

## Application of Flow Injection Technique in Pharmaceutical Analysis. Part I: Spectrophotometric and Chemiluminescence Detection

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### Abstract

A review dealing with the use of flow injection technique (FIA) in the drug analysis is presented. Comments on the application of automated FIA systems in the quality control of pharmaceuticals and in pharmaceutical research are involved in the survey. Part I. comprises papers using spectrophotometry and chemiluminescence as detection techniques.

**Keywords:** Flow injection analysis; automation; drugs; pharmaceutical analysis.

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### 1. Introduction

In recent years more and more strict regulations related to the quality control of pharmaceuticals led to increasing demands on the automation of analytical assays carried out in appropriate control laboratories. At the same time, during twenty-five years of its existence, the FIA technique [1] became a versatile instrumental tool that contributed substantially to the development of automation in pharmaceutical analysis. This can be well documented by a number of reviews on the use of FIA in the analysis of drugs. In the field of flow injection in pharmaceutical analysis several reviews were published by our group [2-4]. The latest reviews on this topic appeared, to our best knowledge, in 1990 [5] (125 references) and 1992 [6,7] (88 references) and the most recent monograph devoted to the application of FIA in pharmaceutical control was published in 1996 [8].

The objective of this paper is to present an overview of FIA papers concerning the analysis of drugs that were published between 1997 and 2000 and thus to implement and update the information provided earlier in the sources cited above [5-8]. In order to facilitate better orientation of the reader in the respective matter we decided to adopt the scheme of sorting the FIA methods according to the type of

detection as the major classification feature (see [6]) regardless of auxiliary on-line procedures employed within the FIA scheme, such as solvent extraction, dialysis, solid-phase pre-concentration, photolysis, use of packed-bed enzyme reactors or immunosorbents, etc.

### 2. Comments on the application of automated FIA procedures in the quality control of pharmaceuticals and in pharmaceutical research

#### A) Pharmacopoeial assays

It is obvious that in the quality control of drugs as bulk substances the inherent advantage of FIA, i.e. high sample throughput, is generally not required in conventional control laboratory; hence in this instance there is no need for FIA to compete with the established official methods. On the other hand, the regulations concerning quality control of pharmaceutical formulations (especially solid dosage forms) require to carry out content uniformity tests with large sets of individual tablets and to examine the liberation of the active substance from the formulation (dissolution tests for tablets or ointments). These tasks may be solved by an automated FIA with its excellent reagent economy and capacity of sampling frequencies close to 100 h<sup>-1</sup>. Application of multi-sensing devices (UV-VIS diode-array detectors, FT-IR detection, multi-channel electrochemical detection with electrode

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Table 1: FIA assays with UV/VIS spectrophotometric detection

