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Supporting information for article:

The effective volumes of waters of crystallization: non-ionic pharmaceutical systems

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Table S1: Volumetric data for 29 non-ionic pharmaceuticals and their hydrates. Columns: V_m/Å^3, parent formula unit volume; **value in bold** = mean formula unit volume of parent, with outliers in *red italics* ignored. V(H_2O)/Å^3: effective volume of water of crystallization per molecule, with outliers in *red italics* ignored. V(H_2O)/Å^3, effective volume of water of crystallization per molecule. Penultimate column: mean effective volume of water of crystallization per molecule. Final column: individual values of V(H_2O)/Å^3: see main text Figure 2 for histogram.

name	parent	hydrate	CSD Refcode	polymorph	V_m/Å^3	V(H_2O) /Å^3
Acemetacin	1	0	FEPJOB	II	481.58	
	1	0	FEPJOB01	I	470.81	
					476.20	
	1	1	CIJYUQ		496.72	20.52
Acyclovir	1	0	MECWIC	II	230.83	
	1	0	MECWIC01	II	235.30	
	1	0	MECWIC02	I	241.60	
	1	0	MECWIC03	I	243.04	
	1	0	MECWIC04	II	227.36	
					235.62	
	1	2	WOZPAE		285.62	23.96
	1	2	WOZPAE01		283.00	22.65
	3	2	CEHTAK10		770.10	28.51
Ampicillin	1	0	AMCILL		419.75	
	1	0	AMCILL01		412.23	
					415.99	
	1	3	AMPCIH		487.36	23.79
	1	3	AMPCIH01		490.15	24.72
Azathioprine	1	0	CIPWUT		277.44	
	1	0	CIPWUT01		282.02	
					279.73	
	1	2			342.75	*31.51*
Calcipotriol	1	0	MIJXUA		**591.02**	
	1	1	WACHIR		610.14	19.11
Carbamazepine	1	0	CBMZPN01		**291.34**	
(many files)	1	2	FEFNOT02		339.07	23.87

Cholesterol	1	0	CHOEST20		629.10	
(many files)	1	0	CHOEST01		634.45	
	1	1	CHOLES20		641.02	9.25
					631.77	
	1	1	CHOLES02		659.93	28.16
	1	1	CHOLES05		657.54	25.77
Colchicine	1	0	ISCHOL	iso	**518.21**	
	1	1	PALYOQ		541.46	23.26
	1	2	COLCDH		560.45	21.12
Cyclophosphamide	1	0	CLEOZP		302.27	
	1	0	CLEOZP01		302.67	
	1	0	CYPHAM		304.91	
					303.28	
	1	1	CETMPA01		323.49	20.21
	1	1	CETMPA10		323.17	19.89
Fluconazole	1	0	IVUQOF01		350.64	
	1	0	IVUQOF02		339.11	
	1	0	IVUQOF03	VI	341.73	
	1	0	IVUQOF04		366.74	
	1	0	IVUQOF05		366.84	
					353.01	
	1	1	IVUQIZ		378.34	25.33
	1	1	IVUQIZ01		366.74	13.73
Flurbiprofen	*1*	*0*	*FLUBIP*		*315.36*	
	1	0	YACZIO	R-	310.16	
	1	0	YACZIO01	R-	300.05	
	1	0	FLUBIP01	I	303.75	
	1	0	FLUBIP02	I	307.82	
	1	0	FLUBIP03	III	305.73	
					305.50	
	1	0.67	NIMRUX		319.89	21.59
Lactitol	1	0	YADSOL		**364.55**	
	1	1	JEXZER		394.47	29.93
	1	2	VPKUA		436.72	*36.09*
	1	2	VPKUA01		436.65	*36.05*
	1	3	SUGBF		449.95	28.47
Mannitol	1	0	DMANTL		203.41	
(many files)	1	0	DMANTL01		205.62	

