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Review

Recent applications of flow-injection and sequential-injection analysis techniques to chemiluminescence determination of pharmaceuticals

Kateřina Mervartová [a,*], Miroslav Polášek [a], José Martínez Calatayud [b]

[a] *Department of Analytical Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, 500 05 Hradec Králové, Czech Republic*
[b] *Department of Analytical Chemistry, University of Valencia, 46100 Burjassot, Valencia, Spain*

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Abstract

A review is presented on the state of the art of the chemiluminescence analysis of pharmaceuticals by the two most relevant automated controlled-flow methodologies—flow-injection analysis (FIA) and sequential-injection analysis (SIA). The current chemiluminometric applications of FIA and SIA in pharmaceutical analysis are discussed with special emphasis on the analytical figures of merit and sample matrix characteristics. The review involving 211 references and covering papers published between 2001 and 2006 is divided into several sections according to the fundamental types of chemiluminescence systems employed.
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Keywords: Pharmaceuticals; Sequential-injection analysis (SIA); Flow-injection analysis (FIA); Chemiluminescence; Review

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1. Introduction

Chemiluminescence (CL) is defined as a process producing electromagnetic (ultraviolet, visible or near-infrared) radiation as a result of a chemical reaction (usually an oxidation) in which one of the reaction products occurs in an excited state and emits light when returning to its ground state. Normally the amount of energy released during a chemical reaction dissipates as heat. Therefore CL is not very common phenomenon.

As written in review [1] CL reached analytical attention in the middle of 20th century when Erdey in 1957 studied the use of several substances such as luminol, lophine and lucigenine as volumetric indicators.

In contrast to spectrophotometry and fluorimetry, the absence of strong background light levels in CL methods reduces noise signals and leads to improved detection limits (better sensitivity)

* Corresponding author. Tel.: +420 495763391; fax: +420 495067164.
E-mail address: Katerina.Mervartova@faf.cuni.cz (K. Mervartová).

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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 [2]. At present the CL detection is applied in many analytical fields such as environmental, biomedical, pharmaceutical, food and beverage, etc., as can be found in recent literature.

There are two basic ways to measure the CL emission, namely by the batch technique and in flow systems. In the batch methods the sample or reagent solution is injected by a syringe into a CL cell containing solution of appropriate reactants; this cell should be placed as close as possible to the photosensor/photomultiplier detector window [3]. In the batch CL mode it is difficult to achieve rapid and efficient mixing of reactants and the process is not easily automated [2]. On the other hand, in flow systems represented by flow-injection analysis (FIA) [4] and sequential-injection analysis (SIA) [5] the analyte and the reagents flow continuously or in a pre-programmed series of flow pulses through manifold channels to the detector flow cell where the CL emission is monitored. Several improvements compared to the batch procedure can be pointed out, namely: higher sample throughput, possibility of on-line preparation of unstable reagents, automation of the system and reduced sample and reagent consumption.

Characteristic feature of FIA and SIA techniques is the ability of automated efficient and reproducible mixing of small volumes of sample and reagents. If the mixing takes place as close as possible to the photodetector window even fast CL reactions can be recorded. Since the timing of the mixing process is fully reproducible it is unnecessary to measure the whole CL emission profile. Therefore with the development of FIA and SIA the use of fast and reproducible chemiluminescence detection became considerably attractive.

The theme of CL as analytical tool was processed in a monograph [2] and the advantageous marriage between the continuous flow techniques and the CL in pharmaceutical analysis has been reviewed in a number of articles [3,6,7]. As far as the authors know, the most recent review considering this topic appeared in 2001 [7] and it dealt with papers published during the period 1997–2000. The present paper deals with papers utilizing CL detection coupled with SIA and FIA for the determination of pharmaceuticals (drugs) that were published during the period 2001–2006 (May–June).

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 luminol, lucigenin, lophine, sulphite or peroxyoxalates.

2. Luminol system

Luminol (5-aminophthalylhydrazide) is so far the most frequently used CL reagent. The CL emission of luminol is based on its oxidation by hydrogen peroxide, hexacyanoferrate(III), permanganate, *N*-bromosuccinimide (or *N*-chlorosuccinimide), periodate, dichromate, persulphate, dichlorocyanurate or trichlorocyanuric acid, chlorate and electrogenerated hypobromite in alkaline medium (see Table 1). According to the well-known mechanism the supposed emitter is excited 3-aminophthalate anion whose maximum emission occurs at 425 nm [2].

The relevance of the luminol 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 (Fig. 1). 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 polyphenol oxidases (from plant juice) are able to catalyze the oxidation of mono-, di- and polyhydric phenols generating activated oxygen species (e.g. superoxide radical) reacting with luminol with CL emission. Such enzymes obtained from raw apple juice were utilized for the CL determination of adrenaline [8].

Some catalysts such as Cu(II), Co(II) and Fe(III)/Fe(II) were implemented into the luminol/oxidant system to improve sensitivity of the indirect assay. Thus Cu(II) was used as a catalyst in the determination of methimazole and carbimazole [9]; these drugs formed complex species with Cu(II) and thus inhibited Cu(II)-catalysed luminol–hydrogen peroxide reaction; with increasing concentration of analyte equilibrium concentration of Cu(II) diminished and this resulted in the decrease of CL

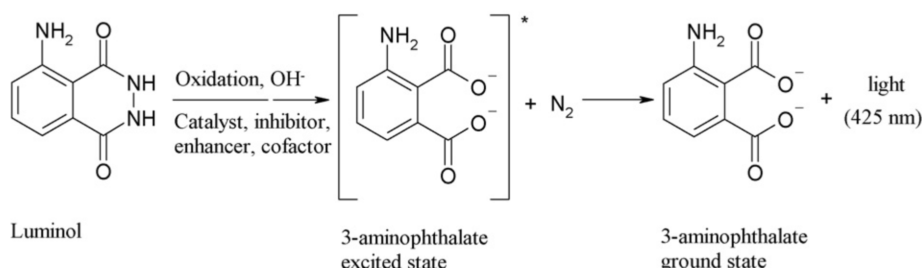


Fig. 1. Luminol CL scheme.