drug	matrix	$\lambda$ (nm)	reagents/ technique	linear range (mg/l)	detect. limit (mg/l)	ST (h <sup>-1</sup> )	ref.
acetylsalicylic acid	tablets	525	Fe <sup>3+</sup>	25 - 250	4	90	9
adrenaline	pharmaceuticals	287	solid phase detection	1 - 12	0.17	12	10
ambroxol	tablets	209			25 $\mu$ M	50	11
amiloride	solution	545	methylene blue, Ce <sup>4+</sup>	up to 120		30	12
ammonium	pharmaceuticals	636	phenantroline	1 - 20	0.35		13
amoxicillin	pharmaceuticals		solid phase detection	0.5 - 50			14
ascorbic acid (L-)		480	Cu <sup>3+</sup>	5 - 40 $\mu$ M	0.3 $\mu$ M	80	15
ascorbic acid (L-)		265	ion pairs	10 - 100 $\mu$ M	2 $\mu$ M	30	16
ascorbic acid	pharmaceuticals	528	Rhodamine 6G	0.1 - 4	80 ng/ml	100	17
ascorbic acid	vitamin tablets	525	KMnO <sub>4</sub> , indirect	up to 200 ppm		90	18
ascorbic acid	pharmaceuticals	267	solid phase detection	0.2 - 20	0.02		19
benzocaine novocain	biological fluids	510	dinitrobenzofuroxan derivatives	0.08 - 5.0	0.04 0.05		20
benzodiazepine	human urine	550, 600	NaNO <sub>2</sub> , naphthol	2.5 - 15 $\mu$ M	0.3-1 $\mu$ M		21
bismuth	pharmaceuticals	363, 505	tetraphenylarsonium	2.3 $\mu$ M - 0.15 mM	1.5 $\mu$ M	40	22
busulphan	tablets	570	dissolution	4 - 24			23
caffeine acetylsalicylic acid paracetamol	pharmaceuticals	220 - 300	diode-array				24
caffeine dimenhydrinate acetaminophen	pharmaceuticals	245 - 310	multivariate calibration				25
cefadroxil	pharmaceuticals	600	phenylenediamine, Fe <sup>3+</sup>	80 - 320	40		26
cephalosporines	human urine	330	Pd <sup>2+</sup>	5 - 60	2		27
chlorhexidine	pharmaceuticals		extraction	10 - 100 $\mu$ M		40	28
chlorpromazine	solution	340	enzyme inhibition	20 - 100 $\mu$ M	20 $\mu$ M		29
cysteine	pharmaceuticals	360	Co <sup>2+</sup>	1 - 90		90	30
diclofenac	tablets	412	acridine yellow	8 $\mu$ M - 0.2 mM		40	31
diclofenac	human urine	580	Ce <sup>4+</sup>	0.2 - 8	0.023		32
diclofenac	pharmaceuticals	281	solid phase detection	0.5 - 140			33
L-dopa carbidopa	tablets	370, 500		0.4 - 10 mM	0.2 $\mu$ M 0.15 $\mu$ M	26	34
dopamine methyldopa	pharmaceuticals	360		0 - 0.2 mM 0 - 0.3 mM	3.5 $\mu$ M 0.43 $\mu$ M		35
epinefrin isoprenaline	pharmaceuticals	530	Fe <sup>2+</sup>	5 - 200 10 - 300	1 1		36
etambutol	tablets	420	dissolution	50 - 300		20	37
fluticasone	solution		o-phthalaldehyde				38
furosemide sulphathiazole	tablets	410	Pd <sup>2+</sup>	20 - 400 $\mu$ M 50 - 300 $\mu$ M	55 $\mu$ M 14 $\mu$ M	50	39
glycine	pharmaceuticals	235	immobilised CuCO <sub>3</sub>	50 $\mu$ M - 1 mM			40
heparin	solution		thiazine dyes	0 - 12	0.1		41
hydrochlorothiazid	pharmaceuticals	220 - 350					42
iron	vitamin tablets		thiocyanate				43
iron	drugs		photometric diode	1.6 - 4.0		133	44
iron	tablets	440	dihydroxybenzaldehyde	up to 8 ppm		20	45
iron	pharmaceuticals	596	dihydroxyphenylacetate	up to 8.3 ppm			46
iron	pharmaceuticals	520	phenantroline			54	47

