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Experimental solubility profiling of marketed CNS drugs, exploring solubility limit of CNS discovery candidate

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ABSTRACT

We determined the experimental solubility of CNS marketed drugs. Of the 98 drugs measured, greater than 90% had solubility >10 μM in pH 7.4 buffer. Only seven drugs had solubility <10 μM. Using these data, we established a solubility criterion to support CNS discovery. The implication of poor solubility with potential safety concerns and undesirable side effects are discussed.

Kola and Landis (2004) pointed out that safety and the lack of efficacy have emerged as the major causes for drug attrition in 2000 compared to 1990.[1] In 2007, we were aware of two drugs that failed FDA approval: Bifeprunox for antipsychotic and Rimonabant for antiobesity indications. Bifeprunox[2] was not approved due to its lack of efficacy and Rimonabant[3] due to adverse events including CNS (central nervous system) side effects. Incidentally, both compounds are poorly soluble. Using solubility method described in the present Letter, the measured solubility of Bifeprunox is 2.3 μM in pH 7.4, and Rimonabant is 2.6 μM in pH 7.4. Poor solubility has emerged as the major concern in modern drug discovery and development. It has been estimated that the number of poorly soluble drugs entering development is around 40%.[4]

Producing compounds in tablet form for oral administration is the major objective in CNS discovery. For orally absorbed drugs, the compound needs to cross two biological barriers, the gastrointestinal barrier (GI) and the blood–brain barrier (BBB). The blood–brain barrier represents a major physical barrier for centrally active compounds due to its tight junction and efflux pumps. Adjusting dose and varying formulation using pH and excipients have been effective to affect dissolution and absorption across the GI. Once a drug formulation is optimized for GI absorption, crossing BBB could still be limited. This makes solubility an even more important attribute when designing orally active CNS compounds.

We would like to establish solubility criteria to help in the design and progression of our candidate drugs through project transitions. We were particularly interested in establishing a limit for poorly soluble compounds that would assist our projects in making go or no-go decisions. To reach this goal, we measured solubility of marketed CNS drugs extracted from three literature sources. The first source was the year 2000 top 500 drugs published by Med Ad News. The sales dollar ranged from $44 million to 2.6 billion.[5] The list represented both branded and generic drugs. The second source was Leeson and Davis's publication in J Med Chem which listed FDA approved drugs from year 1982 to 2002.[6] The list repre-

Table 1
Indications used to extract drugs from the Med Ad News table

Indications	Indications
Alzheimer disease	Narcolepsy
Anesthesia	Obesity
Anxiety disorders	Obsessive-compulsive disorder
Attention deficit hyperactivity disorder	Pain
Depression	Parkinson disease
Epilepsy	Partial seizures
Insomnia	Schizophrenia
Ischemic stroke	Seizure disorders
Migraine	

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Table 2
Data summary of measured solubility in pH 7.4 phosphate buffer