Table 1
CL systems based on the oxidation of luminol/FIA

Analyte	Action of the analyte/chemical system	Calibration range	LOD	Throughput (samples/h)	Sample	References
Oxidant system: hexacyanoferrate(III) in alkaline medium						
Adrenaline	MIP, presence: ferrocyanide	5–100 nM	3 nM	–	Serum	[12]
Berberine	Inhibitor/solid-phase reactor	0.05–300 ng/ml	0.02 ng/ml	–	Tablets	[21]
Captopril	Enhancer; presence: ferrocyanide	0.1–40 μg/ml	–	90	Pharmaceuticals	[22]
Cefmetazole	Presence: ferrocyanide	0.3–1.5 ng/ml	0.06 ng/ml	–	Residues in pharmaceuticals manufacture	[23]
Dipyridamole	Enhancer	0.1–50 ng/ml	–	–	Pharmaceuticals	[24]
Dobesilate	Inhibitor	0.2–16 μg/ml	44 ng/ml	300	Capsules	[25]
Dobesilate	Inhibitor/solid-phase reactor	0.2–100 ng/ml	–	40	Pharmaceuticals, human urine	[26]
Dobutamine	Enhancer, presence: ferrocyanide	0.1–100 ng/ml	0.026 ng/ml	90	Injection	[27]
Dopamine	Inhibitor	4–400 ng/ml	1.14 ng/ml	–	Injection	[28]
Dopamine	Inhibitor	30–100 and 400–3000 ng/ml	5 ng/ml	135	Injections	[29]
Dopamine	Inhibitor	2.0–800 ng/ml	1.14 ng/ml	–	Injection	[30]
Folic acid	Enhancer/solid-phase reactor	0.01–15 μg/ml	3.5 ng/ml	30	Pharmaceuticals	[31]
Gallic acid	Enhancer	8–1000 nM	5.6 nM	–	Tablets	[32]
Hydrazines	–	–	–	–	Pharmaceuticals	[33]
Indapamide	Inhibitor	10–1000 ng/ml	3.4 ng/ml	90	Tablets	[34]
Isoniazid	Inhibitor/solid-phase reactor	1–1000 ng/ml	0.35 ng/ml	30	Tablets	[35]
Ketotifen	Enhancer	0.01–1 μg/ml	5.7 ng/ml	–	Pharmaceuticals	[36]
Levodopa	Enhancers	0.5–50 ng/ml	0.12 ng/ml	–	Tablets	[37,38]
Methyldopa		1–100 ng/ml	0.57 ng/ml	–		
Metronidazole	Enhancer; presence: ferrocyanide	2–400 μM	0.15 μM	–	Pharmaceuticals	[39]
Ornidazole	Inhibitor	0.2–10 μg/ml	0.05 μg/l	–	Tablets	[40]
Paracetamol	Inhibitor	40–1000 ng/ml	2.5 ng/ml	–	Tablets	[41]
Phentolamine	Enhancer	0.01–1 μg/ml	3.0 ng/ml	–	Injections, urine, plasma	[42]
Promazine	–	0.05–15 μg/ml	3 ng/ml	–	Tablets	[43]
Chlorpromazine		0.03–15 μg/ml	5 ng/ml			
Resorcinol	Inhibitor/solid-phase reactor	9.2–920 ng/ml	3.5 ng/ml	–	Tinctures	[44]
Rutin	Enhancer; presence: ferrocyanide	0.1–2 μg/ml	0.03 μg/ml	–	Tablets	[45]
Rutin	Inhibitor/solid-phase reactor	1.0–400 ng/ml	0.35 ng/ml	40	Pharmaceuticals, human urine	[46]
Salbutamol	Sensitizer: MIP	0.05–10 μg/ml	16 ng/ml	–	Urine	[47]
Thiamine	Inhibitor/solid-phase reactor	0.2–4.0 μM	66 nM	30	Pharmaceuticals, human urine	[48]
Oxidant system: periodate in alkaline medium						
Adrenaline		0.02–10 μg/ml	7.0 ng/ml			[19]
Isoprenaline	Enhancer/solid-phase reactor	0.2–50 μg/ml	50 ng/ml	60	Injections	
Cephalosporins						
Cefalexin			0.9 ng/ml			[49]
Cefaclor			0.4 ng/ml			
Cefradine			10 ng/ml			
Cefadroxil	Enhancers	–	10 ng/ml	–	Pharmaceuticals	
Cysteine	Enhancer	0.01–1 μM	5 nM	–	Injection	[50]
Dobesilate	Inhibitor/solid-phase reactor	10–600 pg/ml	3.5 pg/ml	120	Pharmaceuticals, human urine	[51]
Dopamine	Enhancer	0.1–10 ng/ml	0.02 ng/ml	–	Injection	[52]
Hydralazine	Enhancer, MIP	2–800 ng/ml	0.6 ng/ml	–	Human urine	[53]
Isoniazid	Enhancer/solid-phase reactor	8.0–1000 nM	4.2 nM	60	Tablets	[54]
Penfluridol	Enhancer	0.04–10 μg/ml	9.2 ng/ml	–	Tablets	[55]
Peurarin	Enhancer	0.3–100 ng/ml	0.1 ng/ml	180	Nourishment, injections, human urine	[56]
Reserpine	Inhibitor/solid-phase reactor	1.0–300 ng/ml	0.3 ng/ml	120	Pharmaceuticals, biological fluids	[57]
Riboflavine	Enhancer/solid-phase reactor	0.04–200 ng/ml	0.02 ng/ml	120	Tablets, human urine	[18]

Table 1 (*Continued*)