drug	matrix	$\lambda$ (nm)	reagents/ technique	linear range (mg/l)	detect. limit (mg/l)	ST (h <sup>-1</sup> )	ref.
iron	drugs	360		1 – 10 $\mu$ M	0.2 $\mu$ M		48
lactate	pharmaceuticals	562	ferrozine	0.3 – 90	50 ng/ml	30	49
minoxidil	pharmaceuticals	282	solid phase	0.05 – 7	6 ng/ml		50
morphine	solution	480	NaNO <sub>2</sub>	2 – 40	0.6		51
neostigmine	pharmaceuticals	610	extraction	0.1 – 0.5 $\mu$ M	18 nM	48	52
nitroglycerine	tablets	618	stopped flow	2 – 80 mg/l		15	53
isosorbide dinitrate	injections						
paracetamol	pharmaceuticals	264		0.5 – 8.0	0.022	40	54
paracetamol caffeine acetylsalicylic acid	pharmaceuticals	240 – 350	simultaneous determination				55
paracetamol salicylamide	pharmaceuticals	300	solid phase		0.104 0.35	36	56
peroxide hydroperoxide	pharmaceuticals	350	acetic acid, propanol	up to 300 nM			57
phenothiazines	tablets	500	MnO <sub>2</sub>	5 – 250			58
phenothiazines	pharmaceuticals	526	Fe <sup>3+</sup>	250 – 500	8		59
pindolol	solution	635	Fe <sup>3+</sup>	5 – 120		30	60
promazine	injections	512	Fe <sup>3+</sup> , phenantrolin	2 – 12 ppm	0.1 ppm	163	61
pyridoxine	pharmaceuticals	450	cetylpyridinium	up to 1 mM	50 $\mu$ M	60	62
tenoxicam	pharmaceuticals	540, 355	methanolic medium HCl medium	7 – 320 0.5 – 8.5			63
theophylline	solution	270	solid phase extraction	1 – 100	0.5		64
thiamine	tablets, ampoules	420	turbidimetry	50 – 300 $\mu$ M	10 $\mu$ M	90	65
thiamine	vitamin tablets	369	hexacyanoferrate	2.5 – 50	1		66
thioridazine	solution	470	PbO <sub>2</sub>	0.25 – 5		39	67
thioridazine	pharmaceuticals	662		10 – 60	0.5 $\mu$ g/l	50	68
zinc	pharmaceuticals		thiazolazonaphtol	0.04 – 4	0.01	45	69

Table 2: FIA assays with chemiluminescence detection

drug	matrix	reagents/ technique	linear range (mg/l)	detection limit (mg/l)	ST (h <sup>-1</sup> )	ref.
adrenaline dopamine isoprenaline	injections	H <sub>2</sub> O <sub>2</sub> luminol	0.04 – 2 0.01 – 1	20 ng/ml 4 ng/ml		70
amidopyrine	injections	KMnO <sub>4</sub> , formaldehyde	0.1 – 80	30 $\mu$ g/l		71
amidopyrine	solution	KMnO <sub>4</sub> , formaldehyde	0.1 – 80 mM	30 $\mu$ M		72
amitriptyline chlorpromazine	pharmaceuticals	Ru(bipy) <sub>3</sub>	1 – 400 $\mu$ M	0.09 – 0.31		73
analgin	solution	Rhodamine 6G	0.4 – 10	0.15		74
analgin	pharmaceuticals	Rhodamine 6G, Ce <sup>4+</sup>	0.05 – 10	0.02		75
ascorbic acid (L-)	tablets	H <sub>2</sub> O <sub>2</sub> , luminol	0.02 – 40 $\mu$ M	8.6 nM		76
ascorbic acid (L-)	pharmaceuticals	KMnO <sub>4</sub>	0.5 – 1000 $\mu$ M			77
ascorbic acid	pharmaceuticals	luminol, periodate	0.006 – 40	0.8 ng/ml		78
ascorbic acid glucose	pharmaceuticals	luminol, periodate	0.1 – 10 $\mu$ M 0.6 – 110	60 nM 0.08		79