Entry	Name	Ion class	MW	*C* log *P*[a]	Solubility (μM)	Literature solubility[b]	Source
1	Quazepam	Neutral	387	3.2	0.30		J Med Chem
2	Alpidem	Neutral	404	5.58	0.75		J Med Chem
3	Araaipiprazole	Base	448	5.31	1.03		Med Ad News
4	Ziprasidone	Base	413	4.21	1.05	0.08 μg/mL[29]	Med Ad News
5	Pergolide	Base	315	4.4	2.10		J Med Chem
6	Metaclazepam	Neutral	394	4.26	3.52		J Med Chem
7	Nefazodone	Base	470	5.72	9.90		Med Ad News
8	(+)-Propoxyphene	Base	340	5.21	250		Med Ad News
9	Alprazolam	Neutral	309	2.56	213	40 mg/L, pH 7, water[30]	Med Ad News
10	Amisulpride	Base	370	1.8	>500		Med Ad News
11	Amphetamine	Base	135	1.74	>500		Med Ad News
12	Aniracetam	Neutral	219	0.72	500		J Med Chem
13	Atomoxetine	Base	255	3.94	>500		Med Ad News
14	Bromazepam	Neutral	316	1.7	334		Med Ad News
15	Bupivacaine	Base	288	3.69	352	0.42 mg/mL, pH 7.4, 37 °C[31]	Med Ad News
16	Bupropion	Base	240	3.21	328	10 mg/mL, pH 7.4 PBS, 25 °C[32]	Med Ad News
17	Buspirone	Base	386	2.18	>500		Med Ad News
18	Butorphanol	Neutral	327	3.5	>500		Med Ad News
19	Carbamazepine	Neutral	236	2.38	>490	17.7 mg/L, water[31]	Med Ad News
20	Citalopram	Base	324	3.13	>500		Med Ad News
21	Clomipramine	Base	315	5.92	395		Med Ad News
22	Clonazepam	Neutral	316	2.38	30.2	<0.1 mg/mL, water[31]	Med Ad News
23	Clorazepate	Acid	333	0.41	>495		Med Ad News
24	Clozapine	Base	327	3.71	>420		Med Ad News
25	Dexfenfluramine	Base	231	3.3	500		J Med Chem
26	Diazepam	Neutral	285	2.96	257	50 mg/L, water[31]	Med Ad News
27	Dihydroergotamine	Base	583	3.47	37.0		Med Ad News
28	Dolasetron	Base	324	2.34	195		J Med Chem
29	Donepezil	Base	380	4.6	429		Med Ad News
30	Dronabinol	Acid	226	−0.44	>500		J Med Chem
31	Duloxetine	Base	297	4.26	>500		FDA2004
32	Eletriptan	Base	383	3.36	>500		J Med Chem
33	Escitalopram				>500		Med Ad News
34	Etizolam	Neutral	343	2.87	>480		J Med Chem
35	Felbamate	Neutral	238	0.5	>500		J Med Chem
36	Fentanyl	Base	337	3.62	>500	0.74 mg/mL, pH 7.04, 35 °C[33]	Med Ad News
37	Flunitrazepam	Neutral	313	1.78	54.0		Med Ad News
38	Fluoxetine	Base	309	4.57	>500		Med Ad News
39	Flupirtine	Neutral	304	3.05	>500		J Med Chem
40	Fluvoxamine	Base	318	3.32	>500		Med Ad News
41	Gabapentin	Zwitterion	171	−0.66	>500	440.6 μg/mL, pH 7.4, 32 °C[34]	Med Ad News
42	Granisetron	Base	312	1.72	>500		J Med Chem
43	Hydromorphone	Neutral	284	0.49	>500		Med Ad News
44	Ibuprofen	Acid	206	3.68	>500	6.02 mg/mL, pH 7.4 PBS, 37 °C[35]	Med Ad News
45	Idebenone	Neutral	338	3.42	16.0	23.6 μM, water, 25 °C[36]	J Med Chem
46	Ketorolac	Acid	255	1.62	>459		Med Ad News
47	Lamotrigine	Neutral	256	2.53	307	0.48 mg/mL, pH 7.4, McIlvaine buffer[37]	Med Ad News
48	Levetiracetam	Neutral	170	−0.34	>500	1 g/mL, water[38]	Med Ad News
49	Levodropropizine	Base	236	1.34	>500		J Med Chem
50	Lidocaine	Base	234	1.95	>407	6.62 mM, pH 7.4, 37 °C[39]	Med Ad News
51	Lorazepam	Neutral	321	2.37	24	0.08 mg/mL, water[31]	Med Ad News
52	Meptazinol	Base	233	3.71	>500		J Med Chem
53	Methylphenidate	Base	233	2.56	411		Med Ad News
54	Midazolam	Neutral	326	3.42	392	0.055 mg/mL, pH 7.95[40]	Med Ad News
55	Milnacipran	Base	246	1.91	>500		J Med Chem
56	Mirtazapine	Base	265	2.81	>500		Med Ad News
57	Moclobemide	Base	269	2.17	>500		Med Ad News
58	Modafinil	Neutral	273	0.94	>500		Med Ad News
59	Morphine	Base	285	0.57	>500	2 mg/mL, pH 7.13, 35 °C[34]	Med Ad News
60	Naltrexone	Base	341	0.36	>500		J Med Chem
61	Naratriptan	Base	336	1.7	>500		Med Ad News
62	Olanzapine	Base	312	3.01	>500		Med Ad News
63	Ondansetron	Base	293	2.72	120		Med Ad News
64	Oxcarbazepine	Neutral	252	1.21	245	308 mg/L at 25 °C, water[31]	Med Ad News
65	Paroxetine	Base	329	4.24	>500		Med Ad News
66	Phenytoin	Neutral	252	2.08	80.0	32 mg/L, water[31]	Med Ad News
67	Pramipexole	Base	211	1.17	>500	>10 mg/mL, pH 7.4[41]	Med Ad News
68	Progabide	Acid	335	2.9	55.2		J Med Chem
69	Quetiapine	Base	384	2.99	310		Med Ad News
70	Reboxetine	Base	313	3.26	>500		J Med Chem
71	Remoxipride	Base	371	3.25	>500		J Med Chem
72	Riluzole	Neutral	234	3.24	>500		J Med Chem
73	Risperidone	Base	411	2.71	>444		Med Ad News
74	Rizatriptan	Base	269	1.18	>500		Med Ad News

