complex produced a CL signal when it entered the reversed micellar water pool. CL intensities were proportional to concentrations of the studied drug over the range 0,05 approximately 10 μg/ml with a detection limit (DL) of 6 ng/ml. The relative standard deviation (RSD) is 2,6% for 1,25 μg/ml chlorpromazine hydrochloride (n = 11). RSD (precision) of inter-day and intra-day is less than 6%, and accuracy of inter-day and intra-day is satisfactory. The method has been applied to the determination of studied drug in pharmaceutical preparations and biological fluids with satisfactory results.

A gas-diffusion flow-injection system was designed for selective chemiluminescent determination of iodide. Iodide was oxidized to elementary iodine in a donor stream (oxidant+water); the I_2 diffused through a PTFE membrane into an acceptor stream of iodide solution and reacted with a stream of H_2L to produce CL [19].

Use of substrate-specific enzymes is another possibility for attaining selectivity of CL assays. Selective CL determination of β-glucose [20] was based on the on-line oxidation of glucose by glucose oxidase in the presence of dissolved molecular oxygen resulting in the formation of hydrogen peroxide which reacted subsequently with H_2L. Besides conventional aspiration or pumping the reagents in the FIA or SIA system, special technique for introducing CL reagents has been devised. Reagents were separately immobilized on a suitable support (resin) and they were successively eluted in the flow manifold during the analysis. The resin was packed into a column (flow sensor or solid-phase reactor) placed at the merging point of analyte, carrier or other reagent streams [21, 22] or just in front of the detection window [23].

The advantages of such system are operational convenience, simplicity of detection devices as well as lower reagent consumption. On the other hand the capacity of the column packing is limited, the immobilized reagents are spent after some time and the column packing must be renewed (shorter lifetime of the sensor). A secondary CL emission phenomenon was observed in determination of menadion [24]. After finished CL reaction between H_2L and excess of potassium periodate, the analyte menadion was added and so-called secondary CL emission was observed. The oxidized form of menadion presumably transfers its energy to once deactivated 3-aminophtalate which again appears in excited state.

When returning to the ground state the energy emitted is proportional to concentration of menadion. The CL methods using H_2L as reagent were proposed for the assay of various pharmaceu-

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

ticals with different structures and pharmacological effects. Phenethylamine group drugs are typical representatives of such analytes determined.

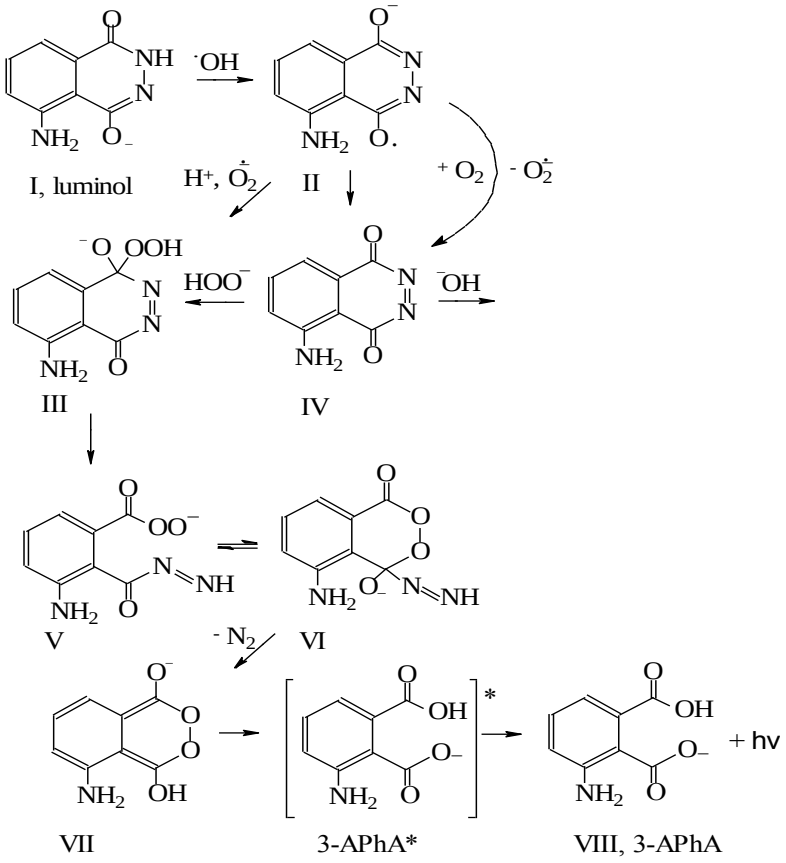
Four cephalosporin antibiotics (cefalexin, cefaclor, cefradine, and cefadroxil) were determined by a FI-CL method based on enhancement of the CL arising from the reaction of H_2L with potassium periodate in alkaline solution . The detection limits of the method are 0,9 ng/ ml cefalexin, 0,4 ng/ ml cefaclor, 10 ng/ ml cefradine, and 10 ng/ ml cefadroxil. The method was successfully applied to the determination cephalosprin antibiotics in pharmaceutical preparations [25].

Li and Lu [26] proposed a FI-CL method for the determination of *β*-lactam antibiotics based on the injection of these drugs into a stream of potassium permanganate with alkaline H_2L.

A review concerns the use of hypochlorite, hypobromite and related oxidants (such as N-bromosuccinimide and 1,3-dibromo-5,5-dimethylhydantoin) as chemiluminescence reagents and includes references to 249 papers that were published prior to mid-2003. Particular emphasis has been placed on proposed emitting species and the mechanisms of the light-producing pathways.

The analytical applications of this chemistry have been summarized in three tables: (1) quantification of hypohalites and related compounds (including halides, which are initially oxidized); (2) enhancement or inhibition of H_2L chemiluminescence; and (3) direct CL reactions with hypohalite reagents [27].

Cefalotin was determined by reaction of this drug with luminol in the presence of potassium hexacyanoferrate(III) as a catalyst/co-oxidant and potassium hexacyanoferrate(II) as an emission depressor in an alkaline solution [28, 29].



Scheme 2. Mechanism of luminol oxidation by hydrogen peroxide

Stadnichuk and Zinchouk [30] described a CL method for determination of ascorbic acid in pharmaceuticals based on the inhibition of emission in H_2L – Mn(II) triethanolamine complex – peroxomonosulfate (borate buffer of pH 10,2) CL system. The limit of quantitation (LOQ) was 18 ng/ml.

The H_2L chemiluminescence of peracetic acid (PAA) in alkaline medium is very weak but is strongly enhanced after the addition of dihydralazine sulfate (DHZS). Based on this phenomenon, a simple, rapid and highly sensitive flow-injection CL method for the determination of DHZS was developed. The CL emission was linearly related to the DHZS concentration in the range of 20–4000 ng/ml with a detection limit (3S) of 1,2 ng/ml. As a preliminary application, the proposed method was suc-

cessfully applied to the determination of DHZS in pharmaceutical preparations; the recovery of DHZS in human urine was between 96,5% and 102,2%. A detailed CL mechanism was proposed and singlet molecular oxygen ($^1O_2$) was suggested to be produced in the CL reaction process [31].

The procedure for the determination of some biological active organic compounds and other substances (ascorbic acid, salicylic acid, *D*,*L*-metionine, ethanol, *p*-phenilendiamine, 2-aminofenol, aniline, resorcin, *D*-glucose et. al) using the H_2L chemiluminescence quenching in the reaction with the peroxydisulphate is proposed. The detection limit to 10^{-5}–10^{-10} mol/l [32, 33].

Knowledge about utilized reactions when hydrogen peroxide is replaced by its organic derivatives is still not satisfactory. The mechanism of H_2L oxidation by hydrogen peroxide is established and is shown in Scheme 2. It can be subdivided into two parts. First one is the path leading to an active intermediate formed from H_2L monoanion and oxidant (with hydroxy radical). The hydroxy radical can be replaced by other organic or inorganic radicals, depending on catalyst and reaction conditions. When peroxydase of hemoglobin (Hb) (or complexes such as hemin) are present, oxo-iron (IV) porphyrin radical cation (oxene) acts as the oxidant of H_2L, as is shown in Scheme 3.

H_2L oxidation to diazaquinone is significantly affected by rate of reaction between catalyst and oxidant. The subsequent reaction between oxidized catalyst and H_2L is faster than between hydrogen peroxide and catalyst (hemin) so last reaction is limiting the rate of formation of active intermediate.

The part of the mechanism is addition of peroxide anion to the diazaquinone IV. Subsequently, through an intermediate compound VI is formed. This part is relatively simple when hydrogen peroxide is used. With organic peroxides (for example, peroxy carboxylic acid) the process is more compicated because all of organic peroxides have at least one carbon-peroxide bond, which of necessity must be broken if reaction V ↔ VI is to complete. This additional step may limit light yield. Another possible path leading to the intermediate III is the reaction between oxygen and H_2L radical followed by superoxide addition to radical II.

$$LFe(III)^+ + H_2O_2 \rightarrow H_2O + LFe(IV)^{+\cdot}=O$$

$$I + LFe(IV)^{+\cdot}=O \rightarrow LFe(IV)^{+}OH$$

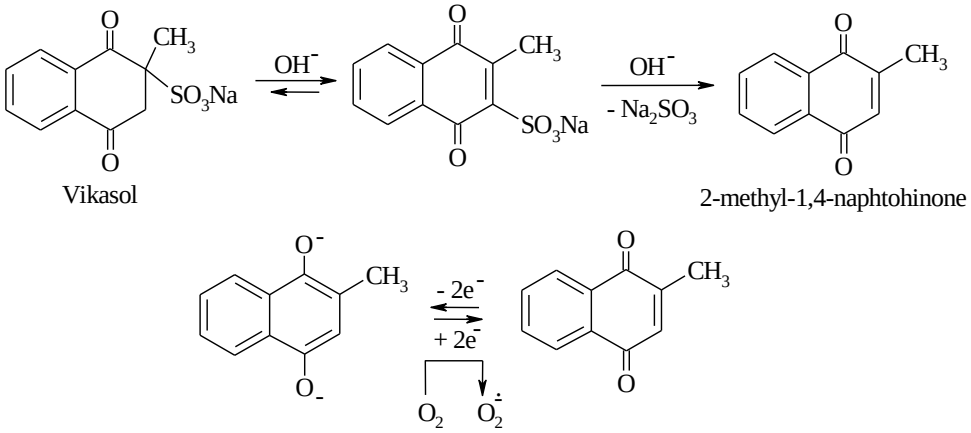
$$I + LFe(IV)^{+}OH \rightarrow II + L\,Fe(III)^+ + H_2O$$

Scheme 3. Hydrogen peroxide decomposition by iron porphyrins.

A CL system H_2L – H_2O_2 – Hb was proposed as indicator for kinetic determination of some biological active organic compounds, pharmaceuticals (paracetamol, caffeine, cathecholamines (adrenaline, dopamine), phlavonoids (rutin, quercetin, dihydroquercetin), ascorbic acid) by its inhibition action [34-39]. The mechanism for CL inhibition was proposed. It is likely that the competition of the -OH or other reducing groups in the molecules with H_2L for active form oxygen ($OH\cdot$ and/or $O\text{-}O\cdot^-$)-led to the CL inhibition. In the CL system H_2L – H_2O_2 – Hb selective inhibitor paracetamol action in the presence of ascorbic acid, also caffeine in the presence of theophiline and theobromine were established.

