Systematic evaluation of 1-chlorobutane for liquid-liquid extraction of drugs

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Introduction

In systematic toxicological analysis (STA), chromatographic methods are widely used for the detection of drugs and other organic toxic substances in biological materials, such as blood, plasma, urine, hair and tissue samples. In most cases the applied analytical methods like gas chromatography-mass spectrometry (GC/MS), high performance liquid chromatography with diode-array detection (HPLC/DAD), HPLC/mass spectrometry (LC/MS), or thin-layer chromatography with remission spectroscopy (TLC/UV), require sample preparation by extraction prior to analysis.

The most widely used procedures for isolation of drugs from biological materials are Liquid-Liquid-Extraction (LLE) and Solid-Phase-Extraction (SPE). The basis of LLE is the application of organic, non-water-miscible solvents at varying pH-values, including basic or acidic back-extraction; sometimes after immobilization onto diatomaceous earth, silica gel, celite or sodium sulfate. Verified information about the extractability of drugs provides the basis for method development in LLE, making the realization of LLE faster in routine analyses and thus providing a cheaper alternative to SPE. The **theoretical basis of LLE** is rather simple. The extraction yield only depends on two constants, as shown in the equation for basic compounds. K_D is the distribution constant (Nernst's law of distribution) and K_B is the dissociation constant of the given basic drug (V_o and V_a stand for the volumes of the organic and aqueous phase, Y^o is the extraction yield in the organic phase). The dissociation constants of many drugs are known [4]. If distribution constants are known too, it is possible to determine the extraction yield for a given condition (pH-value (C_{H+}) and phase volumes). This is only valid for pure aqueous phases and not in the case of biological materials. But the exact determination of K_D-values is rather time consuming, it requires several measurements of extraction yields at different pH-values, near the point of equivalence (Y^o between 0.1 and 0.9) to minimize the error during determination.

$$Y^o = \frac{K_D \times V_o}{K_D \times V_o + V_a(1+10^{14} \times K_B \times c_{H^+})}$$

The **aim** of this study was to obtain data on the extractability of many toxicological and therapeutic relevant drugs using 1-chlorobutane. This solvent showed the cleanest chromatograms with regard to interfering peaks in relation to an external standard; in a pilot study 1-chlorobutane was compared to 7 other solvents and solvent mixtures using a pooled serum and GC-MS and HPLC-DAD [1-3]. Numerous publications applied 1-chlorobutane [18-42], also in comparison to SPE [5-17]; but only a few recent papers exist, or they are restricted to distinct classes of drugs. None of these papers contain the newer drugs developed in the last years on the legal and illegal market. For better reproducibility the determinations should be performed for each drug in different laboratories. For these reasons (great number of drugs and measurement in different laboratories) we did not determine the distribution constants, but focussed on the extraction yield for each substance for a distinct pH-value using aqueous buffer solutions. Furthermore, a very simple analytical method was used, based on UV-VIS-spectrometry.

Experimental

Buffer solutions (pH 9) were obtained by dissolving 10 g Na_2HPO_4 (VWR) in one liter of distilled water. 1-chlorobutane and methanol (analytical grade) were obtained from VWR International (Darmstadt, Germany). Drugs were purchased as pure compounds or as salts from chemical suppliers (Sigma Deissenhofen/Germany and others) or from the pharmaceutical manufacturers and were first dissolved in methanol to achieve a concentration of 1 mg/mL. In some instances the pure drug was not available; in these cases, a methanolic solution of a pharmaceutical preparation was used.

Measurement of extraction yields: For obtaining reference solutions three different procedures have been used: a) drugs soluble in the organic solvent were dissolved in 1-chlorobutane in a concentration of 10 or 20 mg/L, depending on the extinction coefficient; b) water-soluble drugs were dissolved in phosphate buffer (pH 9) and c) salts of basic drugs were transferred to their free bases by extraction with 1-chlorobutane at pH 9 from aqueous solution. From the resulting reference solutions UV-spectra were measured to obtain a reference value (A^{pre}). LLE was then performed by adding 3.0 ml of phosphate buffer (pH 9) or - in case of aqueous reference solutions - 3.0 ml 1-chlorobutane, to 3.0 ml of reference solution. In any case, LLE was performed using equal volumes of aqueous and organic phases (v/v ; 1:1). The samples were vortex-mixed for 1 min and centrifuged to separate the phases. Either the organic phase (for unpolar compounds) or the aqueous phase (for water-soluble compounds) was measured by UV-spectroscopy (A^{post}). Each LLE was performed twice.