(*continued on next page*)

Table 2 (*continued*)

Entry	Name	Ion class	MW	*C* log *P*[a]	Solubility (μM)	Literature solubility[b]	Source
75	Ropinirole	Base	260	2.8	>500		Med Ad News
76	*S*-(−)-Carbidopa	Acid	226	−0.44	>500		Med Ad News
77	Sertindole	Base	441	5.27	18.1		J Med Chem
78	Sertraline	Base	306	5.35	350		Med Ad News
79	Sibutramine	Base	280	5.59	143		Med Ad News
80	Sulpiride	Base	341	1.11	>500		Med Ad News
81	Sumatriptan	Base	295	0.74	>500		Med Ad News
82	Tacrine	Neutral	198	3.27	>500	217 mg/L, water[31]	J Med Chem
83	Talipexole	Base	209	1.14	133		J Med Chem
84	Tiagabine	Zwitterion	376	2.78	>500		Med Ad News
85	Tianeptine	Zwitterion	437	1.52	500		J Med Chem
86	Tizanidine	Base	254	2.09	>500	18.25 mg/mL, pH 7.2[42]	J Med Chem
87	Tolcapone	Acid	273	3.24	>500	115 μg/mL, pH 7.4[43]	J Med Chem
88	Topiramate	Neutral	339	0.04	>500	9.8 mg/mL, water[31]	Med Ad News
89	Tramadol	Base	263	3.1	>500		Med Ad News
90	Triazolam	Neutral	343	2.62	35.9		Med Ad News
91	Tropisetron	Base	284	2.88	>500		J Med Chem
92	Valproate	Acid	144	2.76	>500		Med Ad News
93	Venlafaxine	Base	277	3.27	>500		Med Ad News
94	Vigabatrin	Zwitterion	129	−2.22	>500		Med Ad News
95	Zolmitriptan	Base	287	1.29	>500		Med Ad News
96	Zolpidem	Neutral	307	3.03	260	>250 μM, pH 7.4[44]	Med Ad News
97	Zonisamide	Neutral	212	−0.36	>500		J Med Chem
98	Zopiclone	Base	389	1.25	219		Med Ad News
99	Almotriptan	Base	336	1.79	na		J Med Chem
100	Brotizolam	Neutral	394	2.71	na		J Med Chem
101	Budipine	Base	294	5.58	na		J Med Chem
102	Cabergoline	Base	452	4.17	na		J Med Chem
103	Cimetropium	Cationic	359	−1.5	na		J Med Chem
104	Disoprofol	Neutral	178	3.93	Inhaler		Med Ad News
105	Entacapone	Acid	305	1.76	na		J Med Chem
106	Ethylether	Neutral	200	1.45	Inhaler		Med Ad News
107	Frovatriptan	Base	243	0.72	na		J Med Chem
108	Loprazolam	Base	465	0.89	na		J Med Chem
109	Rivastigmine	Base	250	2.1	na		Med Ad News
110	Tandospirone	Base	384	1.9	na		J Med Chem
111	Tiropramide	Base	468	5.36	na		J Med Chem
112	Zaleplon	Neutral	305	1.44	na		Med Ad News

Poorly soluble drugs having solubility <10 μM are listed on the top of the table. Drugs that are not available (na) are listed at the bottom of the table. The remaining drugs are listed in alphabetical order.

[a] *C* log *P* was calculated using V. 4.3.

[b] Literature solubility data is included for reference only. In most cases, the literature experimental conditions deviate from the present measurement condition.