Analyte	Action of the analyte/chemical system	Calibration range	LOD	Throughput (samples/h)	Sample	References
Rutin	Inhibitor/solid-phase reactor	0.1–30 ng/ml	0.03 ng/ml	120	Tablets, human urine	[58]
Thiamine	Inhibitor/solid-phase reactor	3.3–6700 nM	1.0 nM	100	Tablets, injection, human urine	[16]
Oxidant system: hydrogen peroxide in alkaline medium						
Acetylspiramycin	Enhancer	0.01–2 ng/ml	3 pg/ml	120	Pharmaceuticals, human urine, serum	[59]
Amikacin	Inhibitor, catalyst: Cu(II)	9.89–20 μg/ml	2.97 μg/ml	–	Pharmaceuticals	[60]
Amoxicillin	Inhibitor, sensitizer: Co^{2+}	8–40000 ng/ml	2.7 ng/ml	–	Capsules	[61]
Azithromycin	Enhancer	0.1–1000 pg/ml	0.04 pg/ml	120	Injections, human urine and serum	[62]
Captopril	Enhancer	5–5000 ng/ml	2 ng/ml	180	Tablets	[63]
Diethylstilbestrol	Enhancer; catalyst: Co(II)	0.1–4 μM	6.42 nM	20	Tablets	[10]
Domperidone	Enhancer	0.03–1.0 μg/ml	5.0 ng/ml	–	Tablets, serum	[64]
Estrogens:	Catalyst: tetrasulfonated manganese phthalocyanine	0.1–1.0 μM	51 nM		Injections, tap water	[65]
Estrone						
Estradiol		0.09–1.0 μM	7.2 nM			
Estriol		0.3–2.0 μM	65 nM			
Methimazole	Inhibitors; catalyst Cu(II)	2–100 μg/ml	1 μg/ml	120	Tablets	[9]
Carbimazole		3–120 μg/ml	2 μg/ml			
Risperidon	Catalyst	10–1000 pg/ml	4 pg/ml	120	Tablets	[66]
Thiamine	Enhancer	0.05–8 μg/ml	0.01 μg/ml	90	Tablets, injections	[67]
Oxidant system: potassium permanganate in basic medium						
Doxycycline	Inhibitor	5–5000 ng/ml	2.0 ng/ml	–	Pharmaceuticals	[68]
Oxymetazoline	Inhibitor	1.88–200 ng/ml	1 .88 ng/ml [69], 1.21 ng/ml [70]	–	Drops	[69,70]
Paracetamol	Inhibitor	25–250 nM	10 nM	–	Pharmaceuticals	[71]
Terbutaline	Enhancer	0.5–500 ng/ml	0.17 ng/ml	90	Pharmaceuticals, plasma and urine	[72]
Other oxidant systems						
Adenine	System: luminol–dichromate in alkaline medium, sensitizer: sodium dodecylbenzene sulfonate	0.438–2920 nM	0.246 nM	90	Human serum	[73]
Adrenaline	Adrenaline–luminol–polyphenol oxidase	1.0–25 μg/ml	0.2 μg/ml	20	Injections	[8]
Aminomethylbenzoic acid	Inhibitors of luminol–*N*-bromosuccinimide	0.02–1 μg/ml	7.0 ng/ml	–	Plasma	[74]
Aminophylline		0.1–7 μg/ml	34 ng/ml			
Ascorbic acid	Analytes reduce Fe^{3+} to Fe^{2+} which is detected with luminol–O_2, determination of mixture	0.06–6 μg/ml	0.03 μg/ml	–	Pharmaceuticals, human urine	[75]
L-Cysteine		0.4–40 μg/ml	0.2 μg/ml			
Catecholamines						
Adrenaline	Inhibitor of luminol–potassium chlorate	–	0.2 ng/ml	–	Injections	[76]
Noradrenaline			0.4 ng/ml			
Isoprenaline			0.7 ng/ml			
Dopamine			0.4 ng/ml			
Chlorpromazine	Ion pair chlorpromazine–tetrachloroaurate(III)	0.05–10 μg/ml	6 ng/ml	–	Tablets, injections, urine	[13]
Clindamycin	Inhibition, luminol–myoglobin	0.1–70 ng/ml	0.03 ng/ml	120	Capsules	[77]
Cobalamine (B_{12})	Enhancer, luminol–dissolved oxygen	0.2–1200 pg/ml	50 fg/ml	120	Injection, tablets, human serum, urine, egg, fish	[11]
Gentamicin	Sensitizer: electrooxidation of luminol	1.2–4000 ng/ml	0.8 ng/ml	–	Injection	[78]

Table 1 (*Continued*)

Analyte	Action of the analyte/chemical system	Calibration range	LOD	Throughput (samples/h)	Sample	References
Iodide	Use of gas diffusion, oxidation to iodine which reacted with luminol	0.1–1.0 μg/ml	–	60	Tablets, liquid medicine	[14]
Isoniazid	Inhibitor of luminol–$K_2Fe(CN)_6$	1.4–5500 ng/ml	0.48 ng/ml	–	Tablets	[79]
Isoniazid	Sensitizer: electrooxidation of luminol	0.04–8 μM	28 nM	–	Injection	[80]
Isoniazid	Enhancer luminol–sodium dichloroisocyanurate (D) or trichloroisocyanuric acid (T)	4–200 ng/ml (D) 6–1000 ng/ml (T)	2 ng/ml (D) 3 ng/ml (T)	65	Tablets	[81]
Isoniazid	Enhancer of luminol–*N*-bromosuccinimide (I) or *N*-chlorosuccinimide (II)	8–5000 ng/ml (I) 6–2000 ng/ml (II)	4 ng/ml (I) 3 ng/ml (II)	65	Tablets	[82]
Levodopa	Sensitizer: electrooxidation of luminol	0.4–2000 ng/ml	0.2 ng/ml	–	Pharmaceuticals	[83]
Nifedipine	Enhancer of luminol–sodium persulfate	0.05–5.0 μg/ml	0.017 μg/ml	–	Tablets	[84]
Norfloxacin	Sensitizer: electrooxidation of luminol	0.01–200 μg/ml	4.0 ng/ml	–	Pharmaceuticals, urine	[85]
Novalgin (metamizole)	Inhibitor of luminol–dichromate/solid-phase reactor	0.05–50 ng/ml	0.02 ng/ml	60	Tablets	[17]
Ribavirin	Enhancer of luminol–sodium persulfate	0.01–1.0 μg/ml	4 ng/ml	–	Pharmaceuticals	[86]
Thiamine (B_1)	Inhibitor, luminol–electrogenerated BrO^-	0.01–6.0 μg/ml	3.2 ng/ml	–	Tablets	[87]

intensity. A metal cation forming an metalphthalocyanine or metalporphyrin complex may act as a CL catalyst as demonstrated with Co(II) in the CL assay of diethylstilbestrol [10]. The catalytic effect of Co(II) was also used in the CL determination of vitamin B_{12} (cobalamin) [11] after releasing Co(II) from the vitamin molecule by acidifying the analyte solution.