Statistical comparison of the results with those of the official method showed excellent agreement and proved that there was no significant difference in the accuracy and precision between the official and the proposed methods.

The LOQ-s were 75 ng/ml paracetamol, 0,2 μg/ml caffeine, 75 ng/ml adrenaline, 19 ng/ml dopamine, 0,36 μg/ml rutin, 2,3 μg/ml quercetin, 9 ng/ml dihydroquercetin and 18 ng/ml ascorbic acid.



Scheme 4. Mechanism isomerization and hydrolysation of vikasol in alkaline solution

Vikasol was determined by a CL method based on enhancement of the CL arising from the reaction of H_2L with hydrogen peroxide in alkaline solution. Mechanism isomerization and hydrolysation of vi-

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

kasol in alkaline solution and supperoxide anion-radical generation was proposed (Scheme 4). The method was successfully applied to the determination vikasol in vikasol tablets, and vikasol injections. LOQ was 0,1 μg/ml vikasol. The proposed methods are validated statistically and through recovery studies. The relative error of determination vikasol in vicasol tablets and vikasol injections is 3,0 % and 4,1 % respectively.

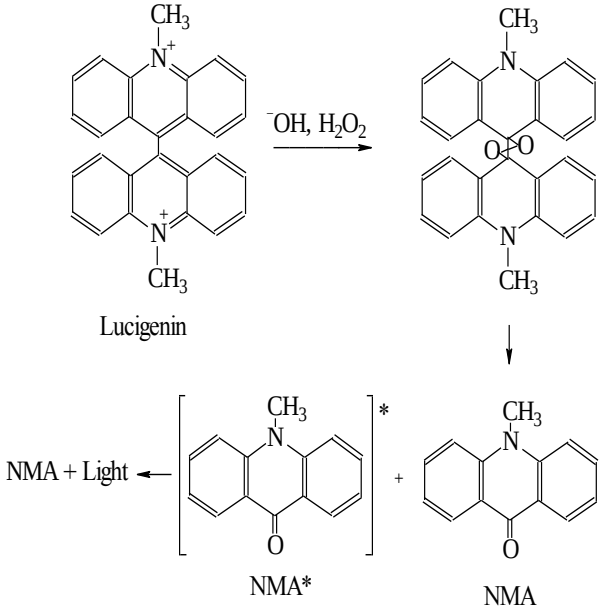
The linear range was 0,1 μg/ml to 270 μg/ml with a regression coefficient of r = 0,996. The results given by the proposed method are in good agreement with those given by the official method [38, 39].

A CL method is proposed for the determination of acetylcholine, based upon its enhancing effect on the CL reaction of H_2L with hydrogen peroxide in an alkaline solution. Acetylcholine was hydrolized in the presence of hydrogen peroxide and the peracetic acid generated was detected using a CL luminol. The method allows the determination of acetylcholine within $(1\text{-}5)\cdot10^{-5}$ mol/l range with a detection limit (3σ) of $2\cdot10^{-6}$ mol/l. The relative standard deviation is ≤3% (n=5, $(3\text{-}5)\cdot10^{-5}$ mol/l acetylcholine). The method was successfully applied to the determination of acetylcholine in pharmaceutical injection preparation [40, 41].

A new CL method for the determination of peracetic acid in disinfection preparation, based upon its enhancing effect on the CL reaction of H_2L with hydrogen peroxide in alkaline solution was developed. The method allows the determination of peracetic acid within $(1\text{-}5)\cdot10^{-5}$ mol/l range with a detection limit (3σ) of $2\cdot10^{-6}$ mol /l. The relative standard deviation is ≤3% (n=5, $(3\text{-}5)\cdot10^{-5}$ mol/l peracetic acid) [42, 43].

ACRIDINIUM SALTS

The CL of the best-known and most widely used acridinium salt, Lc, was fist examined by Glue and Petsch in 1935. Lucigenin is oxidised by hydrogen peroxide in an alkaline medium (Scheme 5). CL oxidation scheme of 9-CMA by hydrogen peroxide in an alkaline medium is analogous (Scheme 6). The reaction is catalysed by a large number of metal ions, some of which (e.g. Bi(III)) fail to catalyse the H_2L reaction. The reaction product is water-insoluble, so it deposits onto the walls of the flow manifold and detector the precludes quantitative analysis. However, the addition of small amound of the surfactant sodium dodecylsulphate prevents the precipitation [44, 45].

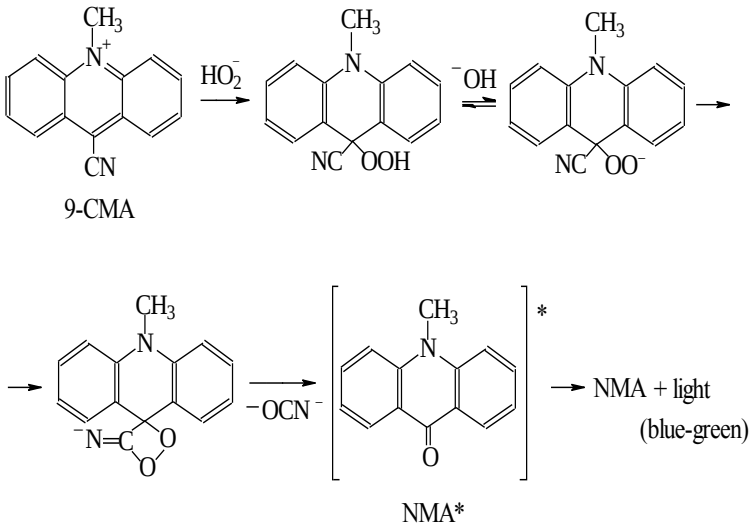


Scheme 5. Chemiluminescence oxidation of lucigenin by hydrogen peroxide

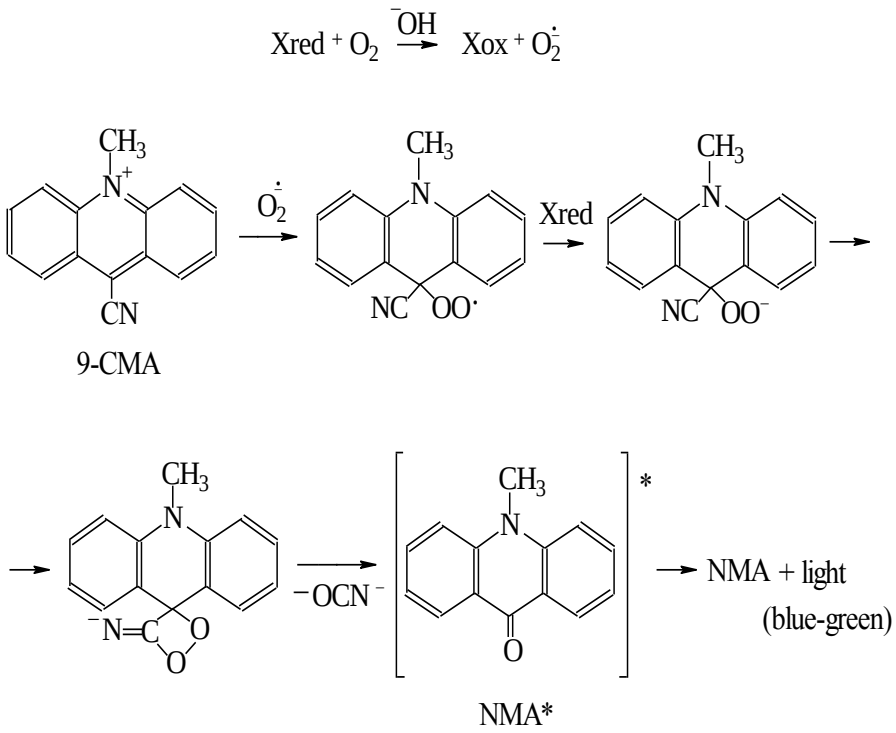
The ionic surfactant Brij 35 Brij 35 $[(C_2H_4O)_{23}C_{12}H_{26}O]$ was used for determination of ascorbic acid [46] and isoprenaline [47] by Lc reaction. The CL-based determination of kanamycin relies on the oxidation of lucigenin by hydrogen peroxide in the presence of Co(II) as catalyst [48].

The CL methods using 9-CMA as reagent were proposed for the assay of various pharmaceuticals with different structures and pharmacological effects. Catecholamines (epinephrine, dopamine), derivatives of hydrazine (isoniazid, phtiazid, flurenizid and hydralazine, dihydralazine) and N-acetylcysteine were oxidized by oxygen in the presence of alkaline and the supperoxide anion-radical generated was detected using a chemiluminescence 9-CMA. A possible CL mechanism proposed by Blazheevskiy et. al may be attributed to the reactions in Scheme 7 [49 - 61].

A simple, fast chemiluminescence injection method for the indirect determination of malathion has been described. Mechanism of chemiluminescence oxidation of 9-CMA in system 9-CMA – O_2 – malathion in an alkaline medium was proposed. The method involves first hydrolysis of the malathion with 3,3 mol/l KOH to N,N-dimethylpenicillamine followed by reaction with oxygen.



Scheme 6. Chemiluminescence oxidation of nitrate 9-cyano-10-methylacridinium by hydrogen peroxide in an alkaline medium



Scheme 7. Mechanism of chemiluminescence oxidation of nitrate 9-cyano-10-methylacridinium in system 9-CMA – O_2 – analyte (reductor) in an alkaline medium

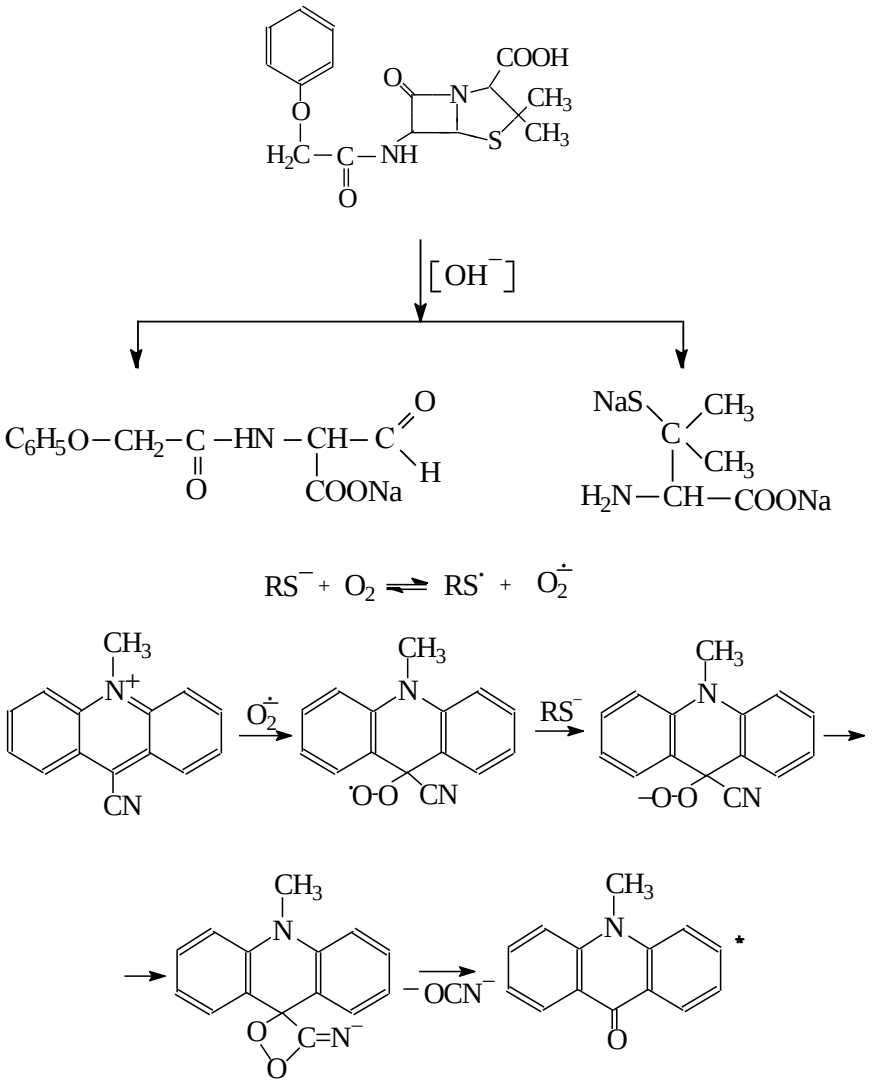
The produced supperoxide anion-radical was detected using a CL reaction with 9-CMA. Under the optimal conditions, the CL intensity was linear to the malathion concentration in the range of 0,01–0,2 μg/ ml (r=0,999, n=5). The relative standard deviation was 4,0 % at 0,1 μg/ ml (n=5), with a detection limit (3σ) of 0,002 μg/ ml malathion.