					204.52	
	1	0.5	MAFSUI		218.74	28.45
Mercaptopurine	1	0	RAKSIG		**160.16**	
	1	1	MERPUM		179.22	19.06
	1	1	MERPUM01		179.01	18.85
	1	3	MMCPUR		254.56	*31.47*
Nevirapine	1	0	PABHIJ		**317.50**	
(see commentary)	1	0	PABHIJ01		*309.63*	
	1	0.5	TISJAH		347.05	*59.10*
	1	0.5	TISJAH01		337.68	*40.36*
Norfloxacin	1	0	VETVOG		364.22	
	1	0	VETVOG01		*399.42*	
	1	0	VETVOG03		356.17	
					360.19	
	1	1.125	COTZIV		387.61	24.37
	1	1.25	CONYIO		392.65	25.97
	1	1.5	PUZGAT		407.54	31.57
	1	1.5	PUZGAT01		399.42	26.15
Olanzapine	1	0	UNOGIN	I	400.22	
	1	0	UNOGIN01	I	399.44	
	1	0	UNOGIN03	I	388.90	
	1	0	UNOGIN02	II	405.69	
	1	0	UNOGIN04	II	396.72	
	1	0	UNOGIN05	IV	*417.82*	
					398.19	
	1	2	AQOMAU01	IB	450.70	26.26
	1	2	AQOMAU03	IB	448.16	24.98
	1	2	AQOMAU	ID	442.00	21.90
	1	2	AQOMAU02	IE	*467.04*	
	1	2.5	AQOMEY		469.65	28.58
	1	2.5	AQOMEY01		469.54	28.54
	1	2.5	AQOMEY02		461.92	25.49
Paracetamol	1	0	COTZAN06		188.59	
(many files)	1	0	HEXACAN01		194.07	
	1	0	HEXACAN13		185.29	
					189.32	
	1	1	HUMJEE		201.05	11.73
	1	2	WAFNAT		213.57	12.13
	1	3	XOMWOL		261.21	23.96

Phenobarbital	1	0	PHBARB	III	283.66	
(many files)	1	0	PHBARB01	I	285.14	
					284.40	
	1	1	PHBARBM		300.29	15.89
Piracetam	1	0	BISMEV		174.26	
(many files)	1	0	BISMEV01		172.82	
					173.54	
	1	1	YAKWAJ		198.12	24.58
	1	2	LIFNOE		207.49	16.97
Praziquantel	1	0	TELCEU		415.03	
	1	0	TELCEU01		421.25	
					418.14	
	1	0.25	LIVFED		*410.33*	
	1	0.5	SIGBUG		425.94	15.61
	1	0.5	SIGBUG01		426.76	17.23
Prednisolone	1	0	JIWPEL	II	449.73	
	1	0	JIWPEL01	I	448.56	
					449.14	
	1	1.5	JIWPIP		487.97	25.88
Rifampicin	1	0	LOPZEX		**1108.20**	
	1	5	HAXWUA		1188.89	16.14
	1	5	RIFAMP		1209.11	20.18
Sorbitol	1	0	DMANTL14		199.82	
	1	0	GLUCIT		196.40	
	1	0	GLUCIT02		200.89	
					199.04	
	1	0.67	HIPKAS		221.00	*32.95*
Sulfaguanidine	1	0	ZZZAYP		242.94	
	1	0	ZZZAYP01		*218.29*	
	1	0	ZZZAYP02		238.73	
					240.83	
	1	1	SOGUAN01		254.87	14.04
Testosterone	1	0	TESTON01		408.28	
	1	0	TESTON10		406.88	
					407.58	
	1	1	TESTOM03		431.65	24.08

	1	1	TESTOM		430.38	22.81
	1	1	TESTOM01		431.96	24.38
	1	1	TESTOM02		431.54	23.96
Zopiclone	1	0	CUHNEY		440.50	
	1	0	CUHNEY10		447.38	
					443.94	
	1	2	UCUVET		468.65	12.36
	1	2	UCUVET01		482.18	19.12
Aspartame	1	0	KETXIR		**375.42**	
	1	0.5	DAWGOX		384.62	18.40
	1	*0.67*	*ODOBAK*		*373.53*	
	1	*2.67*	*EFIFOO*		*330.83*	
	3	*5 or 6*	*EFIFOO01*		*330.83*	
Ephedrine	*1*	*0*	*EPHEDR*		*253.83*	*???*
	1	*0*	*EPHEDR01*		*246.19*	
	1	*0.5*	*EPHEDH*		*203.15*	*???*
	1	*0.5*	*EPHEDH01*		*254.48*	
	1	*0.5*	*EPHEDH02*		*246.11*	
	1	*0.5*	*EPHEDH03*		*245.15*	

Table S2: Mean parent formula volume and mean effective volume of waters of crystallisation for 27 non-ionic pharmaceutical hydrate/parent pairs and water. Volume estimates by the Hofmann[1] density method are compared. Large positive differences for sugars (Lactitol, Mannitol, Sorbitol) are noticeable. Correlations plotted in Fig. S1.