The selectivity of CL analysis can be improved by solid-phase extraction with specific recognition using molecular imprinted polymers (MIPs) in continuous-flow analytical methodologies. Appropriate MIPs are prepared by copolymerization of functional monomer with cross-linker in the presence of template molecules to produce three-dimensional network polymers. Removal of the template molecules results in a functional polymeric matrix with recognition sites complementary in size, shape and functionality to the template molecule. The MIP is packed in a glass tube that serves as a flow cell. The analyte (template molecule) is adsorbed (pre-concentrated) in the flow cell and the other substances except of the analyte are washed out. This MIP technique has been employed for the selective CL determination of adrenaline with use of hexacyanoferrate(II)/hexacyanoferrate(III) reagent [12] and other drugs (see Tables 1, 3 and 5).

Another way of increasing selectivity of CL determination is the use of solvent extraction in micellar aqueous–organic systems. A good example is the CL determination of chlorpromazine hydrochloride [13], which is based on the dichloromethane solvent extraction of ion-pair complex of tetrachloroaurate(III) with chlorpromazinium cation and luminol 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.

A gas-diffusion flow-injection (GD–FI) system was designed for selective CL 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 luminol to produce CL [14].

Use of substrate-specific enzymes is another possibility for attaining selectivity of CL assays. Selective CL determination of beta-glucose [15] 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 luminol.

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

[16–18] or just in front of the detection window [19]. 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).

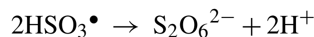
A secondary CL emission phenomenon was observed in determination of menadion [20]. After finished CL reaction between luminol and excess of potassium periodate, the analyte menadion was added and so-called secondary CL emission was observed. The oxidized form of menadion presumably transfers its energy 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 luminol as reagent were proposed for the assay of various pharmaceuticals with different structures and pharmacological effects. Phenethylamine group drugs are typical representatives of such analytes determined (see Table 1).

3. Sulphite system

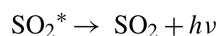
The reaction of sulphite with strong oxidants such as permanganate, Ce(IV) in acid media and electrogenerated Mn(III) is accompanied by a weak CL that can be sensitized by some organic compounds (see Table 2). The excited species formed by the oxidation of sulphite is probably sulphur dioxide [88–90] in accordance with the following mechanism:

$$HSO_3^- + \text{oxidant} \rightarrow HSO_3^{\bullet}$$



$$2HSO_3^{\bullet} \rightarrow S_2O_6^{2-} + 2H^+$$

$$S_2O_6^{2-} \rightarrow SO_4^{2-} + SO_2^*$$



$$SO_2^* \rightarrow SO_2 + h\nu$$

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 (LI) [89,91–94] as observed in the CL determination of the quinolone (Q) grapefloxacin [89]. In the absence of LI the transfer of energy from SO_2^* to Q resulted in subsequent emission of luminescence of Q*. In the presence of LI a complex with quinolone LI(Q) was formed. The energy from SO_2^* was transferred successively to ligand (quinolone) and then by an intramolecular energy-transfer process to LI; the energy of LI(Q*) was emitted at characteristic wavelength of the LI (here Tb^{3+} 490, 546 and 590 nm).

Table 2
CL systems based on sulphite oxidation/FIA

Analyte	Oxidation system/technique	Calibration range	LOD	Throughput (samples/h)	Sample	Reference
Benzamides:	Acidic Ce(IV)	0.05–2.5 μg/ml	0.01 μg/ml	190		[90]
Sulpiride						
Sultopride		0.1–2.5 μg/ml	0.01 μg/ml	150	Tablets, capsules, ampoules, urine, plasma	
Tiapride		0.01–1.5 μg/ml	0.01 μg/ml	144		
Ciprofloxacin	Acidic Ce(IV), sensitizer: Tb^{3+}	9.0–1000 nM	22 pM	–	Tablets, capsules	[97]
Dexamethazone	Electrogenerated Mn(III)	0.1–10 μg/ml	70 ng/ml	–	Pharmaceuticals	[98]
Fluoroquinolones:	Acidic Ce(IV), sensitizer: Eu^{3+}	0.5–3.5 μg/ml	0.100 μg/ml	–	Tablets	[92]
Levofloxacin						
Moxifloxacin	Eu^{3+}	0.2–3.0 μg/ml	0.035 μg/ml			
Trovafloxacin	Tb^{3+}	0.0008–0.4 μg/ml	0.008 μg/ml			
Grepafloxacin	Acidic Ce(IV), sensitizer: Tb^{3+}	0.05–2 μg/ml	0.01 μg/ml	–	Tablets and human urine	[89]
Iproniazid	Acidic Ce(IV)	0.1–4.0 μg/ml	3 ng/ml	121	Synthetic sample, urine	[99]
Lomefloxacin	UV-irradiated sample, Ce(IV) in HCl, sensitizer: Tb^{3+}	0.9–10000 nM	0.22 nM	–	Tablets, serum, urine	[94]
Metoprolol	Ce(IV) in sulphuric acid	0.015–7.3 μM	4.7 nM	180	Tablets, human urine	[100]
Norfloxacin	Acidic Ce(IV), sensitizer: Tb^{3+}	9–1000 nM	45 pM	–	Capsules, human serum, urine	[91]
Ofloxacin	PbO_2 in sulphuric acid/solid-phase reactor	0.2–10 μg/ml	78 ng/ml	–	Tablet, capsule, injection	[96]
Papaverine	Acidic permanganate	0.2–10 μM	0.1 μM	–	Tablets	[88]
Papaverine	Acidic Ce(IV)	0.1–10 μM	87 nM	–	Pharmaceuticals and biological fluids	[101]
Pipemidic acid	Permanganate in tetraphosphoric acid	0.1–80 μg/ml	30 ng/ml	–	Tablets	[102]
Pipemidic acid	Sodium bismuthate in sulphuric acid/solid-phase reactor	0.1–10 μg/ml	62 ng/ml	60	Tablets	[95]
Sparfloxacin	UV-irradiated sample, acidic Ce(IV), sensitizer: Tb^{3+}	0.1–10 μM	25 nM	–	Tablets capsules	[93]