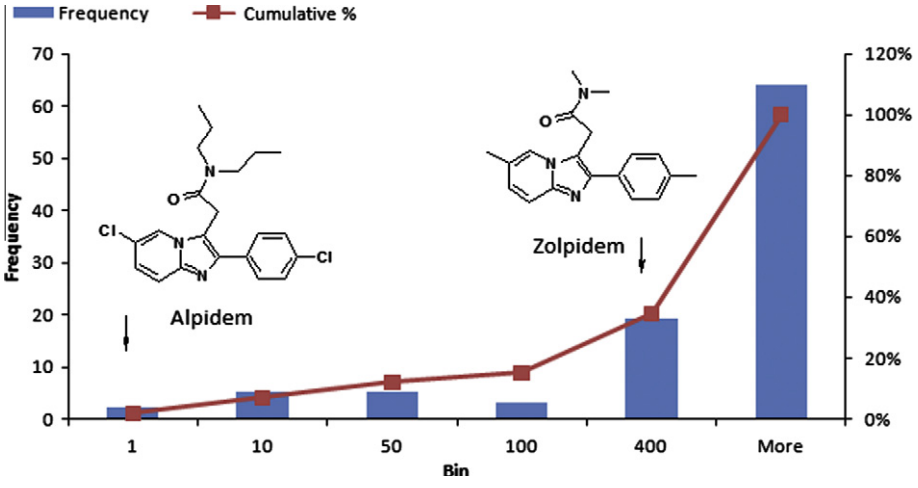

Figure 1. Histogram of measured solubility of CNS marketed drugs in pH 7.4.

sented both successful and withdrawn drugs. The third source was the year 2004 top 200 drugs published in Med Ad News.[7] The list included recently approved drugs. Using CNS indications listed in Table 1, we extracted 112 CNS drugs to be profiled (Table 2). Of the 112 drugs, we measured solubility for 98 drugs. Two analgesia drugs, ethylether and disoprofol administrated through inhalation, were not measured. Twelve of the drugs were not commercially available, 10 of them were not listed in Med Ad News. Note that the exact mechanism of action either central or peripheral is not always fully understood, since receptors responsible for biological

response are often expressed at both peripheral and central sites. Therefore our list may include drugs that act peripherally instead of centrally. The list also does not include drugs outside the indications listed in Table 1 but their mechanism of action is in fact central.

Solubility was determined by suspending ~600 μM compound in 0.1 M phosphate buffer at pH 7.4 at 25 °C for 24 h using either solid method or dried-DMSO method. The solid method used dry powder as the starting material. The dried-DMSO method used liquid DMSO compound stock and dried down before addition of buffer. The solution was centrifuged and the supernatant was qualified by LC/UV and LC/MS/MS. Experimental details including sample preparation, method validation, and data interpretation have been described in our recent publication.[8]

Results indicated that the majority of CNS drugs are highly soluble (Table 2). Greater than 85% of the drugs have solubility >100 μM; greater than 90% drugs have solubility >10 μM (Fig. 1). There are only seven drugs with solubility <10 μM; including two drugs with solubility <1 μM. For the seven, alpidem was not approved,[9] pergolide was withdrawn,[10] and nefazodone was discontinued.[11] The insomnia drugs, quazepam, and metaclazepam, were not on the top sales list.[5] Ziprasidone and aripiprazole introduced after year 2000 have been successful and both were in 2004 Top 200 drug list.[7] But when tested using IonWorks in vitro herg assay,[12] an in vitro assay in early drug discovery for cardiovascular risk, both compounds were potent herg inhibitors with IC_{50} values <1 μM.[13,14] Incidentally, both drugs have black box warnings including cardiovascular warnings.[15,16] We consider candidate drugs with herg values less than 1 μM as high risk and would likely be deprioritized and deselected from further advancement. In short, all seven drugs with solubility <10 μM are either dropped out of market or facing potential liabilities.

In potency driven discovery, poor solubility alone does not necessarily hold a compound's progression into development as evidenced by the large number of poorly soluble compounds moving into development. Poor solubility is generally considered a formulation problem. Only when a suitable formulation could not be found for the compound, its progression in development will be stopped or delayed. Direct correlation of poor solubility with potential safety and side effects are not widely discussed.