Pharmaceutical Hydrates	**Mean V_m(parent) / Å^3**	**V(H_2O) / Å^3**	**Formula**	**Hofmann[1] V_m(parent) / Å^3**	**% diff.**
Acemetacin	476.20	20.52	$C_{21}H_{18}ClNO_6$	488.65	2.6
Acyclovir	235.62	21.50	$C_8H_{11}N_5O_2$	248.62	5.5
Ampicillin	415.99	24.26	$C_{16}H_{19}N_3O_4S$	424.6	2.1
Aspartame	375.42	18.40	$C_{14}H_{18}N_2O_5$	366.17	-2.5
Azathioprine	284.70	29.03	$C_9H_7N_7O_2S$	290.97	2.2
Calcipotriol	591.02	19.11	$C_{27}H_{40}O_3$	611.86	3.5
Carbamazepine	291.34	23.87	$C_{15}H_{12}N_2O$	304	4.3
Cholesterol	631.77	21.06	$C_{27}H_{40}O$	589.08	-6.8
Colchicine	518.21	22.19	$C_{22}H_{25}NO_6$	512.28	-1.1
Cyclophosphamide	303.28	20.05	$C_7H_{15}Cl_2N_2O_2P$	300.77	-0.8
Fluconazole	353.01	19.53	$C_{13}H_{12}F_2N_6O$	345.8	-2.0
Flurbiprofen	305.50	21.59	$C_{15}H_{13}FO_2$	308.04	0.8
Lactitol	364.55	29.20	$C_{12}H_{24}O_{11}$	413.65	13.5
Mannitol	204.52	28.45	$C_6H_{14}O_6$	222.68	8.9
Mercaptopurine	160.16	19.06	$C_5H_4N_4S$	162.07	1.2
Nevirapine	317.50	24.87	$C_{15}H_{14}N_4O$	337.76	6.4
Norfloxacin	360.19	27.01	$C_{16}H_{18}FN_3O_3$	394.1	9.4
Olanzapine	398.19	25.96	$C_{17}H_{20}N_4S$	409.79	2.9
Paracetamol	189.32	15.94	$C_8H_9NO_2$	191.26	1.0
Phenobarbital	284.40	15.89	$C_{12}H_{12}N_2O_3$	285.17	0.3
Piracetam	173.54	20.78	$C_6H_{10}N_2O_2$	180.4	4.0
Praziquantel	418.14	16.42	$C_{19}H_{24}N_2O_2$	431.83	3.3
Prednisolone	449.14	25.88	$C_{21}H_{28}O_5$	490.46	9.2
Rifampicin	1108.20	18.16	$C_{43}H_{58}N_4O_{12}$	1074.93	-3.0
Sorbitol	199.04	32.95	$C_6H_{14}O_6$	222.68	11.9
Sulfaguanidine	240.83	14.04	$C_7H_{10}N_4O_2S$	243.07	0.9
Testosterone	407.58	23.71	$C_{19}H_{28}O_2$	428.55	5.1
Zopiclone	443.94	15.74	$C_{17}H_{17}ClN_6O_3$	452.92	2.0
Water	21.93	21.93	H_2O	21.55	0.98