The possible reaction mechanism was also discussed. This method has been successfully applied to the determination of malathion in the pharmaceutical preparation gel «Pedilin» 0,5 % and results have been compared with that of the standart BP method Fe(II) then reacts with potassium ferricyanide, resulting in the formation of a blue product. [62].

A CL method is proposed for the indirect determination of the phenoxypenicilline in tablets, based upon its alkaline hydrolysis to penicillamine.

A penicillamine was oxidized by oxygen in the presence of alkali and the supperoxide anion-radical generated was detected using a CL 9-CMA as is shown in Scheme 8 [63, 64].

© M. Ye. Blazheevskiy, N.Yu. Bondarenko



Scheme 8. Mechanism of chemiluminescence oxidation of nitrate 9-cyano-10-methylacridinium in system 9-CMA – O_2 – phenoxypenicilline in an alkaline medium.

THE REACTION OF SULPHITE

The reaction of sulphite with strong oxidants such as permanganate, Ce(IV) in acid media and electrogenerated Mn(III) is accompanied by a weak CL that can be sensitized by some organic compounds. The excited species formed by the oxidation of sulphite is probably sulphur dioxide [65-67] in accordance with the following mechanism:

$$HSO_3^- + Ox \rightarrow HSO_3^{\cdot}$$
$$2\ HSO_3^{\cdot} \rightarrow S_2O_6^{2-} + 2H^+$$
$$S_2O_6^{2-} \rightarrow SO_4^{2-} + [SO_2]^*$$
$$[SO_2]^* \rightarrow SO_2 + h\nu.$$

The energy of the excited $[SO_2]^*$ molecule can be easily transferred to a fluorescent molecule (fluorophore).

The sulphite CL system was especially useful in determination of fluoroquinolones. The CL signal can be considerably enhanced in the presence of trivalent lanthanoid family ion (L) [68–70] as observed in the CL determination of the quinolone (Q) grapefloxacin [66]. In the absence of L the transfer of energy from $[SO_2]^*$ to Q resulted in subsequent emission of luminescence of [Q]*. In the presence of L a complex with quinolone L(Q) was formed.

The energy from $[SO_2]^*$ was transferred successively to ligand (quinolone) and then by an intramolecular energy-transfer process to L; the energy of L([Q]*) was emitted at characteristic wavelength of the L (here Tb^{3+} 490, 546 and 590 nm).

A sulphite – sodium bismuthate (oxidant) CL system was used for determining pipemidic acid [71] in acidic medium. Sodium bismuthate was immobilized inside a CL flow cell as a solid-phase oxidant. Pipemidic acid is a fluorogenic compound that could sensitize the weak CL emission from the sulphite–bismuthate reaction.

A similar solid-phase reaction system was proposed for the CL assay of ofloxacin [72] (fluorophor) with immobilized lead dioxide as oxidant.

DIRECT CL METHODS

Recently special attention was paid to looking for new direct CL reactions. Generally, the CL reagent is a strong or moderate oxidant such as potassium permanganate, tris(2,2'-bipyridine)-ruthenium(III) complex, potassium hexacyanoferrate(III), Ce(IV), hydrogen peroxide, oxygen or N-bromosuccinimide among others. Other less frequently used CL reagents are bromine or sodium hypochlorite. The CL emission can be usually enhanced by using a catalyst, an organized medium or a sensitizer. The direct CL strategy has attracted the attention of some authors [73, 74] dealing with molecular connectivity calculations applied to predict the CL behavior of organic substances, pharmaceuticals and pesticides when reacting with common strong oxidants in liquid phase and first non-empirical rule for the prediction of the CL behavior of organic compounds was devised. The success in prediction was about 93% for CL behaviour of pharmaceuticals and pesticides and 100% for phenols and polyphenols. The calculations were also applied to ergot alkaloids [75] and a review [76] concerning this topic was published.

Oxidation with potassium permanganate

Potassium permanganate is the most common oxidant used in CL reactions [77]. The report of Townshend [78] on morphine determination blossomed the application of acidic potassium permanganate to the analysis of drugs and organic compounds. The reaction of acidic potassium permanganate with a wide range of compounds is known to produce a broad red emission, and there is strong evidence for an excited manganese(II) emitting species. Nevertheless, numerous researchers have proposed other emitters for reactions with acidic potassium permanganate, particularly for systems where fluorescent compounds were present, either as enhancers and/or reaction products.

A possible CL mechanism proposed by Aly et. al [79] may be attributed to the following reactions:

$$\text{Analyte} + MnO_4^- + 8\,H^+ \rightarrow \text{Ox-analyte}^* + Mn^{2+} + 4\,H_2O.$$

In the presents of fluorofore (quinine), the energy resalting from the redox reaction can be effectively transferred to quinine which in turn generates CL emission:

$$\text{Ox-analyte}^* + F \rightarrow \text{Ox-analyte} + F^*$$
$$F^* \rightarrow F + \text{light}.$$

Now, acidic potassium permanganate has been successfully employed, generally with flow analysis, as a strong oxidant to generate chemiluminescence. Of the methodologies described, many have demonstrated that this chemistry is capable of detecting a wide variety of analytes with good sensitivity, using batch techniques, flow analysis, after separation by either liquid chromatogram or, more recently, capillary electrophoresis. The $KMnO_4$-based FI-CL methods are mainly based on the direct oxidation of the analyte by $KMnO_4$ [80 - 87], or based on the enhancement of CL intensity of the $KMnO_4$-sulfite system by the analyte [88 -90], using quinine, formaldehyde, glyoxal, formic acid and some surfactants as a sensitizer. Among the wide range of compounds, the most analytes in $KMnO_4$-based CL system possess either an amine or a phenolic moiety [91]. In a word, as one of a few of acidic CL systems, $KMnO_4$-based CL holds still a wide potential applications with a deeper understanding of the mechanisms that lead to the production of light. Recently cephalosporin and penicillin class antibiotics appear among the drugs determined most frequently with this reagent by the FIA–CL technique. A comprehensive review by Hindson and Barnett concerning a wide range of analytical applications of permanganate in CL reactions [92] postulated excited beside of Mn(II) or its complexes and/or fluorescent oxidation products of the analyte singlet oxygen and sulphur dioxide as CL-emitting species. A further article was devoted to investigation of the origin of CL in systems involving Mn(III), Mn(IV) and Mn(VII) in phosphate solutions [93]. It was confirmed that the emitter is elicited from the oxidant and that it is most probably the excited Mn(II). Judging by the number of published articles sulphuric acid or polyphosphoric acid is the preferred medium for permanganate based CL reactions. However, the suitability of sulphuric or polyphosphoric acid is also subject of controversy. The optimization of the acidic medium mostly shows that the use of sulphuric acid leads to better reproducibility. The role of polyphosphoric acid is double: on one hand, it provides the required acidic medium for the oxidation, and on the other hand it acts as promoter of the CL since it most likely stabilizes reaction intermediates [94].

Similar role is played by polyphosphate (hexametaphosphate) in sulphuric acid medium [95, 96].

The presence of chemical additives such as sensitizers or organized media can increase the emission intensity even by several orders of magnitude. Some surfactants (Tween 60 [97], benzalkonium chloride [98] protect the microenvironment of CL emitter through formation of micelles or they can facilitate energy transfer [99]. There are some other chemicals of non-surfactant character, such as β-cyclodextrin, that also protect the emitter and minimize the non-electromagnetic emission pathway during relaxation of the excited species [100]. On the other hand, there is variety of other substances which can increase the CL intensity. Many fluorophores have been tested and proposed in different drug determinations. Quinine [101 -103] and formic acid [104] were utilized as fluorophores where the energy from excited state of intermediate or product is transferred to this fluorescing compound which is the final emitter (glutaraldehyde [105], formaldehyde [106 - 108]).

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

Cephalosporines antibiotics (cefalexin, cefadroxil, and cefazolin sodium**)** [109] were determined by permanganate-induced CL in sulphuric acid medium enhanced by glyoxal as sensitizer. The detection limits of the method are 10 ng/ml cefalexin, 2 ng/ml cefadroxil, and 2 ng/ml cefazolin sodium. An attempt was made to solve the problem of CL drug determination in complicated matrices such as human serum by using on-line solid-phase extraction and SIA with CL detection [110]. The authors determined salbutamol that was initially adsorbed from the matrix on a cartridge packed with silica-gel (modified with carboxylic acid) and then eluted by sulphuric acid; the CL determination of eluted salbutamol was performed by oxidation with permanganate in sulphuric acid medium. The transformation of non-chemiluminescent compounds into chemiluminescent intermediates by prior UV-irradiation is a real possibility how to achieve CL reaction. Photo-induced CL was employed for the determination of chloramphenicol [111] and sulphonamides [112]. A screening test for the development of photo-induced FIA–CL of pharmaceuticals has been also reported [113].

Cefadroxil was determinated by a FI-CL method based on the chemiluminescence emitting reaction between cefadroxil and potassium permanganate in sulphuric acid medium, enhanced by formaldehyde. Under the optimum conditions, calibration graphs over the ranges of 0,05–0,8 and 1,0–10,0 μg /ml were obtained. The proposed method is suitable for application to other antibiotics containing phenolic hydroxyl groups, and was successfully applied to the determination of cefadroxil in pharmaceutical formulations with no evidence of interference from common excipients. The detection limit (3σ) of this method is 25 ng/ ml ($6{,}9\cdot10^{-8}$ mol/l). The relative standard deviation was less than 2% for 0,4 and 4,0 μg /ml cefadroxil (n = 20). The sample throughput was found to be 120 h^{-1}. [114]. A rapid and sensitive chemiluminescence method using FI has been developed for the determination of a second generation cephalosporin, cefprozil. The method is based on the CL reaction of cefprozil with acidic potassium permanganate and tris(2,2′-bipyridyl) ruthenium(II), $Ru(bipy)_3^{2+}$. The CL intensity is greatly enhanced when quinine sulfate is used as a sensitizer. After optimization of the different experimental parameters, a calibration graph was obtained over a concentration range of 0,1–3,0 μg/ ml with minimum detectability of 0,005 μg /ml (S/N = 3). The correlation coefficient was 0,999 (n = 6) with a relative standard deviation (RSD) of 1,63% for 2,0 μg /ml. The proposed method was successfully applied to commercial tablets. The average percentage recovery (n = 6) was 99,9 ± 1,40. [115].