There is large literature data relating lipophilicity with safety and undesirable side effects. In drug discovery, high lipophilicity is linked to undesirable ADMET (absorption, disposition, metabolism, excretion, and toxicity) properties, including poor solubility,[17] poor bioavailability,[18] high protein binding,[19] high affinity to microsomes and hepatocytes,[20,21] and in vivo toxicological observations.[22] In marketed drugs, when comparing the toxicity profiles for the same disease indication based on the same target and mechanism, the class side effects are typically more pronounced in the more highly lipophilic congeners. For example, the statin family of drugs for lowering cholesterol carries the same side effects including toxic myopathy, which 'ranges from asymptomatic creatine kinase elevations or myalgias to muscle necrosis and fatal rhabdomyolysis'.[23] Among the five drug studied,[24] the most lipophilic statin, cerivastatin ($\log D_7 = 2.32$[24]) marketed as Baycol, is reported to have had the highest incidence of rhabdomyolysis resulting in its withdrawal post marketing.[25] The less lipophilic atorvastatin ($\log D_7 = 1.53$[24]), marketed as Lipitor, continued to be widely prescribed.

The relationship of lipophilicity with biochemical processes can be explained based on the classical Michaelis–Menten kinetics (Eq. 1).[26] According to the equation, for a biochemical process to occur, the substrate (S) first interacts reversibly with enzyme (E) to form a substrate–enzyme intermediate (ES). The intermediate then undergoes irreversible enzyme catalyzed reaction to form the product (P). High lipophilic compounds, by definition, having high affinity to membranes and receptors compare to hydrophilic compounds, can favor the enzymatic reaction by shifting the equilibrium toward the ES complex.

$$E + S \rightleftarrows ES \rightarrow E + P \quad (1)$$

Consequently, one can relate solubility with safety through its relationship with lipophilicity based on Yalkowsky's solubility equation (Eq. 2).[27] The equation states that two factors, a lipophilicity term ($C \log P$) and a melting point term (mp, often expressed in terms of crystallinity), are the major contributors to solubility ($\log S_w$). Increasing lipophilicity and/or increasing crystallinity result in decreased solubility. One example is insomnia drugs. Comparing the highly soluble zolpidem (260 μM in pH 7.4) with poorly soluble alpidem (0.1 μM in pH 7.4), zolpidem is not toxic and was the number one prescribed drug in the class in year 2004.[7] Alpidem is toxic and was not approved.[9] Developing compounds with better solubility than those either on the market or in development has been commonly used in fast follow up projects.

$$\log S_w = 0.5 - C \log P - 0.01(\mathrm{mp} - 25^\circ\mathrm{C}) \quad (2)$$

Yalkowsky's equation also relates high crystallinity with poor solubility. It is possible to formulate a drug candidate such that its initial free plasma concentration in the systemic circulation is higher than its equilibrium solubility. Drug precipitation in vital organs would raise safety concerns. For example, in preclinical toxicity studies, observations of drug's precipitation in lung or kidney would most likely result in its discontinuation. The recent infant milk episode was another example of toxicity stemming from precipitation. In that case, the milk was adulterated with melamine to increase nitrogen count in analysis, precipitation in kidney from melamine and cyanuric acid co-crystals resulted in kidney failure.[28]

The present solubility profiling of marketed drugs presented two cut offs, 1 μM and 10 μM, that can be used to guide CNS discovery. We believe that when the measured solubility is <1 μM, the compound is unlikely to become a CNS drug. Projects are recommended to deprioritize the compound from further in vitro and in vivo studies unless it is used to build SAR (structure–activity relationships). We also believe that when the measured solubility is <10 μM, there are high risks associated with the compound's advancement. The risks are two folds: (1) potential toxicity and side effect profiles that are not realized in preclinical or clinical studies and (2) market competition. The risk of market competition is the result of multiple companies working on the same biological targets. Advancing a poorly soluble drug by one company runs the risk of being outperformed by a more soluble drug from a competitor with implied better safety profiles. Our solubility guidelines coupled with CNS specific structural design including molecular weight, $C \log P$, polar surface area, and the number of hydrogen bond donors has resulted in a drastic reduction of poorly soluble compounds synthesized.[8] In conclusion, we believe maximizing solubility in CNS discovery is essential to secure future market success.

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