A sulphite–sodium bismuthate (oxidant) CL system was used for determining pipemidic acid [95] 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 [96] (fluorophor) with immobilized lead dioxide as oxidant.

4. 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 [103,104] 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 behavior of pharmaceuticals and pesticides and 100% for phenols and polyphenols. The calculations were also applied to ergot alkaloids [105] and a review [106] concerning this topic was published.

4.1.1. Oxidation with potassium permanganate

Potassium permanganate is the most common oxidant used in CL reactions; recently cephalosporin and penicillin class antibiotics appear among the drugs determined most frequently with this reagent by the FIA–CL technique (see Table 3). The emitting molecule is under discussion. A comprehensive review by Hindson and Barnett concerning a wide range of analytical applications of permanganate in CL reactions [107] postulated excited Mn(II) or its complexes, singlet oxygen, sulphur dioxide, fluorescent oxidation products of the analyte, etc. 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 [108]. 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 [109]. Similar role is played by polyphosphate (hexametaphosphate) in sulphuric acid medium [110,111].

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 [109], benzalkonium chloride [112]) protect the microenvironment of CL emitter through formation of micelles or they can facilitate energy transfer [109]. 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 [113].

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 [112,114–116] and formic acid [117] 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 [118], formaldehyde [119–125]). Cephalosporines [126] were determined by permanganate-induced CL enhanced by glyoxal as sensitizer.

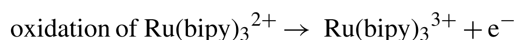
An attempt was made to solve the problem of CL drug determination in complicated matrices such as human serum by using on-line solid-phase extraction and SIA with CL detection [110]. The authors determined salbutamol that was initially adsorbed from the matrix on a cartridge packed with silica-gel (modified 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 [127] and sulphonamides [128]. A screening test for the development of photo-induced FIA–CL of pharmaceuticals has been also reported [129].

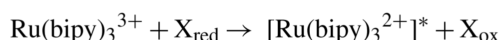
4.1.2. Oxidation by (2,2′-bipyridine)ruthenium(III) complex

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 obtain active $Ru(bipy)_3{}^{3+}$ by oxidation of relatively stable $Ru(bipy)_3{}^{2+}$ including chemical, photochemical and electrochemical oxidation [143]. An analyte is oxidized by the $Ru(bipy)_3{}^{3+}$ to produce excited $[Ru(bipy)_3{}^{2+}]^*$ species emitting CL at around 600 nm [143].

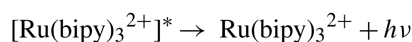
The CL is generated by the reaction with a reductant (X_{red}) as follows:



$$\text{oxidation of } Ru(bipy)_3{}^{2+} \rightarrow Ru(bipy)_3{}^{3+} + e^-$$



$$Ru(bipy)_3{}^{3+} + X_{red} \rightarrow [Ru(bipy)_3{}^{2+}]^* + X_{ox}$$



$$[Ru(bipy)_3{}^{2+}]^* \rightarrow Ru(bipy)_3{}^{2+} + h\nu$$

Table 3
Direct oxidation of analyte by potassium permanganate in acidic media

Analyte	CL reaction/flow-methodology	Calibration range	LOD	Throughput (samples/h)	Sample	Reference
Amidopyrine (=Aminopyrine or Aminophenazon)	Sensitizer: formaldehyde/FIA	0.1–80 µg/ml	30 ng/ml	–	Injection solutions	[119]
Amoxicillin	Sensitizer: quinine/FIA	0.05–10 µg/ml	0.02 µg/ml	90	Pharmaceuticals	[114]
Ampicillin	Degradation of ampicillin, sensitizer: formaldehyde/FIA	0.04–20 µg/ml	9.1 ng/ml	–	Capsules	[130]
Ascorbic acid	FIA, solid-phase reactor	0.05–10 µg/ml	5 ng/ml	120	Tablets, vegetables	[131]
Ascorbic acid	Oxidation by soluble Mn(IV) or permanganate/FIA or SIA	Mn(IV): 0.1–50 µM (FIA), 0.05–50 µM; Mn(VII): 0.01–5 µM (FIA), 0.5–5 µM (SIA)	Mn(IV): 50 nM (FIA, SIA); Mn(VII): 10 nM (FIA), 5 nM (SIA)	180	Tablets, injections	[132]
Brucine	MIP/FIA	0.005–1 µg/ml	2 ng/ml	–	Urine	[133]
Cefadroxil	Sensitizer: formaldehyde/FIA	0.05–0.8 µg/ml, 1.0–10.0 µg/ml	25 ng/ml	120	Pharmaceuticals	[134]
Cephalosporins: Cefalexin	Sensitizer: glyoxal/FIA	0.01–1 µg/ml	10 ng/ml	–	Capsules, tablets, injections	[126]
Cefadroxil		0.01–1 µg/ml	2 ng/ml			
Cefazolin		0.1–5 µg/ml	2 ng/ml			
Chloramphenicol	UV-irradiation/FIA	<14 µg/ml	30 ng/ml	60	Collyria, pomade	[127]
Cinnarizine	Enhancer ethanol, Tween 60, polyphosphoric acid medium/FIA	0.5–6.0 µg/ml	18 ng/ml	130	Tablets	[109]
Cysteine	Enhancer quinine/FIA	0.02–2 µg/ml	0.01 µg/ml	120	Pharmaceuticals	[115]
N-Acetylcysteine		0.05–2 µg/ml	0.02 µg/ml			
Glutathione		0.05–2 µg/ml	0.02 µg/ml			
Captopril		0.02–1 µg/ml	0.006 µg/ml			
Dobutamine	Sensitizer: formaldehyde/FIA	0.1–100 µg/ml	0.07 µg/ml	–	Injection solutions	[120]
Ethamsylate	Sensitizer: formic acid/FIA	0.01–2 µg/ml	5 ng/ml	–	Pharmaceuticals	[117]
Estrogens: Dienestrol	Enhancer formaldehyde/FIA	0.008–8 µg/ml	2.61 ng/ml	–	Tablets, tap water	[135]
Diethylstilbestrol		0.005–4.75 µg/ml	1.08 ng/ml			
Hexestrol		0.02–5 µg/ml	6.28 ng/ml			
Isoniazid	MnO_4^- in basic medium/FIA	0.01–5.0 µg/ml	7.0 ng/ml µg/ml	–	Tablets	[136]
Metoclopramide	Sensitizer: formaldehyde/FIA	0.06–60 µg/ml	0.03 µg/ml	–	Tablets, injections	[121]
Metoclopramide	Sensitizer: formaldehyde/FIA	0.4–100 µg/ml	0.2 µg/ml	–	Tablets, injection solutions	[122]
Penicillins: Phenoxymethylpenicillin, Amoxicillin, Ampicillin, Ampicillin sodium	Sensitizers of glyoxal–permanganate system in sulphuric acid	0.1–1.0 µg/ml	0.05 µg/ml	–	Pharmaceuticals	[137]
			0.03 µg/ml			
			0.03 µg/ml			
			0.05 µg/ml			
Phentolamine	Sensitizer: formaldehyde/FIA	0.01–5.0 µg/ml	5 ng/ml	–	Formulations, plasma, urine	[123]
Phenylephrine	Under 80 °C/FIA	0.03–8 µg/ml	–	134	Pharmaceuticals	[138]
Promethazine	SIA	15.58–1869.7 µM	–	–	Tablets	[139]
Propranolol	FIA	1.0–17.5 µg/ml	70 ng/ml (IUPAC), 0.87 µg/ml (Clayton)	–	Tablets	[140]
Propranolol	Presence: ferrous ions, polyphosphoric acid/FIA	0.4–10 µg/ml	0.1 µg/ml	–	Tablets	[141]
Salbutamol	Sensitizer: hexametaphosphate/SIA	0.05–10 µg/ml	0.03 µg/ml	42	Human serum, urine	[110]
Salicylic acid	Sensitizer: formaldehyde/FIA	0.5–1000 µM	0.3 µM	–	Liquid medicine	[124]
Sulphonamides	UV-irradiation/FIA	0.06–8 µg/ml or 0.08–100 µg/ml	30 ng/ml or 80 ng/ml	60	Tablets, capsules	[128]
Sulphonamides (Sulphacetamide and Sulphafurazole)	Sensitizer: glutaraldehyde/SIA	≈0.01–0.5 mM	–	120	Eye drops, tablets	[118]
Tannic acid	Sensitizer: quinine/SIA	0.5–20 µg/ml	100 ng/ml	54	Pharmaceutical and galenic formulations, human urine, surface water	[116]
Terbutaline	Sensitizer: formaldehyde/FIA	0.1–20 mM	0.03 mM	–	Study of protein binding in vitro	[125]
Trimethoprim	Sensitizer: hexametaphosphate/SIA	20–100 µg/ml	0.1 µg/ml	120	Tablets	[111]
Trimethoprim	MIP/FIA	0.05–5 µg/ml	0.02 µg/ml	–	Pharmaceuticals, body fluids	[142]

Table 4
CL systems based on ruthenium complex

Analyte	Oxidation	Calibration range	LOD	Throughput [samples/h]	Sample	Ref.
Amiodarone	UV-irradiation and peroxodisulphate/FIA	3.0–60.0 µg/ml	0.28 µg/ml	120	Pharmaceuticals	[146]
Cefadroxil	Electrochemically/FIA	0.05–100 µM	–	–	Capsules	[145]
Cephalosorins: Cefoxitin, Cefazolin, Cefalexin, Cefadroxil, Cefaclor, Cefoperazone	Permanganate, presence of perchloric acid, catalysed by Mn (II)/FIA	≈0.1–10 µg/ml	≈0.3–0.08 µg/ml	90	Pharmaceuticals	[147]
Cefprozil	Permanganate in sulphuric acid, sensitizer: quinine/FIA	0.1–3.0 µg/ml	5 ng/ml	120	Tablets	[148]
L-Cysteine	UV-irradiation and peroxodisulphate/FIA	2–500 µM	0.5 µM	240	Pharmaceuticals	[144]
L-Cystine		1–200 µM				
Enalapril	Permanganate in sulphuric acid/FIA	0.005–0.2 and 0.7–100 µg/ml	1.0 ng/ml	–	Tablets, urine, serum	[149]
Fluoroquinolones: Ofloxacin	Ce(IV) in sulphuric acid/FIA				Tablets, urine, plasma	[150]
Norfloxacin		0.003–0.7 µg/ml	5.5 nM	98		
Ciprofloxacin		0.05–7 µg/ml	31 nM	35		
		0.05–6 µg/ml	26 nM	45		
Metoclopramide	Permanganate in sulphuric acid/FIA	0.005–3.5 µg/ml	1 ng/ml	–	Tablets, syrup, urine, serum	[151]
Naproxen	Lead dioxide in sulphuric acid/FIA	0.02–6 µM	10 nM	–	Human serum	[152]
Paracetamol	Permanganate in sulphuric acid, sensitizer: Mn (II)/FIA	0.3–50.0 µg/ml	0.2 µg/ml	90	Tablets	[153]
Pyrrolizidine alkaloids: Heliotrine, Retronecine, Supinine, Monocrotaline, Echinatine *N*-oxide	Use of Ru(III) complex and Ru(II) complex immobilized; oxidation by permanganate/SIA and FIA	–	–	–	–	[154]
Tetracycline	Permanganate in nitric acid, catalyst: Mn(II)/FIA	50–500 µM	2.0 µM	50	Tablets, ointment	[155]
Chlortetracycline			1.9 µM			
Oxytetracycline			1.0 µM			
Thioxanthenes: Zuclopenthixol	Ce(IV) in sulphuric acid/FIA				Tablets, ampoules, spiked urine, plasma	[156]
Flupentixol		0.002–6 µg/ml	4.2 nM	116		
Thiothixene		0.5–15 µg/ml	20 nM	133		
		0.05–7.5 µg/ml	45 nM	100		
Thyroxine	Enhancer; immobilized alcohol dehydrogenase, presence of NADH/FIA	0.05–1 µM	0.05 µM	80	Tablets	[157]