Hydrogen peroxide, potassium permanganate, potassium dichromate, potassium hexacyanoferrate(III), cerium(IV) sulphate and sodium peroxydisulphate was tested as potential reagents for CL generation from the oxidation of phenothiazine derivatives. Only with potassium permanganate in acidic medium were satisfying results achieved. A total of 13 different phenothiazine derivatives produce luminescence of different intensities on oxidation. Thioridazine hydrochloride was chosen to develop a rapid and simple method for its determination in pharmaceutical formulations. The limit of detection is $1{,}2\cdot10^{-6}$ mol/l, and 110 samples per hour can be determined [116].

A flow injection chemiluminescence method was described for the determination of four phenothiazine drugs, namely, chlorpromazine hydrochloride, perphenazine hydrochloride, fluphenazine hydrochloride and thioridazine hydrochloride. Strong chemiluminescence signal was produced when above-mentioned drug was injected into the mixed stream of luminol with $KMnO_4$. The linear ranges of the method were 0,0020–1,0 μg/ml chlorpromazine hydrochloride, 0,0040–3,0 μg/ml perphenazine hydrochloride, 0,0020–5,0 μg/ml fluphenazine hydrochloride and 0,0050–1,0 μg/ml thioridazine hydrochloride. The detection limits were 0,4 ng/ml chlorpromazine hydrochloride, 0,7 ng/ml perphenazine hydrochloride, 2 ng/ml fluphenazine hydrochloride and 0,7 ng/ml thioridazine hydrochloride. The proposed method was applied to the determination of chlorpromazine hydrochloride in injections and in mental patient's urine samples and the satisfactory results were achieved. [117].

The chemiluminescent behaviour of captopril when reacted with a common oxidant, potassium permanganate in different acidic media is described, using the stopped-flow technique in a continuous-flow system. A 22 bit analogue-to-digital converter that acquires analogue signals at -10 and +10V and allows the power supply to the peristaltic pump to be interrupted is used in the time-resolved chemiluminescence manifold to ensure rapid, efficient mixing of chemiluminescent reagent and sample immediately before reaching the detector; this results in high precision and detectability, particularly with fast, short-lived emissions. The optimum chemical conditions for the chemiluminescence emission were investigated. It was found that a weak CL emission was emitted during the oxidation of this drug with potassium permanganate in acidic solution. The effect of common emission enhancers such as formic acid, formaldehyde, glutaraldehyde, acetaldehyde, quinine, fluorescein, rhodamine B and rhodamine 6G was studied. The parameters selected were 4,0 mol/l sulphuric acid, 0,25 mmol/l permanganate and 0,75 mol/l formaldehyde. Four quantitative parameters adjustable via software settings, two of them typically kinetic parameters, such as rate of the light-development reaction and rate of the light-decay reaction, and the other conventional parameters, such as maximum emission intensity and total emission area, were used to obtain linear calibration graphs with each measurement parameter. The detection limits ranged from 0,01 to 0,026 μg/ml and RSD values (n = 10) of 1,21–3,93 at a 0,50 μg/ml and 2,01–

3,41 at a 1,60 μg/ ml concentration levels were obtained. The method was satisfactorily applied to the determination of captopril in pharmaceutical preparations [118].

Oxidation by Ce(IV)

Compared with acidic $KMnO_4$-based CL system, Ce(IV)-related CL reaction is not subject to the chloride ion. Moreover, $KMnO_4$ has strong absorption to light emission and consequently the CL intensity could decrease when the concentration of $KMnO_4$ is too high. Instead, the sensitivity for Ce(IV)-based CL system can be improved by increasing Ce(IV) concentration since the selfabsorption of light is reduced largely in the system. Therefore, the Ce(IV)-based CL reaction in an acidic media (generally in sulfuric acid medium) has also been carried out for the determination of biochemical species in dosage forms. A possible CL mechanism of the reaction may be attributed to the following reactions:

$$Ce(IV) + Analite\ (Red) \rightarrow Ce(III)^{*} + Analite\ (Ox)$$
$$Ce(III)^{*} \rightarrow Ce(III) + light$$

and/or

$$Ce(III)\text{-analite complex}^{*} \rightarrow Ce(III) + analite + light.$$

A few of pharmaceuticals can reduce the Ce(IV) directly and produce luminescence. A most determinations involving Ce(IV) as the oxidant are of the indirect type, which based on the enhancement effect of some analytes on the CL intensity of Ce(IV)-sulfite system, Ce(IV)-$Ru(bpy)_3^{2+}$ system or Ce(IV)-Tween 20 system, etc. This type of process, named sensitization, is used to determine reducing compounds. According to the investigation of CL properties of the fluorophore-senitized Ce(IV) reaction system by Zang et al. [119], a possible CL mechanism of the reaction may be attributed to the following reactions:

$$Ce(IV) + Analite\ (Red) \rightarrow Ce(III)^{*} + Analite\ (Ox)$$
$$Ce(III)^{*} + fluorophore \rightarrow Ce(III) + fluorophore^{*}$$

and/or

$$Ce(III)\text{-analite complex}^{*} + fluorophore \rightarrow Ce(III) + analite + fluorophore^{*}$$
$$fluorophore^{*} \rightarrow fluorophore + light.$$

In the present of a fluorophore, Ce(III) ions or the Ce(III)-analyte complex transfer the excess energy to the fluorophore which in turn generates CL emission. This type of process is used to determine reducing compounds, such as ofloxacin [120], nomoxacin, ciprofloxacin, lomefloxacin [121], flufenamic acid, mefenamic acid [122] and salicylic acid [123]. In particular, light emission resulting from the chemical reaction of Ce(IV) with some mercapto-containing compounds in pharmaceutical preparations can be enhanced by certain fluorometric reagents such as quinine [129], or by lanthanide ions like Tb (III) and Eu (III), etc. [133,127].

The determinations utilizing Ce(IV)-based CL that sensitized by rhodamine compounds are discussed as a separated section in consideration that rhodamine compounds have also been used as a CL reagent in the literatures [128 - 131]. Table 2 summarizes as the analytical applications of Ce (IV)-based FI-CL methods not including that involving rhodamine compounds, with respect to the analytes, the used detection system, samples and detection limits.

Rhodamine Compounds-Based CL System

Rhodamine compounds, as a series of xanthene dyes, have been extensively applied in analytical chemistry and especially in spectrometry, fluorescence analysis, catalytic and kinetic analysis since it has high efficiency to generate light emission. In recent years, rhodamine compounds, including rhodamine B (RhB) and rhodamine 6G (Rh6G), have utilized gradually in FI-CL analysis. Nevertheless, rhodamine compounds are often considered as a sensitizer for other CL systems (especially for Ce (IV)-based CL system) and the detailed mechanism for the detection has little reports in the open literatures. In 1986, Zhang [132] observed that the redox reaction between RhB and hydrogen peroxide produced CL in alkaline aqueous solutions, and the effect of chromium (IV) concentration on the CL intensity was also discussed. In 2002, Ma and coworkers [128] discovered that the oxidation of RhB by cerium (IV) in sulfuric acid could produce strong light emission directly and a new CL system applying RhB as a CL reagent was established and applied for the determination of ascorbic acid in vegetables. Before long, the possible chemiluminescence mechanism of the system was investigated in detail. The formation of a complex in excited state between RhB and cerium (IV) was affirmed and the chemiluminescent emissive wavelength was indicated at ca. 425 nm [129].

The fluorescent dye RhB, in combination with a strong oxidant Ce(IV), was used to investigate the properties of three important polyphenols, resorcinol, catechol and hydroquinone. The reaction of RhB with Ce(IV) solution in acidic medium was found to elicit strong CL. The CL signal remarkably weakened in the presence of resorcinol whereas the two other isomers, catechol and hydroquinone, hardly had any effect in the same range of concentrations. Based on these observations, a new flow-injection CL method was developed for the determination of resorcinol. In addition, a brief discussion of possible mutual interaction mechanism between the three polyphenols and the components of the system is also presented [133]. Further, based on the enhancement of CL of RhB-Ce (IV) system in sulfuric acid medium, thermally denatured DNAs and DNAs activated previously by imidazole-HCl buffer solution were determined respectively [130, 131]. Similarly, the related reports in-

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

volving rhodamine compounds-based CL with FI technique for the determination of biochemical species are described in Table 3. It is worth hoping that the development of the CL system of rhodamine compounds with Ce (IV) in an acidic media helps to broaden the analytical applications of CL methods with FI technique.

A new CL method is described for the determination of synephrine. It is based on the reaction between synephrine and Ce(IV) in a nitric acid medium and measurement of the CL intensity produced by rhodamine B used as a luminophore, similar to luminol or lucigenin in basic-edta, instead of as a sensitizer. In the optimum conditions, the increase of CL intensity was correlated with synephrine concentration over the range $5{,}0\cdot10^{-9}$–$1{,}0\cdot10^{-6}$ g/ml with a detection limit of 1,0 ng/ml. The relative standard deviation was 2,9% for 100 ng/ml synephrine (n = 11). The method was applied to the determination of a drug in herbal products, citrus fruit and biological samples, with satisfactory results. The results given by the proposed method are in good agreement with those given by HPLC-UV and UV spectrophotometry [134, 135].

Oxidation by (2,2-bipyridine)ruthenium(III) Complex

A frequently applied CL reaction uses tris(2,2-bipyridine)ruthenium(III) complex ($Ru(bipy)_3^{3+}$) as reagent. This rather unstable molecule should be freshly prepared just prior the reaction or in situ. A variety of methods have been employed to btain active $Ru(bipy)_3^{3+}$ by oxidation of relatively stable $Ru(bipy)_3^{2+}$ including chemical, photochemical and electrochemical oxidation. An analyte is oxidized by the $Ru(bipy)_3^{3+}$ to produce excited $[Ru(bipy)_3^{2+}]^*$ species emitting CL at around 600 nm [136]. The CL is generated by the reaction with a reductant (Xred) as follows:

$$Ru(bipy)_3^{2+} + Ox \rightarrow Ru(bipy)_3^{3+} + e^-$$
$$Ru(bipy)_3^{3+} + X_{red} \rightarrow [Ru(bipy)_3^{2+}]^* + X_{ox}$$
$$[Ru(bipy)_3^{2+}]^* \rightarrow Ru(bipy)_3^{2+} + h\nu.$$

In recent years chemical oxidation of $Ru(bipy)_3^{2+}$ to $Ru(bipy)_3^{3+}$ has been achieved with Ce(IV) in acidic medium, permanganate in acidic medium or by lead dioxide as oxidants. The drugs determined with $Ru(bipy)_3^{3+}$ as reagent contain typically nitrogen in their structure (mainly heterocyclic compounds and primary, secondary and tertiary amines) except of naproxen which is derivate of 2-arylpropionic acid (profen). Generation of $Ru(bipy)_3^{3+}$ was carried out by photochemical oxidation of $Ru(bipy)_3^{2+}$ (involving UV-irradiation in the presence of peroxodisulphate) in the CL determination of *L*-cysteine and *L*-cystine [137]. Direct CL determination of cysteine was possible whereas cystine had to be preliminarily transformed to cysteine by using a reduction column. Electrochemically generated $Ru(bipy)_3^{3+}$ was used for the CL determination of antibiotic cefadroxil [138]. The flow cell of the proposed system contained a platinum working electrode, a silver chloride reference electrode and a steel needle as an auxiliary electrode. Cefadroxil was oxidized by $Ru(bipy)_3^{3+}$ generated from $Ru(bipy)_3^{2+}$ in situ on the surface of the platinum electrode.