The extraction efficiency (yield) Y^o in the organic phase was determined by the ratio of the absorbance obtained after and before the extraction:

UV-measurement using the **organic** phase:

$$Y^o = \frac{A_o^{post}}{A_o^{pre}}$$

UV-measurement using the **aqueous** phase:

$$Y^o = \frac{A_a^{pre} - A_a^{post}}{A_a^{pre}}$$

A_o^{post}, A_o^{pre} absorbance of the organic phase (o) pre- and post-extraction.

A_a^{post}, A_a^{pre} absorbance of the aqueous phase (a) pre- and post-extraction.

For a minor number of substances, which did not show a typical UV-spectrum in sufficient intensity, quantitation was performed by GC/MS using calibration with external standards.

Results

The extraction yields for 333 compounds of clinical or forensic interest have been determined, including psychopharmaceuticals and narcotics (e.g., benzodiazepines, tricyclic antidepressants, phenothiazines, thioxanthenes, butyrophenones), analgesics, antiepileptics, cardiovascular drugs (e.g., ß-blockers, Ca-antagonists), illicit drugs and pesticides.

Extraction yields are listed in alphabetical order (in the table on this poster only drugs with the initial letter A and B with their yield in the organic phase Y^o can be shown). Average values of two to four laboratories are given (one reference laboratory and one to three other laboratories). Since each analyte was extracted twice in each laboratory, the extraction efficiencies obtained by 4 to 8 single measurements were averaged, and the average value is given with one digit behind the decimal point, except in those cases with very poor or very good extraction yields (Y^o<0.2 or Y^o >0.8), when the average value is given with a precision of 0.05. In the last column, references for the extraction with 1-chlorobutane from biological material are given. 228 of 333 drugs (68 %) were extracted by 1-chlorobutane with extraction yields $\geq$ 80 % ($Y^o \geq 0.8$) from aqueous buffer at pH 9. For 56 compounds, analytical methods have been published using 1-chlorobutane for the extraction of biological material.

However, low extraction efficiencies were obtained, when the drug was not soluble enough in 1-chlorobutane (e.g., morphine, benzoylecgonine, caffeine), and with acidic compounds since the extraction was performed at pH 9 (e.g. diclofenac, indomethacin, phenobarbitone).

The complete table and list of references is available via web: www.gtfch.org/chlorobutaneextraction.pdf

N°	drug	Y^o	Ref.
24	Acebutolol	0.05	
25	Adenosin	0	
26	Ajmaline	0.5	
27	Alfentanil	1	
28	Alimemazine	1	
29	Alprazolam	0.95	[43-45]
30	Alprenolol	1	
31	Amantadine	0.5	
32	Amfebutamon	1	
33	Amfepramon	1	
34	Amfetaminil	1	
35	Amiodarone	0.95	
36	Amisulprid	0.6	
37	Amitriptyline	1	[46]
38	Amitriptyline-Oxid	0.1	
39	Amlodipine	1	
40	Amphetamine	0.5	[47-55]
41	Apomorphin	0.8	
42	Aprindin	0.95	
43	Articain	1	
44	Atenolol	0	
45	Atropine	0.6	
46	Azathioprine	0	
47	Azinphos-ethyl	1	
48	Azinphos-methyl	1	
49	Benperidol	1	
50	Benserazid	0	
51	Benzatropin	1	
52	Benzoylecgonine	0	
53	Betaxolol	1	
54	Biperidene	1	
55	Bisacodyl	0.7	
56	Bisoprolol	0.9	
57	Bromazepam	0.9	
58	Bromocriptin	1	
59	Bromophos-ethyl	1	

(cont. : see www.gtfch.org/chlorobutaneextraction.pdf)

Discussion

The presented list of extraction yields of 333 compounds allows the analyst an easy estimation of the extractability of common drugs using 1-chlorobutane. A high recovery from the aqueous solution is a "necessary but not sufficient" condition for the extraction of biological matrices such as serum, blood or urine; in other words, it is not necessary to test the extraction of a given drug from serum with 1-chlorobutane, if recovery from the aqueous solution is low or even zero. Therefore, and due to a large number of compounds of interest in forensic toxicology, extraction from the aqueous solution (phosphate buffer, pH 9) was investigated. 68 % of the tested drugs were extractable with high yields (> 80%) at pH 9 using 1-chlorobutane. For 56 compounds with high recovery from buffer solution, a successful extraction by 1-chlorobutane from serum was confirmed in the literature and a comprehensive bibliography is given (see Table). In these cases, extraction yields were similar to those found for aqueous solutions in our work. Therefore, in cases of target compound analysis (e.g. detection of poisoning with - or misuse of - a known drug and therapeutic drug monitoring), the table allows the analyst to decide whether an extraction with 1-chlorobutane seems useful in this particular case. For systematic toxicological analysis (STA) it should be taken into account that only 228 of the listed compounds could be extracted with a sufficient extraction yield, and about 32 % of the 333 compounds tested showed poor extraction yields. Therefore, a more polar solvent, mixture of polar solvents or even another methodology (e.g. SPE) should be applied for STA. For the use of a more polar solvent (e.g. ethylacetate) the table can also be very useful, because it can be assumed that drugs with a medium recovery rate in 1-chlorobutane are extractable in this solvent. Future work will include extraction yields for the extraction of the tested compounds from serum samples with 1-chlorobutane.