Table 5
Other CL methods/FIA

Analyte	CL reaction/special technique	Calibration range	LOD	Throughput (samples/h)	Sample	Reference
Oxidation by ferricyanide in alkaline media						
Cimetidine	Sensitizer: Tween 80	0.1–500 μg/ml	20 ng/ml	–	Tablets, injections	[164]
Dihydralazine	Sensitizer: eosin Y	0.02–2.8 μg/ml	12 ng/ml	–	Tablets	[165]
Dobutamine	–	0.5–100 μg/ml	0.3 μg/ml	–	Medicine	[166]
Ergonovine	Solid-phase reactor	0.005–1.0 μg/ml	2.6 ng/ml	–	Injections, urine	[167]
Ergot alkaloids (Ergotamine)	Sensitizer: dioxane, 70 °C	0.1–500 ng/ml	0.6 pg/ml	73	Tablets	[105]
Folic acid	–	0.1–21 μg/ml	0.03 μg/ml	30	Pharmaceuticals	[168]
Isoniazid	–	0.05–2 μg/ml	0.01 μg/ml	120	Pharmaceuticals	[169]
Rifampin	–	0.1–30 μg/ml	0.06 μg/ml	–	Capsules, ocustilla	[170]
Rutin	Sensitizer: ethanol	1–100 μg/ml	0.34 μg/ml	60	Pharmaceuticals	[171]
Terbutaline	Sensitizer: rhodamine 6G	0.01–1.2 μg/ml	0.0067 μg/ml	–	Tablets	[172]
Tyrosine	Sensitizer: formic acid, organised medium (β-cyclodextrin)	1.0–10 μg/ml	50 ng/ml	98	Synthetic formulation	[113]
Oxidation by Ce(IV) in acidic media						
Cephalexin	Temperature degradation of analyte, sensitizer: rhodamine 6G	0.1–10 μg/ml	0.06 μg/ml	–	Capsules, tablets	[173]
Cephradine	Thermal degradation of analyte, sensitizer: rhodamine 6G	0.1–40 μg/ml	0.05 μg/ml	–	Capsules	[174]
Chlorpromazine	Sensitizer: rhodamine 6G	0–10 μg/ml	6.5 ng/ml	–	Tablets, injection, plasma, urine	[175]
Fleroxacin	Sensitizer: Tb^{3+}	2–80 nM	0.83 nM	–	Tablets, urine	[176]
Lomefloxacin	Sensitizer: rhodamine 6G	0.1–15 μg/ml	0.06 μg/ml	–	Capsules	[177]
Perphenazine	–	0.1–70 μg/ml	80 ng/ml	–	Tablets	[178]
Peurarin	Sensitizer: rhodamine 6G	1.3–800 ng/ml	0.84 ng/ml	120	Injection	[179]
Phentolamine	Sensitizer: rhodamine 6G	1–1000 ng/ml	0.4 ng/ml	–	Injection, biological fluids	[180]
Thiazides: Indapamide	UV-irradiation	0.5–12 μg/ml		65	Pharmaceuticals	[181]
Metolazone		0.5–12 μg/ml				
Hydroflumethiazide		0.5–12 μg/ml	0.06 μg/ml			
Chlorthalidone		0.5–12 μg/ml	0.005 μg/ml			
Bendroflumethiazide						
Hydrochlorothiazide		0.5–5 μg/ml				
Oxidation by *N*-bromosuccinimide in alkaline media						
Adrenaline	–	6–200 μg/ml	6 μg/ml	40	Pharmaceuticals	[182]
Amino acids: Glycine	Increased reactivity by humic acid	1–30 μg/ml	0.2 μg/ml	115	Emulsion, injection	[183]
Arginine			0.25 μg/ml			
Meloxicam	Sensitizer: fluorescein	0.22–28 μM	77 nM	144	Pharmaceuticals	[184]
Metformin	Sensitizer: fluorescein, tensoactives cetyltrimethylammonium bromide	0.007–30 μg/ml	2.3 ng/ml	90	Pharmaceuticals	[185]
Moroxydine	Presence of dichlorofluorescein, cetyltrimethylammonium chloride	0.01–100 μg/ml	3.0 ng/ml	–	Tablets	[186]
Phenformin	Sensitizer: fluorescein, tensoactives cetyltrimethylammonium bromide	0.006–10 μg/ml	2 ng/ml	90	Tablets	[187]
Phenformin	Sensitizer: fluorescein, tensoactive cetyltrimethylammonium bromide	0.01–30 μg/ml	3.4 ng/ml	–	Tablets	[188]
Electrogenerated oxidants						
Amidopyrine (=Aminopyrine, Aminophenazon)	Mn(III)	0.5–100 μM	0.2 μg/ml	–	Injections	[159]
Captopril	Mn(III)	0.3–100 μM	80 nM	–	Tablets	[160]

Table 5 (*Continued*)