A FI method using the tris(2,2′-bipyridyl) ruthenium(II) $[Ru(bpy)_3^{2+}]$-potassium permanganate CL was reported for the rapid and sensitive determination of cephalosporins such as cefoxitin, cefazolin, cephalexin, cefadroxil, cefaclor and cefoperazone. The method is based on the CL reaction of cephalosporins and $Ru(bpy)_3^{2+}$ with potassium permanganate in the presence of perchloric acid, catalyzed by Mn(II). Under the optimum conditions, the calibration curves are linear over the range 0,10–12,0 μg/ml for cefoxitin, 0,10–10,0 μg/ ml for cefoperazone and 0,10–15,0 μg/ ml for cefazolin, cephalexin, cefadroxil, and cefaclor, respectively. The limits of detection (3σ) are 0,03 μg/ml for cefoxitin and cefadroxil, 0,06 μg/ml for cefoperazone and 0,08 μg/ml for cefazolin, cephalexin and cefaclor, respectively. The method was successfully applied to the determination of cefoxitin, cefazolin, cephalexin and cefadroxil in pharmaceutical formulations with a sample throughput of 90 h^{-1}. There were no interference effects from some common excipients used in pharmaceutical preparations [139]. Aly et al. [140] proposed a method for the determination of cefadroxil in pharmaceutical samples and biological fluids based on flow injection chemiluminescence reaction of cefadroxil and potassium permanganate in sulphuric acid, sensitized by quinine.

Other oxidation CL reactions

In addition to permanganate and $Ru(bipy)_3^{3+}$ some other oxidants, namely $[Fe(CN)_6]^{3-}$, N-bromosuccinimide or periodate in alkaline medium or Ce(IV), manganese dioxide and soluble manganese(IV) in acidic medium were utilized as reagents in CL assay of drugs. Some CL reactions can occur at the surface of an electrode when the CL reagent (often an unstable species) is produced from a passive precursor in a flow system. Such electro-CL analyses are characterized by good sensitivity but they may suffer from some drawbacks such as electrode fouling, narrow linear range due to small area of the working electrode, poor repeatability and complicated design of the electrochemical/CL flow cell. In the recent years the electrogenerated oxidants applied in the CL analysis of drugs were hydrogen peroxide [141], Mn(III) [142, 143], Ag(II) [144], Co(III) [145] and $[Cu(HIO_6)_2]^{5-}$ [146, 147].

Miscellaneous reactions

This section is dealing with CL assays that could not be included in the previous sections because the nature of the CL reaction utilized is different. Song and coauthors [148] devised a CL method for the assay of fluoroquinolones (ciprofloxacin, nor-

floxacin, ofloxacin) that enhanced weak CL from peroxynitrous acid (nitrite + hydrogen peroxide in acidic medium). The peroxynitrous acid was converted into a metastable excited species OHOON*. Fluoroquinolones served as energy-transfer species responsible for CL emission. The oxidation of peroxyoxalate by hydrogen peroxide gives an intermediate which may transfer its energy to other molecules. Under the optimum conditions, the calibration curves are linear over the range $3{,}0\cdot10^{-7}$ - $1{,}0\cdot10^{-5}$mol/l for ofloxacin and $1{,}0\cdot10^{-7}$-$1{,}0\cdot10^{-3}$ mol/l for ciprofloxacin and norfloxacin respectively. The limits of detection (*S*/*N* = 3) are $4{,}5\cdot10^{-8}$ mol/l, $5{,}9\cdot10^{-8}$ mol/l and $1{,}1\cdot10^{-7}$ mol/l for ciprofloxacin, norfloxacin and ofloxacin, respectively. The method was successfully applied to the determination of ciprofloxacin, norfloxacin and ofloxacin in pharmaceutical formulations. The reaction is suitable for determination of fluorophores or compounds labeled with fluorescent tags.

Thus albumin [149, 150] was derivatized off-line with fluorescamine in acetone and bis(2,4,6-trichlorophenyl)oxalate (in acetonitrile) was oxidized with hydrogen peroxide to form an intermediate which transferred its excitation energy to the labeled albumin in the presence of sodium dodecyl sulphate and imidazole (bases such as imidazole, pyridine, TRIS and triethylamine catalysed the peroxyoxalate CL reaction).

Another CL reaction was used for the determination of ethamsylate (2,5-dihydroxybenzenesulfonic acid with diethanolamine) [151]. This analyte is hydrolyzed in alkaline medium to 2,5-dihydroxybenzensulfonate and diethylamine. A strong CL was generated in the presence of dissolved oxygen, Tween 80 and rhodamine 6G (energy-transfer reagent).

CL is a very attractive detection technique mostly due to the instrument simplicity, low-detection limits and wide calibration ranges. At present the “marriage” of CL detection and automated flow techniques such as FIA and SIA stimulated more extensive use of CL in drug analysis. Other flow methodologies not considered in this review (multicommutation, multi-syringe, stopped-flow, multi-pumping, etc.) have not yet contributed significantly to the analysis of drugs. The discovery of newdirect selective CL reactions can potentially increase the number of analytes of pharmaceutical interest which could be determined through CL. To succeed in such developments a deeper knowledge of mechanisms of the CL reactions is prerequisite. In the authors’ opinion further progress in the field of electro-CL concept can probably contribute to further improvement of selectivity of CL assays, while wider implementation of automated on-line separation techniques in this sense is straightforward. Most of the reported CL drug assays are performed by means of lab-made flow luminometers which makes difficult comparison of the analytical numbers of merit of methods devised in different laboratories. Moreover, a CL reaction which could be used as a CL standard still remains a challenge opened to CL researchers.

REFERENCES

1. Бабко А.К., Дубовенко Л.И., Луковская Н.М. Хемилюминесцентный анализ.- Киев: Техника, 1966. – 250 с.
2. Зуй О.В., Гончарук В.В. Хемилюминесцентный анализ сегодня и завтра// Укр. хим. журн. – 2005. – Т. 71, №1. – С. 61-67.
3. Пономаренко А. А. О хемилюминесцентном количественном анализе // Докл. АН СССР. – 1955. – Т. 102, № 3. – С. 539-542.
4. Nauš J. García- Campaña A.M., Baeyens W.R.G. (Ed.) Chemiluminescence in Analytical Chemistry.– Photosynthetica. – 2001.– Vol. 3, № 2. – P. 204-204.
5. García-Campaña A.M., Baeyens W.R.G. Chemiluminescence in Analytical Chemistry.– New York: Marcel Dekker, Inc., 2001. 621 p.
6. Mervartová K., Polášek M., Martínez Calatayud J. Recent applications of flow-injection and sequential-injection analysis techniques to chemiluminescence determination of pharmaceuticals // J. Pharm. Biomed. Anal.– 2007.– 45.– P. 367–381.
7. Hanaoka S., Lin Jin-Ming, Yamada M. Chemiluminescence behavior of the decomposition of hydrogen peroxide catalyzed by copper(II)–aminoacid complexes and its application to the determination of tryptophan and phenylalanine // Anal. Chim. Acta. – 2000. – 409. – P. 65-73.
8. Economou A., Tzanavaras P.D., Notou M., Themelis D.G. Determination of methimazole and carbimazole by flow-injection with chemiluminescence detection based on the inhibition of the Cu(II)-catalysed luminol–hydrogen peroxide reaction //Anal.Chim.Acta. –2004. –505.– P.129–133.
9. Fernández J.M.R., Bosque-Sendra J.M., García-Campaña A.M., Barrero F. A. Chemiluminescence determination of amikacin based on the inhibition of the luminol reaction catalyzed by copper //J. Pharm. Biomed. Anal. – 2005. – 36. – P. 969–974.
10. Du J., Li Y., Lu J. Flow injection chemiluminescence determination of thiamine based on its enhancing effect on the luminol–hydrogen peroxide system //Talanta. – 2002. – 57. – P. 661–665.
11. Safavi A., Karimi M. A., Hormozi Nezhad M. R. Flow-injection determination of isoniazid using sodium dichloroisocyanurate- and trichloroisocyanuric acid-luminol chemiluminescence systems // Il Farmaco. – 2004. – 59. – P. 481–486.
12. Song Z., Wang C. Sensitive chemiluminescence assay for risperidone in pharmaceutical preparations // J. Pharm. and Biomed. Anal. – 2004. – 36. – P. 491–494.
13. Cui H., Shi M.J., Meng R., Zhou J., Lai C.Z., Lin X.Q. Effect of pH on inhibition and enhancement of luminol-H_2O_2-Co^{2}+ chemilumines-

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

cence by phenolic compounds and amino acids // Photochem Photobiol. – 2004. – 79. – P. 233–241.

14. García-Campaña A. M., Sendra J. M. B., Vargas M. P. B., Baeyens W. R. G., Zhang X. Flow injection analysis of oxymetazoline hydrochloride with inhibited chemiluminescent detection **//** Anal. Chim. Acta. – 2004. – 516. – P. 245–249.

15. Jian Wang, Huazhen Ye, Zhou Jiang, Naisheng Chen, Jinling Huang Determination of diethylstilbestrol by enhancement of luminol–hydrogen peroxide–tetrasulfonated cobalt phthalocyanine chemiluminescence // Anal. Chim. Acta. – 2004. – 508. – P. 171–176.

16. Zhenghua Song, Shuang Hou. Subpicogram determination of Vitamin B_{12} in pharmaceuticals and human serum using flow injection with chemiluminescence detection // Anal. Chim. Acta. – 2003. – 488. – P. 71–79.

17. Sagaya Selva Kumara, Raghuraj Singh Chouhana and Munna Singh Thakur Enhancement of chemiluminescence for vitamin B_{12} analysis // Analytical Biochemistry.–2009.–388.– P.312–316.

18. Shi, W., Yang, J., Huang, Y. Ion-pair complex-based solvent extraction combined with chemiluminescence determination of chlorpromazine hydrochloride with luminol in reverse micelles // J. Pharm. Biomed. Anal.–2004. – 36. – P.197–203.

19. Ratanawimarnwong N., Amomthammarong N., Choengchan N., Chaisuwan P., Amatatongchai M., Wilairat P., McKelvie I.D., Nacapricha D. // Talanta. – 2005. – 65. – P. 756-761.

20. Panoutsou P. and Economou A. Rapid enzymatic chemiluminescent assay of glucose by means of a hybrid flow-injection/sequential-injection method // Talanta.– 2005. – 67. – P.603–609.