drug	matrix	reagents/ technique	linear range (mg/l)	detection limit (mg/l)	ST (h <sup>-1</sup> )	ref.
atropine scopolamine	pharmaceuticals	luminol micelar medium	0.01 – 100	1 ng/ml		80
aztreonam penicillin G	solutions	luminol hexacyanoferrate		100 60		81
beta-lactam antibiotics	pharmaceuticals	luminol hexacyanoferrate	0.2 – 200 ng	60 pg – 4.5 ng		82
chloramphenicol	pharmaceuticals	luminol, Co <sup>2+</sup>	up to 0.3 μM	3 nM	60	83
chlorpromazine	solution	H <sub>2</sub> O <sub>2</sub> , luminol	0.01 – 10 mM			84
chlorotetracycline	solution, urine	H <sub>2</sub> O <sub>2</sub>	40 nM – 4 μM			85
ciprofloxacin	tablets, capsules	Ce <sup>3+</sup>	1 – 20	0.27		86
clavulanic acid sulbactam	pharmaceuticals blood serum	H <sub>2</sub> O <sub>2</sub> luminol	0.1 – 150 0.01 – 12	0.05 0.01		87
codeine	pharmaceuticals	Ru(bipy) <sub>3</sub>		50 μM		88
codeine	solution	Ru(bipy) <sub>3</sub>				89
cysteine glutathione	pharmaceuticals	Ce <sup>4+</sup>	1 – 100 μM 2 – 100 μM	1.4 μM 0.2 μM		90
cytarabine	solution	hypochlorite	10 – 100 ng/l	8 ng/l		91
dipyridamole	pharmaceuticals	KMnO <sub>4</sub>	0.2 – 80	58 ng/ml	11	92
dopamine	pharmaceuticals	lucigenin	10 – 200 nM	2 nM	40	93
L-dopa	tablets	KMnO <sub>4</sub>	0.4 – 80	62 μg/l	120	94
emetine	solution	Ru(bipy) <sub>3</sub>	1 – 10 μM	0.1 nM		95
ergonovine	pharmaceuticals	hexadecylpyridinium	0.07 – 1000 ppb	0.07 ppb	118	96
flufenamic acid mefenamic acid	pharmaceuticals biological fluids	Ru(bipy) <sub>3</sub>	0.07 – 6.0 0.05 – 6.0	3.6 nM 0.21 μM		97
fluoroquinolones	pharmaceuticals	Ce <sup>4+</sup> , sulphite	0.04 – 30	0.016		98
folic acid	tablets	KMnO <sub>4</sub> formaldehyde	0.1 10 μM	24 nM		99
furosemide	pharmaceuticals	Ce <sup>4+</sup> , Rhodamine 6G	1 – 50 μM	0.22 μM		100
gentamycin	pharmaceuticals	Co <sup>3+</sup>	0.01 – 80	5 ng/ml		101
hydrochlorothiazide	solution, tablets	Ce <sup>4+</sup> , rhodamine	0.33 – 130 μM	7.5 pM		102
imipramine	tablets	KMnO <sub>4</sub>	40 ng/ml – 1	12 ng/ml		103
isoniazid	solution	Mn <sup>2+</sup> , luminol	0.1 – 10	30 ng/ml		104
isoniazid	pharmaceuticals	Mn <sup>3+</sup>	0.1 – 10	0.003		105
isoniazid	pharmaceuticals	hypobromite	0.02 – 1	7 ng/ml	60	106
isoniazid	pharmaceuticals	hypochlorite	10 nM – 1 μM	6 nM		107
mercaptoethane- sulfonate	pharmaceuticals	Ce <sup>4+</sup> , quinine	0.29 – 2.21 ng	0.21 ng		108
methotrexate	pharmaceuticals	hypochlorite	20 – 400 μg/l	10 μg/l		109
morphinan alkaloids	injections, tablets	H <sub>2</sub> O <sub>2</sub> , luminol		60 ng/ml		110
nitroprusside	injections	H <sub>2</sub> O <sub>2</sub>	0.2 μM – 0.1 mM	9 nM	40	111
ofloxacin	tablets, injections	Ce <sup>4+</sup> , sulphite	0.04 – 4.0	0.016		112
perphenazine	pharmaceuticals	KMnO <sub>4</sub>	50 – 350 ppm		110	113
persantin	tablets	hypobromite	0.01 – 2	4 μg/l		114
phenacetin	pharmaceuticals	Ce <sup>4+</sup>	0.004 – 1 μM	1 nM		115
phenothiazines	tablets plasma, urine	Ce <sup>4+</sup> rhodamine-B	0.5 – 90	0.01	129	116
phenothiazines	pharmaceuticals		2 – 20 μM		110	117
prednisone	solution, tablets	Ce <sup>4+</sup>	0.2 – 20	31 μg/l		118
promethazine	solutions, tablets	KMnO <sub>4</sub>	0.1 – 6 μM	35 nM		119