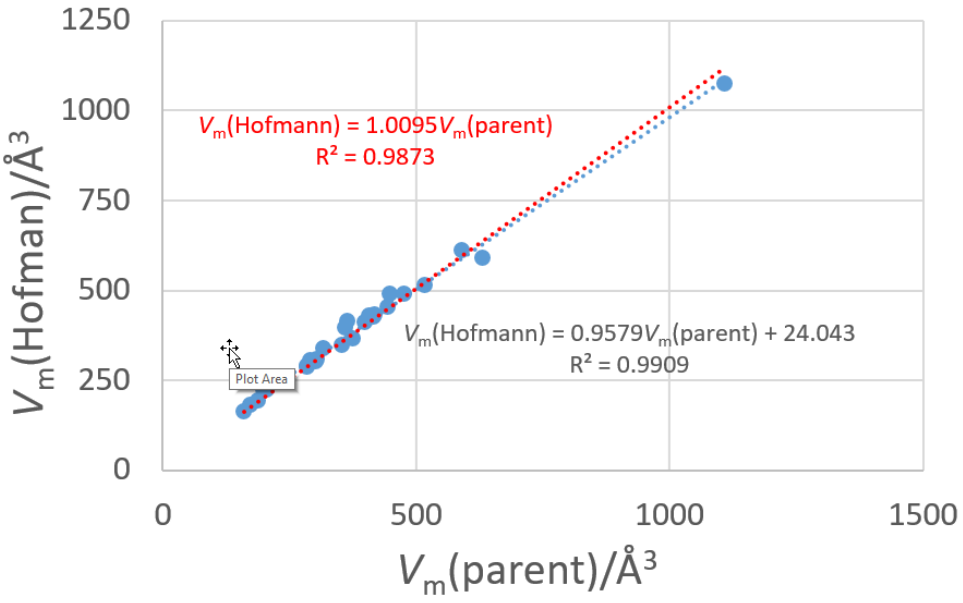


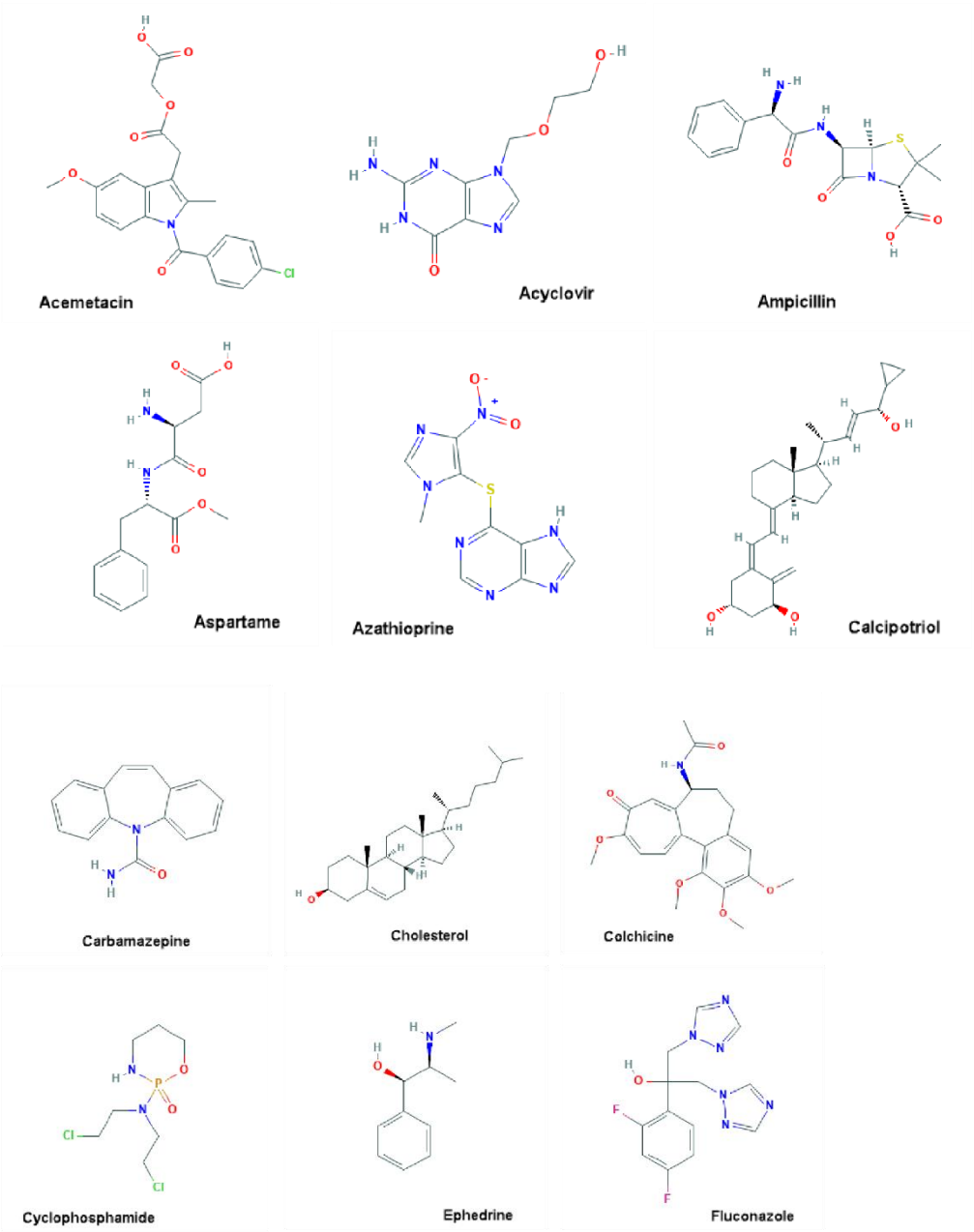
Figure S1: Plot of calculated formula volume[1] versus formula volumes from CSD database. See Table S2. Trendline in red constrained to pass through the origin.

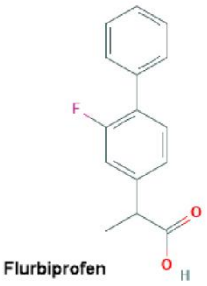
Table S3: Paracetamol formula unit volumes from 47 CSD datafiles, for 3 polymorphs and temperatures from 20 to 360 K. Values in *red italics* are outliers. See Figure 1.