21. Song Z., Hou S. Determination of picomole amounts of thiamine through flow-injection analysis based on the suppression of luminol – KIO_4 chemiluminescence system // Journal of Pharmaceutical and Biomedical Analysis. – 2002. – 28. – P. 683–691.

22. Song Z.H., Zhang N. In vitro detecting ultra-trace novalgin in medicine and human urine by chemiluminescence / Talanta.– 2003. – № 1. – P.161–170.

23. Zhou G.-J., Zhang G.-F., Chen H.-Y. Development of integrated chemiluminescence flow sensor for the determination of adrenaline and isoprenaline // Anal. Chim. Acta. – 2002. – 463. – P. 257–263.

24. Li B., Zhang X., Zhang C. The second chemiluminescence emission of luminol–periodate–menadione sodium bisulfite system and its analytical application // Anal. Chim. Acta. – 2006. – 575. – P. 212–216.

25. Yao H., Tang Ý., Li Y., Sun Y. Flow Injection Chemiluminescence Determination of Cephalosporin Antibiotics by Their Enhancing Effects on Luminol-Potassium Periodate System // Anal. Lett. – 2003. – 36. – P. 2975–2983.

26. Li Y. and Lu J. Chemiluminescence flow-injection analysis of β-lactam antibiotics using the luminol-permanganate reaction // Luminescence. – 2006. – 21. – P. 251–255.

27. Francis P.S., Barnett N.W., Lewis S.W., Lim K.F. Hypohalites and related oxidants as chemiluminescence reagents: a review // Luminescence. – 2004. – 19. – P. 94–115.

28. Kubo H., Saitoh M. Chemiluminescence Determination on a Luminol Reaction of β-Lactam Antibiotics by FIA // Anal. Sci. – 1999. – 15. – P. 919–921.

29. Kubo H., Saitoh M., Murase S., Inomato T., Yoshimora Y., Nakazawa H. Chemiluminescence of β-lactam antibiotics based on the luminol reaction // Anal. Chim. Acta. – 1999. – 389. – P. 89–94.

30. Стадничук Е.Н., Зинчук В.К. Хемилюминесцентное определение аскорбиновой кислоты в фармпрепаратах // Заводская лаборатория. – 2001. – 67, № 1. – С. 18–21.

31. Yao H., Yang X. , Li H. Chemiluminescence of Peracetic Acid in Alkaline Medium and its Application to Dihydralazine Sulfate Determination // Microchimica Acta. – 2006. – 153. – P. 171–178.

32. Калиниченко И.Е., Шевченко И.Н. Хемилюминесцентное определение ингибитоов с помощью некаталитической реакции люминола с пероксидисульфатом // Укр. хим. журн. – 1996. – 62, № 3. – С. 40–43.

33. Пат. № 17855, МПК[5] G 01 N 21/76. Спосіб визначення антиоксидантів/ Калініченко І.О., Шевченко І.М., Бакай Е.А., Сенчик Н.І; заявник та патентовласник Науковий та інженерно-технологічний центр біотехнічних систем „Сонар" НАН України (Україна), Інститут колоїдної хімії та хімії води ім. А.В. Думанського НАН України (Україна); заявл. 17.05.96, опубл. 31.10.97, Бюл. № 5.

34. Блажеєвський М.Є., Бондаренко Н.Ю. Кінетичне визначення парацетамолу в лікарських формах методом хемілюмінесценції // Фармац. журн. – 2004. – № 5. – С. 68–73.

35. Блажеєвський М.Є. Бондаренко Н.Ю. Визначення катехоламінів у лікарських формах методом інгібування хемілюмінесценції // Журн. органічної та фармац. хімії. – 2005. – 3, Вип. 3. – С. 79– 82.

36. Блажеєвський М.Є., Бондаренко Н.Ю. Кількісне визначення флавоноїдів в лікарських засобах методом хемілюмінесценції // Фармаком. – 2005. – № 2-3. – С. 177–181.

37. Бондаренко Н.Ю., Блажеєвський М.Є. Кількісне визначення кофеїну хемілюмінесцентним методом в лікарських формах // Фармац. журн. – 2005. –№ 2.–С.75–79.

38. Бондаренко Н.Ю., Блажеєвський М.Є. Методика кількісного визначення кофеїну в каві методом хемілюмінесценції: інформ. лист. / К. Укрмедпатентінформ МОЗ України, 2005. – № 216. – 4 с.

39. Блажеєвський М.Є., Бондаренко Н.Ю. Кількісне визначення вікасолу в лікарських формах методом хемілюмінесценції // Фармац. журн. – 2006. – № 3. – С. 74–78.

40. Блажеєвський М.Є. Кінетико-хемілюмінесцентний метод визначення ацетилхоліну // Науково-технічний прогрес і оптимізація технологічних процесів створення лікарських препаратів: матеріали 1-ї Міжнар. наук.-практ. конф., м. Тернопіль, 6-7 квіт. 2006 р. – Тернопіль: Укрмедкнига, 2006. – С. 78–79.

41. Блажеєвський М.Є., Карпушина С.А., Баюрка С.В. Методи визначення ацетилхоліну. Кінетико-хемілюмінесцентне визначення ацетилхоліну та його застосування у холінестеразно-інгібіторних системах // Актуальні питання фармацевтичної та медичної науки та практики: зб. наук. ст.– Запоріжжя: Вид.- во ЗМУ, 2007. – Вип. 20. – С. 7–13.

42. Блажеєвський М.Є. Визначення надоцтової кислоти методом хемілюмінесценції // Наука і соціальні проблеми суспільства: медицина, фармація, біотехнологія: тез. доп. III міжнар. наук. – практ. конф., м. Харків, 21-23 трав. 2003 р. – Х., 2003. – С. 40.

43. Блажеєвський М.Є. Хемілюмінесцентне визначення надоцтової кислоти / М.Є. Блажеєвський // Наукові записки ТДПУ. Серія: Хімія. – 2004. – №8. – С. 25–31.

44. Klopf L.L., Nieman T.A. Use of surfactants to improve analytical performance of lucigenin chemiluminescence // Anal. Chem. – 1984. – 56. – P. 1539–1542.

45. Veazey R.L., Nieman T.A. Chemiluminescent determination of clinically important organic reductsnts // Anal. Chem. – 1979. – 51. – P. 2092–2095.

46. HasebeT., Kawashima T. Flow-injection determination of ascorbic acid by iron(III)-catalysed lucigenin chemiluminescence in micellar system // Anal. Sci. – 1996. – 12. – P. 773–777.

47. Alwarthan A.A., Al-Lohedan H.A., Issa Z.A. Micellar effect upon the lucigenin chemiluminescent reaction system with isoprenaline // Anal. Lett. – 1996. – 29. – P. 1589–1602.

48. Alwarthan A.A., AL-Tamrah S.A., Ake A.A. Flow-injection determination of kanamycin by inhibition of the lucigenin-hydrogen peroxide-cobalt system // Anal. Chim. Acta. – 1994. – 292. – P. 201–208.

49. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення адреналіну в розчині для ін'єкцій // Матеріали наук.-практ. конф. з міжнар. участю „Створення, виробництво, стандартизація, фармакоекономіка лікарських засобів та біологічно активних добавок". – Тернопіль: Укрмедкнига, 2004. – С. 249–252.

50. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення адреналіну гідротартрату в розчині для ін'єкцій // Фармац. журн. – 2007. – № 2. – С. 73–77.

51. Блажеєвський М.Є., Миронюк П.Л. Кількісне визначення допаміну в ін'єкційних розчинах методом хемілюмінесценції з солями акридинію // Досягнення та перспективи розвитку фармацевтичної галузі України: Матеріали VI Національного з'їзду фармацевтів України (28-30 вересня 2005 р., м. Харків)/ Ред. кол.: Черних В.П. та ін. – Харків: Вид-во НФаУ, 2005. – С. 135–136.

52. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення допаміну в ін'єкційних розчинах за допомогою нітрату 9-ціано-10-метилакридинію // Фармац. журн. – 2006. –№ 6. – С. 69–73.

53. Блажеєвський, М.Є., Миронюк П.Л. Хемілюмінесцентне визначення ізоніазиду в пігулках // Матеріали наук.-практ. конф. з міжнар. участю „Створення, виробництво, стандартизація, фармакоекономіка лікарських засобів та біологічно активних добавок". – Тернопіль: Укрмедкнига, 2004. – С. 252–254.

54. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення ізоніазиду в таблетках по 0,3 г // Фармаком. – 2006. – № 3. – С. 52–55.

55. Блажеєвський М.Є., Миронюк П.Л., Нізельский Ю.М. Кількісне визначення флуренізиду в пігулках методом хемілюмінесценції за реакцією з нітратом 9-ціано-10-метилакридинію // Лекарства – человеку. Современные проблемы создания, исследования и апробации лекарственных средств:/ Материалы XXV Юбилейной научно-практической конференции с международным участием (19 марта 2008 года). – Харьков: Изд. – во НФаУ, 2007. – С. 209–214.

56. Миронюк П.Л., Блажеєвський М.Є. Кількісне визначення фтивазиду у пігулках методом хемілюмінесценції // Актуальні питання створення нових лікарських засобів: матеріали всеукр. наук.-практ. конф. студ. та молодих вчених, м. Харків, 16–17 квіт. 2008 р. – Харків, 2008. – С. 106.

57. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення дигідралазину сульфату в пігулках „Трирезид К" // Матеріали I Міжнародної науково-практичної конференції „Науково-технічний прогрес і оптимізація технологічних процесів створення лікарських препаратів". – Тернопіль: Укрмедкнига. – 2006. – С. 84–85.

58. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення гідразинових похідних фталазину за реакцією з нітратом 9-ціано-10-метилакридинію // Тези доповідей II Міжнародної науково-практичної конференції „Створення, виробництво, стандартизація, фармакоекономічні дослідження лікарських засобів та біологічно активних добавок". – Харків: Вид-во НФаУ. – 2006. – С. 78–79.

59. Блажеєвський М.Є., Миронюк П.Л., Баюрка С.В., Карпушина С.А., Степаненко В.І. Хемілюмінесцентне визначення гідразинових похідних фталазину в лікарських формах // Вісник фармації. – 2008. № 3.– С. 13–16.

© M. Ye. Blazheevskiy, N.Yu. Bondarenko

60. Блажеєвський М.Є., Миронюк П.Л. Кількісне визначення несиметричного диметилгідразину у водах методом хемілюмінесценції // Матеріали III Міжнародної науково-практичної конференції ”Динаміка наукових досліджень’2004”. – 34. Екологія. – Дніпропетровськ: Наука і освіта, 2004. –С.13–15.

61. Миронюк П.Л., Блажеєвський М.Є. Хемілюмінесцентне визначення N-ацетилцистеїну за реакцією з нітратом 9-ціано-10-метилакридинію // Сучасні проблеми судово-токсикологічної науки і прктики: Матер. всеукр. наук.- практ. конф. з міжнар. участю (9–10 квітня 2009 р., м. Харків)/ – Харків: Вид-во НФаУ, 2009. – С. 44–45.

62. Блажеєвський М.Є. Хемілюмінесцентне визначення малатіону у препараті "Педилін" / М.Є. Блажеєвський // Фармац. журн. – 2005. – № 1. – С. 77–81.