drug	matrix	reagents/ technique	linear range (mg/l)	detection limit (mg/l)	ST (h <sup>-1</sup> )	ref.
pyridoxine	tablets	H <sub>2</sub> O <sub>2</sub> , oxalate	10 – 250			120
quinine	pharmaceuticals	Co <sup>3+</sup>	0.1 – 100	0.033		121
ranitidine salbutamol	pharmaceuticals	Ru(bipy) <sub>3</sub>	0.001 – 1 mM 50 nM– 0.1 mM	0.6 μM 25 nM		122
reserpine	injections	H <sub>2</sub> O <sub>2</sub> , KMnO <sub>4</sub>	1 – 80	0.3		123
reserpine rescinnamine yohimbine	pharmaceuticals	KMnO <sub>4</sub> phosphoric acid	0.05 – 3.0			124
riboflavine	tablets, injections	KMnO <sub>4</sub>	0.7 – 10	62 ng/ml		125
riboflavin	tablets, injections	KMnO <sub>4</sub> phosphoric acid	0.1 – 10	30 ng/ml		126
rutin	extracts	luminol hexacyanoferrate	0.02 – 8	6.7 ng/ml		127
rutin	pharmaceuticals	hypochlorite	40 pg/l – 10 ng/l	13 pg/l		128
rutin	extracts	luminol, H <sub>2</sub> O <sub>2</sub> , Cr <sup>3+</sup>	0.02 – 10	7 ng/ml		129
salicylamide	urine	KMnO <sub>4</sub>	up to 8	20 ng/ml	142	130
sulphite	injections	Rhodamine 6G	0.01 – 5			131
tetracyclines	solution	KMnO <sub>4</sub>	1 – 1000	0.4		132
tetracycline + metabolites	solution	hexacyanoferrate	0.04 – 2 μg			133
thiamine	solution, tablets	Fe <sup>3+</sup>		20 μM		134
thioridazine	pharmaceuticals	KMnO <sub>4</sub>		1.2 μM	110	135
tiopronin	pharmaceuticals	Ce <sup>4+</sup>	1 – 400 μM	0.34 μM		136
trimipramine	pharmaceuticals	KMnO <sub>4</sub>	0.02 – 0.22			137
vitamin B <sub>6</sub>	tablets	KMnO <sub>4</sub>	0.1 – 80	58 ng/ml		138
vitamin B <sub>12</sub>	pharmaceuticals	H <sub>2</sub> O <sub>2</sub> , luminol	0.001 – 10	0.35 μg/l	60	139
vitamin K <sub>3</sub>	pharmaceuticals	immobilised Rhodamine 6G	0.5 – 10	2,6 μg/l		140
vitamin K <sub>3</sub> dipyrone	pharmaceuticals biological fluids	Rhodamine 6G Tween 80	0.05 – 50 0.05 – 10	0.01 0.003		141
vitamin K <sub>3</sub>	injections	bisulfite, Ce <sup>4+</sup>	0.01 – 10	2 ng/ml		142
vitamin K <sub>3</sub>	pharmaceuticals	photoreactor	0.1 – 500 μM	2.03 nM	30	143

ST – sample throughput

arrays and combination of two or more serial or parallel detectors in a single FIA manifold) offers possible solution of the selectivity problems that may occur when analysing multicomponent formulations.

#### B) Pharmaceutical research and industry

FIA with its capability of automated analytical data collection represents a method of choice in drug discovery activities (screening of potential drugs, namely *in vitro/in vivo* monitoring of their biological effects reflected in specific chemical changes of examined systems in real time) in pharmacological drug testing (in addition to conventional pharmacokinetic and drug-protein binding studies

also examination of responses of cells, tissues, isolated organs and biological membranes to the effect of drugs) and in pharmaceutical technology (e.g., optimisation and monitoring of technological processes in drug production including biotransformations in biotechnology).

#### C) Comments on tables

The above tables cover the period 1997-2000. Because of a large number of methods using FIA in pharmaceutical applications, they have been divided according to the detection technique used. The Part I. includes main optical detection methods that are often applied in pharmaceutical assays. Table 1

describes spectrophotometric detection in UV and VIS region. Table 2 shows FIA applications with chemiluminescence mode that was widely used for pharmaceutical analyses. The following Part II. will comment other optical and mostly electrochemical detection techniques.

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