Table: Extraction yields using 1-chlorobutane from aqueous solution (pH 9).

No.	Compound	Y°	References
1	10-Hydroxy-Carbazepin	0	
2	2-(2,3-methylendioxyphenyl)butan-1-amin	0 .8	
3	2-(2,3-methylendioxyphenyl)propan-1-amin	0 .7	
4	2-(3,4-methylendioxyphenyl)2-methylpropan-1-amin	0 .9	
5	2-(3,4-methylendioxyphenyl)butan-1-amin	0 .8	
6	2-(3,4-methylendioxyphenyl)propan-1-amin	0 .5	
7	2,3 – MDA	0 .6	
8	2,3 – MDMA	0 .9	
9	2,3-Methylendioxo-N-methylphenethylamin	0 .6	
10	2,3-Methylendioxo-N-phenethylamin	0 .3	
11	2,4,5-Trimethoxy-amphetamin (TMA-2)	0 .2	
12	2,4,6-Trimethoxy-amphetamin (TMA-6)	0 .5	
13	2,5-Dimethoxy-4-brom-phenethylamin (2-CB)	0 .8	
14	2,5-Dimethoxy-4-methyl-amphetamin (DOM)	0 .8	
15	2,5-Dimethoxy-4-methyl-phenethylamin (2-CD)	0 .5	
16	2,5-Dimethoxy-phenethylamin (2-C-A)	0 .3	
17	3-(2,3-methylendioxyphenyl)pentan-2-amin	0 .95	
19	3,4-Methylendioxo-N-methylphenethylamin	0 .5	
20	3,4-Methylendioxo-N-phenethylamin	0 .3	
21	4-Methoxy-2-pyrrolidinopropiophenon	1	
22	4-Methoxy-amphetamin (PMA)	0 .5	
23	4-Methyl-2- pyrrolidinopropiophenon (MPPP)	1	
24	Acebutolol	0.05	
25	Adenosin	0	
26	Ajmaline	0.5	
27	Alfentanil	1	
28	Alimemazine	1	
29	Alprazolam	0.95	(*43 - 45*)
30	Alprenolol	1	
31	Amantadine	0.5	
32	Amfebutamon	1	
33	Amfepramon	1	
34	Amfetaminil	1	
35	Amiodarone	0.95	
36	Amisulprid	0 .6	
37	Amitriptyline	1	(*46*)
38	Amitriptylin-Oxid	0 .1	
39	Amlodipine	1	
40	Amphetamine	0.5	(*47 - 55*)
41	Apomorphin	0 .8	
42	Aprindin	0 .95	
43	Articain	1	
44	Atenolol	0	
45	Atropine	0.6	
46	Azathioprine	0	
47	Azinphos-ethyl	1	
48	Azinphos-methyl	1	
49	Benperidol	1	
50	Benserazid	0	
51	Benzatropin	1	
52	Benzoylecgonine	0	

No.	Compound	Y^o	References
53	Betaxolol	1	
54	Biperidene	1	
55	Bisacodyl	0 .7	
56	Bisoprolol	0.9	
57	Bromazepam	0.9	
58	Bromocriptin	1	
59	Bromophos-ethyl	1	
60	Bromophos-methyl	1	
61	Bromperidol	1	
62	Brotizolam	1	
63	Budipine	1	
64	Bupivacaine	1	
65	Bupranolol	1	
66	Buprenorphine	1	
67	Buspiron	0.95	(56)
68	Caffein	0.3	
69	Carazolol	0.9	
70	Carbamazepine	0.95	
71	Carbamazepine-Epoxide	0.6	
72	Carbidopa	0	
73	Carteolol	0.06	
74	Carvedilol	1	
75	Cathin	0 .07	
76	Celiprolol	0 .1	
77	Chlordiazepoxide	0.95	
78	Chlormezanone	0.9	
79	Chloroquine	0.95	
80	Chlorovinphos	1	
81	Chlorpromazine	1	
82	Chlorprothixene	1	
83	Citalopram	1	(57)
84	Clobazam	1	
85	Clobutinol	1	
86	Clomethiazol	1	
87	Clomipramine	1	
88	Clonazepam	1	(58, 59)
89	Clopamid	0 .06	
90	Clopenthixol	1	
91	Clotiazepam	1	
92	Clozapine	1	(60)
93	Cocaine	1	(61- 64)
94	Codeine	0.8	(65)
95	Colchicin	0 .13	
96	Cotinine	0.1	(66)
97	Cyamemazin	1	
98	Deanol	0.4	
99	Demelverine	1	
100	Desipramine	1	(46)
101	Detajmium	0.9	
102	Dialifos	1	
103	Diazepam	0.95	(59,65,67)
104	Dibenzepine	1	
105	Dichlorovos	1	
106	Diclofenac	0.2	