63. Блажеєвський М.Є., Миронюк П.Л. Кількісне визначення феноксиметилпеніцилину в пігулках методом хемілюмінесценції // Досягнення та перспективи розвитку фармацевтичної галузі України: Матеріали VI Національного з’їзду фармацевтів України (28-30 вересня 2005 р., м. Харків)/ Ред. кол.: Черних В.П. та ін. – Харків: Вид-во НФаУ, 2005. – С. 137–138.

64. Блажеєвський М.Є., Миронюк П.Л. Хемілюмінесцентне визначення феноксиметилпеніциліну в пігулках за допомогою нітрату 9-ціано-10-метилакридинію // Фармац. журн. – 2007. – № 1. – С. 78–82.

65. Zhuang Y.F., Zhang S.C., Yu, J.S., Ju, H.X. Flow injection determination of papaverine basedon its sensitizing effect on the chemiluminescence reaction of permanganate-sulfite //Anal. Bioanal. Chem. – 2003. – 375. – P. 281–286.

66. Ocaña J.A., Callejón M., Barragán F.J., De la Rosa F.F. Lanthanide sensitized chemiluminescence determination of grepafloxacin in tablets and human urine // Anal. Chim. Acta. – 2003. – 482. – P. 105–113.

67. Aly F.A., Alarfaffj N.A., Alwarthan A.A. Flow-injection chemiluminometric analysis of somebenzamides by their sensitizing effect on the cerium-sulphite reaction // Talanta. – 2001. – 54. – P. 715–725.

68. Wang X. L., Li A. Y., Zhao H. C., Jin L. P. A lanthanide sensitized chemiluminescence method of flow-injection for the determination of ulifloxacin and prulifloxacin // Ж. аналит. химии. – 2009. – 64. – С. 84–90.

69. Chen J., Fang Y. Flow Injection Technique for Biochemical Analysis with Chemiluminescence Detection in Acidic Media // Sensors. – 2007. – 7. – P. 448–458.

70. Sun C.Y.,Lian N., Zhao H.C.,Yi L. ,JinL.Flow Injection Determination of Lomefloxacin Based on Photochemically Sensitized Chemiluminescence // Microchim. Acta. – 2004. – 148. – P. 65–70.

71. Li B., Zhang Z., Zhao L, Xu C. Chemiluminescence flow-through sensor for pipemidic acid using solid sodium bismuthate as an oxidant //Anal. Chim. Acta. – 2002. – 459. – P. 19–24.

72. Li B., Zhang Z., Zhao L, Xu C. Chemiluminescence flow-through sensor for ofloxacin using solid-phase PbO_2 as an oxidant // Talanta. – 2002. – 57. – P.765–771.

73. Mestre Y.F., Zamora L.L., Calatayud J.M. Flow-chemiluminescence: a growing modality of pharmaceutical analysis // Luminescene. – 2001. – 16. – P. 213–235.

74. Corominas B. Gómez-Taylor, Antón-Fos G.M., García Mateo J.V., Zamora L. L., Calatayud J. M. Prediction of the chemiluminescent behaviour of phenols and polyphenols // Talanta. – 60. – P. 623–628.

75. Merti E. P., Icardo M. C., Zamora L.L., Antón-Fos G.M., Calatayud J. M. Theoretical prediction of the chemiluminescence behaviour of the ergot alkaloids: Direct flow injection chemiluminescence determination of ergotamine tartrate // Anal. Chim. Acta. – 2004. – 527. – P. 177–186.

76. Icardo M. C., Zamora L. L., Antón-Fos G.M., Calatayud J. M., Duart M.J. Molecular connectivity as a relevant new tool for predicting analytical behavior: A survey of chemiluminescence and chromatography // Trends Anal. Chem. 2005. – 24. –P. 782–791.

77. Adcock J. L., Francis P. S. and Barnett N. W. Acidic potassium permanganate as a chemiluminescence reagent. – A review // Anal. Chim. Acta. – 2007. – 601. – P. 36–67.

78. Abbot R.W., Townshend A., Gill R. Determination of morphine by flow injection analysis with chemiluminescence detection // Analyst. – 1986. – 111. –P.635–640.

79. Alwarthan A.A., Aly F.A. Chemiluminescent determination of pyridoxine hydrochloride in pharmaceutical samples using flow injection // Talanta. – 1998. – 45. – P. 1131–1138.

80. Sultan S.M., Almuaibed A.M., Townshend A. Flow injection chemiluminescence determination of medazepam // Fresenius J. Anal. Chem. –1998. – 362. – P. 167–169.

81. Barnet N.W., Hindson B.J., Lewis S.W. Determination of Ranitidine and Salbutamol by Flow Injection Analysis with Chemiluminescence Detection // Anal. Chim. Acta. – 1999. – 384. – P. 151–158.

82. Mestre Y.F., Zamora L.L., Calatayud J.M. Direct flow injection chemiluminescence determination of salicylamide// Anal. Chim. Acta. – 1999. – 394. – P. 159–163.

83. Feng M.L., Zhang G.F., Zhang Z.J. FIA determination of pyruvate in serum based on direct chemiluminescence oxidation // Fresenius J. Anal. Chem. – 1999. – 363. – P. 320–322.

84. Sultan S.M., Abdennabi A.M.S., Almuaibed A.M. Chemiluminescence method for the assay of perphenazine in drug formulation using permanga-

nate in sulphuric acid with flow injection technique and a chemometrical optimization approach // Talanta. – 1999. – 49. – P. 1051–1057.

85. Deftereos N.T., Grekas N., Calokerinos A.C. Flow injection chemiluminometric determination of albumin // Anal. Chim. Acta. – 2000. – 403. – P. 137–143.

86. Kojo A., Michaowski J., Woyniec E. Chemiluminescence determination of thioridazine hydrochloride by flow-injection analysis // J. Pharm. Biomed. Anal. – 2000. – 22. – P. 85–91.

87. Pinotsis N., Calokerinos A.C., Baeyens W.R.G. Chemiluminometric determination of reserpine and related alkaloids // Analyst. – 2000. – 125. – P. 1307–1312.

88. Li B.X., Zhang Z.J., Zhao L.X. Flow-injection chemiluminescence detection for studying protein binding for drug with ultrafiltration sampling // Anal. Chim. Acta. – 2002. – 468. – P. 65–70.

89. Zhuan Y.F., Zhang S.C., Yu J.S., Ju H.X. Flow injection determination of papaverine based on its sensitizing effect on the chemiluminescence reaction of permanganate-sulfite// Anal.Bioanal. Chem. – 2003. – 375. – P. 281–286.

90. Zhuang Y.F., Cai X.L., Yu J.S., Ju H.X. Flow injection chemiluminescence analysis for highly sensitive determination of noscapine// J. Photochem. Photobiol. A: Chemistry. – 2004. – 162. – P. 457–462.

91. Barnett N.W., Hindson B.J., Lewis S.W. Determination of 5-hydroxytryptamine (serotonin) and related indoles by flow injection analysis with acidic potassium permanganate chemiluminescence detection // Anal. Chim. Acta. – 1998. – 362. – P. 131–139.

92. Hindson B.J., Barnett N.W. Analytical applications of acidic potassium permanganate as a chemiluminescence reagent // Anal**.** Chim**.** Acta.– 2001. – 445. **–** P. 1**–**19.

93. Barnett N. W., Hindson B. J., Jones P., Smith T. A. Chemically induced phosphorescence from manganese(II) during the oxidation of various compounds by manganese(III), (IV) and (VII) in acidic aqueous solutions // Anal. Chim. Acta. – 2002. – 451. – P.181–188.

94. Townshend A., Youngvises N., Wheatley R. A. , Liawruangrath S. Flow-injection determination of cinnarizine using surfactant-enhanced permanganate chemiluminesence // Anal. Chim. Acta. – 2003. – 499. – P. 223–233.

95. Huclová J., Satínský D., Sklenárová H., Karlícek R. Determination of salbutamol using on-line solid-phase extraction and sequential injection analysis. Comparison of chemiluminescence and fluorescence detection // Anal. Bioanal. Chem. – 2003. – 376. – P. 448–454.

96. Polasek M.; Jambor M. Chemiluminescence determination of antibacterial drug trimethoprim by automated sequential injection technique with permanganate and hexametaphosphate as reagents // Talanta. – 2003. – 58. – P. 1253–1261.

97. Townshend A., Youngvises N., Wheatley R. A. , Liawruangrath S. Flow-injection determination of cinnarizine using surfactant-enhanced permanganate chemiluminesence // Anal. Chim. Acta. – 2003. – 499. – P. 223–233.

98. Corominasa B. G.-T., Icardoa M. C., Zamorab L.L., Mateob J. V. G., Calatayud J. M. A tandem-flow assembly for the chemiluminometric determination of hydroquinone // Talanta. –2004. – 64. – P. 618–625.

99. Townshend A., Youngvises N., Wheatley R. A. , Liawruangrath S. Flow-injection determination of cinnarizine using surfactant-enhanced permanganate chemiluminesence // Anal. Chim. Acta. – 2003. – 499. – P. 223–233.

100. Alonso M. C. Sanfeliu, Zamora L. L., Calatayud J. M. Determination of tyrosine through a FIA-direct chemiluminescence procedure // Talanta. – 60. – P. 369–376.

101. Corominasa B. Gómez-Taylor, Icardoa M. C., Zamorab L. L., Mateob J. V. G., Calatayud J. M. A tandem-flow assembly for the chemiluminometric determination of hydroquinone // Talanta. 2004. – 64. – P. 618–625.

102. Du J.X., Li Y.H., Lu J.R. Chemiluminescence flow injection analysis of amoxycillin by a permanganate-based reaction // Anal. Lett. 2002. – 35. – P. 2295–2304.

103. Li Y.H., Zhang A.H., Du J.X., Lu J.U. Flow Injection Chemiluminescence Determination of Thiol-Containing Drugs Based on a Quinine-Sensitized Permanganate Reaction //Anal. Lett. – 2003. – 36. – P. 871–879.

104. Du J., Li Y., Tang Y. J., Lu Y. Flow injection chemiluminescence determination of ethamsylate based on permanganate oxidation // Anal. Lett. – 2002. – 35. – P. 463–472.

105. Paseková H., Polášek M., Cigarro J.F., Dolejšová J. Determination of some sulphonamides by sequential injection analysis with chemiluminescence detection // Anal. Chim. Acta. – 2001. – 438. – P. 165–173.

106. Fan. S.L, Wu Z.H., Zhang C. Lv. Chemiluminescence determination of metoclopramide // Anal. Lett. – 2002. – 35. – P.1479–1489.

107. Pan J., Huang Y.M. Chemiluminescence determination of phentolamine based on reactian sensitized by formaldehyde // Anal. Lett. – 2004. – 37. – P. 2321–2335.

108. Wang Z.P., Zhang Z.J., Fu Z.F., Chen D.L., Zhang X. Flow-injection chemiluminescence detection for studying protein binding of terbutaline sulfate with on-line microdialysis sampling // J. Pharm. Biomed. Anal. – 2003. – № 4. – P. 765–773.