Analyte	CL reaction/special technique	Calibration range	LOD	Throughput (samples/h)	Sample	Reference
Captopril	Ag(II) in acidic medium	0.02–10 μg/ml	6 μg/ml	60	Pharmaceuticals	[161]
Dexamethasone	Co(III) in sulphuric acid	1–20 μg/ml	0.32 μg/ml	–	Injections	[162]
Chlortetracycline	$[Cu(HIO_6)_2]^{5-}$	0.1–100 μg/ml	53 ng/ml	60	Urine	[163]
Other oxidants						
Analgin (Metamizol)	Oxidation by manganese dioxide in acidic medium, sensitizer: rhodamine 6G/flow sensor	0.04–1 mg/ml	27 μg/ml	120	Dissolution tests of tablets	[189]
Ascorbic acid	Oxidation by soluble Mn(IV), sensitizer: formaldehyde	0.06–20 μM	0.02 μM	–	Tablets, injections	[190]
Hemin	Oxidation by H_2O_2 in NaOH, sensitizer: Rhodamine B, sodium dodecyl sulphate	0.86–860 nM	86 pM	100	Tablets, animal blood	[191]
Indapamide	Oxidation by soluble Mn(IV), sensitizer: formaldehyde, MIP	0.02–5.0 μg/ml	8 ng/ml	–	Urine	[192]
Isoniazid	Oxidation by periodate in basic medium	0.5–100 μg/ml	0.16 μg/ml	120	Dissolution tests of tablets	[193]

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 (see Table 4).

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 [144]. 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 [145]. 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.

4.1.3. *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 (see Table 5).

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-chemiluminescence 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 [158], Mn(III) [159,160], Ag(II) [161], Co(III) [162] and $[Cu(HIO_6)_2]^{5-}$ [163].

5. 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 (Table 6). Song and coauthors [194] devised a CL method for the assay of fluoroquinolones 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. The reaction is suitable for determination of fluorophores or compounds labeled with fluorescent tags. Thus albumin [195] 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) [196]. 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).

Table 6
Miscellaneous reactions/FIA

Analyte	CL reaction/special technique	Calibration range	LOD	Throughput (samples/h)	Sample	Reference
Albumin	Derivatized by fluorescamine; bis(2,4,6-trichlorophenyl)oxalate in acetonitrile–H_2O_2 system	0.31–12 μg/ml	–	–	Pharmaceuticals and biological fluids	[195]
Amidopyrine (=Aminopyrine, Aminophenazone)	$Na_2S_2O_4$–$KmnO_4$ system in H_2SO_4	0.2–80 μg/ml	60 ng/ml	–	Tablets	[197]
Analgin (metamizol)	Polyethylene–glycol-400–rhodamine 6G system in acidic medium	0.01–10 μg/ml	0.003 μg/ml	–	Pharmaceuticals	[198]
Antipyrin (Fenazon)	$NaIO_4$–H_2O_2 system in H_3PO_4	0.1–70 μg/ml	23 ng/ml	–	Pharmaceuticals	[199]
Ceftriaxone	Inhibition of acridine orange–potassium permanganate system	2–20 μg/ml	8 ng/ml	–	Powder injection preparations	[200]
Ethamsylate	Hydrolytic product (in NaOH) reacts with dissolved oxygen in Tween 80; sensitizer: rhodamine 6G	0.05–2.0 μg/ml	0.02 μg/ml	–	Tablets, injection	[196]
Fluoroquinolones	Enhancers of nitrite–hydrogen peroxide system in acidic medium	0.1–10 μM	45 nM	–	Tablets, eye drops	[194]
Ciprofloxacin		0.1–10 μM	59 nM			
Norfloxacin		0.3–30 μM	110 nM			
Ofloxacin						
Gentamicin	Gentamicin derivatized with *o*-phthalaldehyde; peroxyoxalate system, catalyst: imidazole, dodecyl sulfate	3.93–30 μg/ml	1.18 μg/ml	–	Pharmaceuticals	[201]
Isoprenaline	Peroxide–periodate–Cu(II), 80 °C	1–700 ng/nl	0.4 ng/ml	–	Injection	[202]
Pentoxyverine	Sodium hypochlorite–hydrogen peroxide system	3.0–0.03 μM	28 nM	–	Tablets	[203]
Pipemidic acid	Sodium hydrosulfide/potassium permanganate system in tetraphosphoric acid	0.01–10 μg/ml	3.3 ng/ml	–	Pharmaceuticals	[204]
Piroxicam	Quencher of acridine orange–permanganate system in basic medium	10–700 μg/ml	4.5 μg/ml	–	Pharmaceuticals	[205]
Propranolol	Pyrogallol–periodate system	up to 1.0 μg/ml	37.4 ng/ml	–	Injection	[206]
Reserpin	Hydrogen peroxide/potassium periodate system in sulphuric acid	0.001–10 mM	0.27 μM	–	Tablets	[207]
Rufloxacin	Sensitizer with Eu(III) (complex) of Ce(IV)-sulfurous acid	20–500 nM	5 nM	–	Capsules, human serum	[208]
Salbutamol	Inhibition of *N*-bromosuccinimide/fluorescein system in alkaline condition	0.08–10 μg/ml	26 ng/ml	–	Tablets	[209]
Tetracycline	Enhancers of oxidation of electrogenerated bromine with hydrogen peroxide	0.03–50 μg/ml	10 ng/ml	60	Pharmaceuticals	[158]
Oxytetracycline		0.2–24 μg/ml	70 ng/ml			
Chlortetracycline		0.1–50 μg/ml	150 ng/ml			
Trimethoprim	Thiosulfate/permanganate system in sulphuric acid	0.1–10 μg/ml	38 ng/ml	–	Tablets	[210]
Tryptophan	Peroxidation and epoxidation by peroxynitrous acid, subsequent decomposition of dioxetane	0.6–30 μM	0.18 μM	50	Injection, human serum	[211]

6. Conclusions

Chemiluminescence 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 new direct selective CL reactions can potentially increase the number of analytes of pharmaceutical interest which could be determined through chemiluminescence. To succeed in such developments a deeper knowledge of mechanisms of the CL reactions is pre-requisite. In the authors' opinion further progress in the field of electro-chemiluminescence 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.

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