No.	Compound	Y°	References
107	Dihydrocodeine	0.7	
108	Dihydroergocryptin	1	
109	Diltiazem	1	(68)
110	Dimethoate	0 .7	
111	Dimetindene	0.98	
112	Diphenhydramine	1	(65)
113	Disopyramide	0.8	(69)
114	Dosulepine	1	
115	Doxazosine	0.95	
116	Doxepine	1	(46,70,71)
117	Doxylamine	1	
118	Droperidol	0.9	
119	Enalapril	0	
120	Entacapon	0	
121	Ephedrine	0.2	
122	Esmolol	0.8	
123	Ethosuximide	0.2	
124	Etomidate	1	
125	Felodipin	0 .95	
126	Fenethylline	0.9	
127	Fenofos	1	
128	Fentanyl	1	(72 - 74)
129	Fenthion	1	
130	Flecainide	0.95	(75, 76)
131	Fluconazol	0 .1	
132	Flumazenil	0 .8	
133	Flunitrazepam	1	(59, 67)
134	Fluoxetine	0.8	(77, 78)
135	Flupentixol	1	
136	Fluphenazine	1	
137	Flupirtine	1	
138	Flurazepam	0.95	
139	Fluspirilen	0 .9	
140	Fluvoxamine	0.8	
141	Furosemide	0	
142	Gabapentin	0	
143	Gallopamil	1	
144	Gamma-hydroxybutyric acid	0	
145	Glibenclamid	0 .2	
146	Glutethimide	1	
147	Haloperidol	1	(79)
149	Heptenophos	0 .8	
148	Hydrochlorothiazide	0	
150	Hydromorphon	0 .1	
151	Hydroxyzin	1	
152	Ibuprofen	0	
153	Imipramine	1	(46)
154	Indomethacin	0	
155	Ipratropium	0	
156	Isofenphos	0 .95	
157	Kavain	0 .7	
158	Ketamine	1	
159	Lamotrigine	0.17	(80)
160	Levetiracetam	0	

No.	Compound	Y°	References
161	Levodopa	0	
162	Levomepromazine	1	
163	Lidocaine	1	
164	Lisinopril	0	
165	Lofepramin	0 .9	
166	Loprazolam	1	
167	Lorazepam	0.85	(44)
168	Lormetazepam	1	
169	Loxapine	1	
170	LSD	0.95	(81, 82)
171	Maprotiline	1	
172	MBDB	1	
173	MDA	0.6	(55,83)
174	MDEA	0.9	(55)
175	MDMA	0.7	(55, 83)
176	Medazepam	1	
177	Mefenorex	0.95	
178	Melperone	1	
179	Mepindolol	0.4	
180	Mepivacain	1	
181	Meprobamat	0 .1	
182	Meptazinol	0 .9	
183	Mesuximid	1	
184	Metamizol	0 .35	
185	Methadone	0.95	(84 - 86)
186	Methamphetamine	0.7	(47,48,50,52 - 54,87)
187	Methaqualone	1	(65,88)
188	Methohexital	0.95	
189	Methylphenidate	0.75	
190	Metixen	1	
191	Metoclopramide	0.9	
192	Metoprolol	0.8	(89)
193	Mevinphos	0 .9	
194	Mexiletine	0.9	(90, 91)
195	Mianserine	1	
196	Midazolam	0.9	(59,92, 93)
197	Mirtazapine	0.9	(94)
198	Moclobemide	0.9	(95)
199	Modafinil	0.35	
200	Morphine	0	
201	MTA	0 .6	
202	N-(1-Phenylcyclohexyl)-2-methoxy-ethylamin (PCMEA)	1	
203	N-(1-Phenylcyclohexyl)-3-ethoxy-propylamin (PCEPA)	1	
204	N-(1-Phenylcyclohexyl)-3-methoxy-propylamin (PCMPA)	1	
205	N-(1-Phenylcyclohexyl-1)-propylamin	1	
206	N,N-Diethyltryptamin	0 .95	
207	Nadolol	0	
208	Nalbuphine	0.8	
209	Nalorphin	0 .3	
210	Naloxon	0 .9	