109. Sun Y.Y., Tang Y.H., Yao H., Zheng X.H. Potassium permanganate–glyoxal chemiluminescence system for flow injection analysis of cephalosporin antibiotics: cefalexin, cefadroxil, and cefa-

 © M. Ye. Blazheevskiy, N.Yu. Bondarenko

zolin sodium in pharmaceutical preparations // Talanta. – 2004. – 64. – P. 156–159.

110. Huclová J., Satínský D., Sklenárová H., Karlícek R. Determination of salbutamol using on-line solid-phase extraction and sequential injection analysis. Comparison of chemiluminescence and fluorescence detection // Anal Bioanal Chem. – 2003. – 376.– 448–454.

111. Icardo M. C., Misiewicz M., Ciucu A., García Mateo J.V., Calatayud M. J. Fl-on line photochemical reaction for direct chemiluminescence determination of photodegradated chloramphenicol // Talanta. – 2003. – 60. – P. 405–414.

112. Icardo M. C., García Mateo J.V., Lozano M. F., Calatayud M. J. Enhanced flow-injection-chemiluminometric determination of sulphonamides by on-line photochemical reaction // Anal. Chim. Acta. – 2003. –. 499. – P. 57–69.

113. Gómez-Taylor B., Palomeque M., García Mateo J. V., Calatayud M. J. Photoinduced chemiluminescence of pharmaceuticals // J. Pharm. Biomed. Analysis. – 2006. – 41. – P. 347–357.

114. Thongpoon C., Liawruangrath B., Liawruangrath S., Wheatley R. A., and A. Townshend A. Flow injection chemiluminescence determination of cefadroxil using potassium permanganate and formaldehyde system // Journal of Pharmaceutical and Biomedical Analysis. – 2006. –42.–P.277–282.

115. Alarfaj N. A., Abd El-Razeq S. A. Flow-injection chemiluminescent determination of cefprozil using tris (2,2′-bipyridyl) ruthenium (II)-permanganate system // J. Pharm. Biomed. Anal. – 2006. – 41. – P. 1423–1427.

116. Kojło A., Michałowski J., Wołyniec E. Chemiluminescence determination of thioridazine hydrochloride by flow-injection analysis // J. Pharm. Biomed. Anal. – 2000. – 22. – P. 85–91.

117. Li Yinhuan, Niu Weifen and Lu Jiuru. Sensitive determination of phenothiazines in pharmaceutical preparation and biological fluid by flow injection chemiluminescence method using luminol–$KMnO_4$ system // Talanta.–2007. – 71.– P.1124–1129.

118. Murillo Pulgarin José A., Garcia Bermejo Luisa F., Fernandez Lopez Pablo. Sensitive determination of captopril by time-resolved chemiluminescence using the stopped-flow analysis based on potassium permanganate oxidation // Anal. Chim. Acta. – 2005. – 546. – P. 60–67.

119. Zhang X.R., Baeyens W.R.G., Weken G.V.D., Calokerino, A.C., Nakashima K. Chemiluminescence determination of captopril based on a Rhodamine B sensitized cerium (IV) method// Anal. Chim. Acta. – 1995. – 303 – P.121–125.

120. Rao Y., Tong Y., Zhang X.R., Luo G.A., Baeyens W.R.G. Determination of ofloxacin using a chemiluminescence flow-injection method // Anal. Chim. Acta. – 2000. – 416. – P. 227–230.

121. Rao Y. Flow-injection chemiluminescence determination of fluoroquinolones // Anal. Lett. – 2000. – 33. – P. 1117–1129.

122. Aly F.A., Al-Tamimi S.A., Alwarthan A.A. Determination of flufenamic acid and mefenamic acid in pharmaceutical preparations and biological fluids using flow injection analysis with tris (2,2'-bipyridyl)ruthenium(II) chemiluminescence detection // Anal. Chim. Acta. – 2000. – 416. – P. 87–96.

123. Cui H., Li S.F., Li F., Sun Y.G., Lin X.Q. A novel chemiluminescent method for the determination of salicylic acid in bactericidal solutions // Anal. Bioanal. Chem. – 2002. – 372. – P. 601–604.

124. Capitán-Vallvey L.F., Mirón M.C.V., Acosta R.A. Chemiluminescence determination of sodium 2-mercaptoethane sulfonate by flow injection analysis using cerium(IV) sensitized by quinine // Talanta. – 2000. – 51. – P. 1155–1161.

125. Wang X., Zhao H.C., Nie L.H., Jin L.P., Zhang Z.L. Europium sensitized chemiluminescense determination of rufloxacin // Anal. Chim. Acta. – 2001. – 445. – P. 169–175.

126. Nie L.H., Zhao H.C., Wang X., Yi L., Lu Y., Jin L.P., Ma H.M. Determination of lomefloxacin by terbium sensitized chemiluminescence method // Anal. Bioanal. Chem. – 2002. – 374. – P. 1187–1190.

127. Ocaña J.A., Barragán F.J., Callejón M., Rosa F.D.L. Application of Lanthanide-Sensitised Chemiluminescence to the Determination of Levofloxacin, Moxifloxacin and Trovafloxacin in Tablets // Microchim. Acta. – 2004. – 144. – P. 207–213.

128. Ma Y.J., Zhou M., Jin X.Y., Zhang B.Z., Chen H., Guo N.Y. Flow-injection chemiluminescence determination of ascorbic acid by use of the cerium (IV)-Rhodamine B system // Anal. Chim. Acta. – 2002. – 464. – P. 289–293.

129. Ma Y.J., Jin X.Y., Zhou M., Zhang Z.Y., Teng X.L., Chen H. Chemiluminescence behaviour based on oxidation reaction of rhodamine B with cerium(IV) in sulfuric acid medium // Anal. Chim. Acta. – 2003. – 489. – P. 173–181.

130. Chen H., Zhou M., Jin X.Y., Song Y.M., Zhang Z.Y., Ma Y.J. Chemiluminescence determination of ultra-micro DNA with a flow-injection method // Anal. Chim. Acta. – 2003. – 478. – P. 31–36.

131. Ma Y.J., Zhou M., Jin X.Y., Zhang Z.Y., Teng X.L., Chen H. Flow-injection Chemiluminescence Assay for Ultra-trace Level Determination of DNA Using Rhodamine B-Ce IV)-DNA Ternary System in Sulfuric Acid Media // Anal. Chim. Acta. – 2004. – 501. – P. 25–30.

132. Zhang F.; Cheng Y.L. A new method of chemiluminescent determination of chromium (VI) in waste water // Anal. Lab. – 1986. – 5. – P. 1–3. (Chinese).

133. Ren A., Yuan H., Lv B., Zhou Z., Xiao D. Flow injection analysis of resorcinol using inhibited rhodamine B /cerium(IV) chemiluminescence system // Z. Anal. Khim. – 2009. – 64.–S. 428–432.

134. Wang R., Wan L., Li Q., Liu X., Huang Y. Chemiluminescence of synephrine based on the cerium(IV)-rhodamine B system // J. Biolum. Chemilum. – 2006. – 22. – P. 140–146.

135. Huang Y., Chen Z. Chemiluminescence of chlorpromazine hydrochloride based on cerium(IV) oxidation sensitized by rhodamine 6G // Talanta. – 2002. – 57. – P. 953–959.

136. Gerardi R.D., Barnett N.W., Lewis S.W. Analytical applications of tris(2,2-bipyridyl)ruthenium(III) as a chemiluminescent reagent // Anal. Chim. Acta. – 1999. – 378. – P. 1–41.

137. Perez-Ruiz T., Martnez-Lozano C., Tomas V., Martin J. Flow injection chemiluminescent method for the successive determination of l-cysteine and l-cystine using photogenerated tris(2,2'-bipyridyl) ruthenium (III) // Talanta. – 2002. – 58. – P. 987–994.

138. Bulhöes L.O.S., Tomita I.N. Electrogenerated chemiluminescence determination of cefadroxil antibiotic // Analytica Chimica Acta. – 2001. – 442. – P. 201–206.

139. Thongpoon C., Liawruangrath, S. Liawruangrath B., Wheatley R. A., and Townshend A. Flow injection chemiluminescence determination of cephalosporins in pharmaceutical preparations using tris (2,2′-bipyridyl) ruthenium (II)-potassium permanganate system // Anal. Chim. Acta. - 2005. – 553. – P. 123–133.

140. Aly F. A., Alarfaffj N. A., and Alwarthan A. A. Permanganate-based chemiluminescence analysis of cefadroxil monohydrate in pharmaceutical samples and biological fluids using flow injection // Talanta. – 1998. – 47. – P. 471–478.

141. Zheng X.W., Mei Y., Zhang Z.J. Flow-injection chemiluminescence determination of tetracyclines with in situ electrogenerated bromine as the oxidant // Anal. Chim. Acta. – 2001. – 440. – P. 143–149.

142. Alarfaj N.A.A. Flow-Injection Chemiluminescence Determination of Enalapril Maleate in Pharmaceuticals and Biological Fluids Using Tris(2,2'-bipyridyl)ruthenium(II) // Anal. Sci. – 2003. – 19. – P. 1145–1149.

143. Zheng X.W., Zhang Z.J., Li B.X. Flow Injection Chemiluminescence Determination of Captopril with In Situ Electrogenerated Mn3+ as the Oxidant // Electroanalysis. – 2001. – 13. – P. 1046–1050.

144. Li B.X., Zhang, Z.J., Wu M.L. Flow-injection chemiluminescence determination of captopril using on-line electrogenerated silver (II) as the oxidant // Microchem. J. – 2001. –70.–P.85–91.

145. Wu M.L., Li B.X., Zhang Z.J. // Fenxi Huaxue =Anal. Chem. – 2001. – 29. – P. 267–270.

146. Li B.X., Zhang Z.J., Liu W. Flow-injection chemiluminescence determination of chlortetracycline using on-line electrogenerated (Cu(HIO6)2)5- as the oxidant // Talanta. – 2001.– 55. – P. 1097–1102.

147. Sun Y., Zhang Z, Zhang Y., Wei Y. Determination of Sugars by LC with On-Line Electrogenerated Cu(HIO6)2]5−– Luminol Chemiluminescence Detection // Chromatographia. – 2008. – 67. – P. 825–827.

148. Liang Y.D., Song J.F., Yang X.F. Flow-injection chemiluminescence determination of fluoroquinolones by enhancement of weak chemiluminescence from peroxynitrous acid // Anal. Chim. Acta. – 2004. – 510. – P. 21–28.

149. Gracia L. G., García-Campaña A.M., Barrero F. A., Rodriguez L. C., Schiavone M, Baeyens W.R.G. Optimization of the chemiluminescent determination of proteins in micellar medium by flow injection analysis using experimental design // Luminescence. – 2002. – 17. – P. 201–203.

150. Gámiz-Gracia L., García-Campaŋa A.M., Alés B. F., Rodriguez L. C. Determination of albumin in biological fluids by flow injection analysis using the peroxyoxalate chemiluminescent system in micellar medium // Analytical and Bioanalytical Chemistry. – 2003. – 273. – P. 281–286.

151. Yang F.Z., Zhang C., Baeyens W.R.G., Zhang X.R. Determination of ethamsylate in pharmaceutical preparations based on an auto-oxidation chemiluminescence reaction // J. Pharm. Biomed. Anal. – 2002. – 30. – P. 473–478.

© M. Ye. Blazheevskiy, N.Yu. Bondarenko