No.	Compound	Y^o	References
211	Nefazodon	1	
212	Nefopam	0.95	
213	Nicotine	0.9	(66)
214	Nifedipin	1	
215	Nikotinamide	0	
216	Nimodipin	1	
217	Nisoldipin	1	
218	Nitrazepam	1	
219	N-Methyl-4-methoxy-amphetamin (PMMA)	0 .7	
220	Nordazepam	0.95	(44, 67)
221	Nortriptyline	1	(46, 96)
222	Noscapine	1	
223	Olanzapin	1	
224	Opipramol	1	
225	Orciprenaline	0	
226	Oxazepam	0.85	(59, 67)
227	Oxcarbazepine	0.9	
228	Oxitriptan	0	
229	Oxprenolol	0.9	
230	Oxycodone	0.95	
231	Paracetamol	0	
232	Paraoxon	0 .9	
233	Parathion ethyl	1	
234	Parathion methyl	1	
235	Paroxetine	1	(95, 97)
236	Pemoline	0	
237	Penbutolol	1	
238	Pentazocine	0.8	
239	Pentobarbital	0 .2	
240	Pentoxyverine	1	
241	Perazine	1	
242	Perphenazine	1	(98)
243	Pethidine	1	
244	Phenazone	0.35	
245	Phencyclidine	0.9	(99)
246	Phenobarbitone	0.1	
247	Phenolphthalein	0 .7	
248	Phenprocoumon	0.2	
249	Phenytoin	0.5	
250	Pholedrin	0	
251	Phosphamidon	0 .8	
252	Phoxim	1	
253	Pimozid	1	
254	Pindolol	0.4	
255	Pindolol	0 .2	
256	Pipamperone	1	
257	Pirimiphos	1	
258	Piritramid	0 .9	
259	Piroxicam	0	
260	Prajmaline	0.9	
261	Pramipexol	0	
262	Prazepam	1	
263	Prilocain	0 .95	
264	Primidone	0	

No.	Compound	Y^o	References
265	Procain	0 .9	
266	Procainamid	0 .1	
267	Procyclidin	1	
268	Promazine	1	
269	Promethazine	1	
270	Propafenon	0.95	
271	Propofol	0.95	
272	Propoxyphene	1	
273	Propranolol	1	
274	Propyphenazone	1	
275	Prothipendyl	0.95	
276	Pseudoephedrine	0.2	
277	Quetiapine	1	(100)
278	Quinidine	0.95	
279	Quinine	1	
280	Ranitidine	0	
281	Reboxetine	1	
282	Remifentanil	1	
283	Risperidon	1	
284	Ropivacain	1	
285	Salicylat	0	
286	Scopolamine	0.7	
287	Sertindol	1	
288	Sertraline	1	(101 - 103)
289	Sildenafil	1	
290	Sotalol	0	
291	Strychnine	0.9	(104)
292	Sulfentanil	1	
293	Sulfotep	1	
294	Sulpiride	0	
295	Sultiam	0	
296	Talinolol	0.2	
297	Temazepam	1	(67, 105)
298	Terbufos	1	
299	Tertatolol	1	
300	Tetrazepam	0.95	
301	Theobromin	0	
302	Theophylline	0	
303	Thiopental	0.9	(106)
304	Thioridazine	1	(107)
305	Tiagabin	0 .5	
306	Tiapride	0.4	
307	Ticlopidine	1	
308	Tilidine	1	
309	Timolol	0 .6	
310	Tocainide	0.3	
311	Tolperison	1	
312	Topiramat	0.2	
313	Tramadol	1	(108)
314	Tranylcypromine	1	(109, 110)
315	Trazodone	1	(111, 112)
316	Triazolam	1	(44, 45, 113)
317	Trichlorophos	1	
318	Trifluperidol	1	

No.	Compound	Y°	References
319	Triflupromazine	1	
320	Trihexyphenidyl	1	
321	Trimipramine	1	
322	Tryptophan	0	
323	Valproinsäure	0 .07	
324	Venlafaxine	0.95	(114 - 117)
325	Verapamil	1	(118 - 120)
326	Vigabatrin	0	
327	Viloxazine	0.85	
328	Zaleplon	1	
329	Ziprasidon	1	
330	Zolpidem	1	(121)
331	Zopiclon	0.9	(122)
332	Zotepine	0.95	
333	Zuclopenthixol	1	

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