CSD Refcode	Space Group	V_m/Å^3	polymorph	T/K
HXACAN12	$P2_1/n$	*155.47*	I	295
HXACAN11	$P2_1/n$	*162.84*	I	295
HXACAN10	$P2_1/n$	*168.00*	I	295
HXACAN09	$P2_1/n$	*177.93*	I	295
HXACAN43	$P2_1/n$	*152.82*	I	293
HXACAN13	$P2_1/a$	185.29	I	20
HXACAN36	$P2_1/n$	185.78	I	20
HXACAN14	$P2_1/a$	185.89	I	50
HXACAN15	$P2_1/a$	186.06	I	80
HXACAN28	$P2_1/n$	186.06	I	85
HXACAN30	$P2_1/n$	187.60	I	100
HXACAN27	$P2_1/n$	187.75	I	100
HXACAN06	$P2_1/a$	188.63	I	100
HXACAN07	$P2_1/n$	188.49	I	123
HXACAN16	$P2_1/a$	188.40	I	150
HXACAN04	$P2_1/n$	189.77	I	150
HXACAN17	$P2_1/a$	189.95	I	200
HXACAN18	$P2_1/a$	190.98	I	250
HXACAN35	$P2_1/n$	190.56	I	293
HXACAN20	$P2_1/n$	189.77	I	295
HXACAN26	$P2_1/a$	193.35	I	295
HXACAN02	$P2_1/c$	193.37	I	295
HXACAN03	$P2_1/n$	193.72	I	295
HXACAN01	$P2_1/a$	194.07	I	295
HXACAN05	$P2_1/a$	196.03	I	295
HXACAN34	$P2_1/n$	193.57	I	298
HXACAN19	$P2_1/a$	192.63	I	330
HXACAN37	Pbca	180.14	II	20
HXACAN31	Pbca	181.48	II	100
HXACAN38	Pbca	181.67	II	100
HXACAN32	Pcab	182.03	II	100
HXACAN21	Pcab	182.17	II	100
HXACAN41/42	Pcab	182.43	II	100
HXACAN08	Pbca	182.25	II	123
HXACAN22	Pcab	184.78	II	200

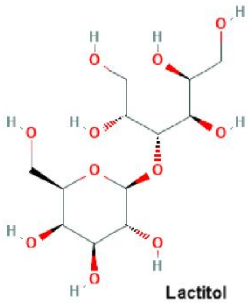
HXACAN25	Pbca	183.26	II	220
HXACAN33	Pbca	187.52	II	293
HXACAN	Pcab	187.25	II	295
HXACAN44	Pbca	183.99	II	296
HXACAN45	Pbca	187.19	II	296
HXACAN46	Pbca	187.50	II	296
HXACAN23	Pcab	188.06	II	300
HXACAN24	Pcab	190.14	II	360
HXACAN29	$Pca2_1$	187.68	III	300
HXACAN39	Pc11	181.87	III-m	100
HXACAN40	$Pca2_1$	187.89	III-o	293

Table S4: Structures of Parents of Pharmaceutical Hydrates[2]

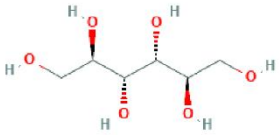




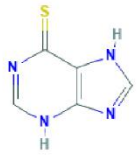
Flurbiprofen



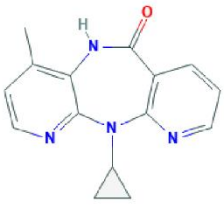
Lactitol



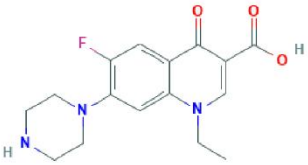
Mannitol



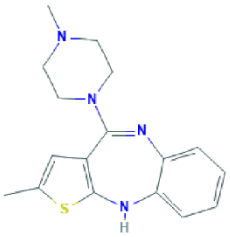
Mercaptopurine



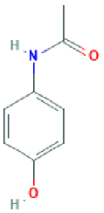
Nevirapine



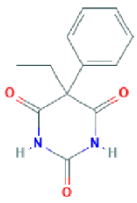
Norfloxacin



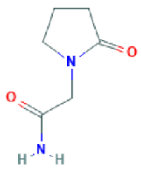
Olanzapine



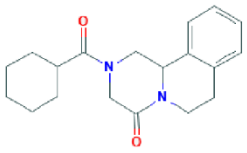
Paracetamol Acetaminophen



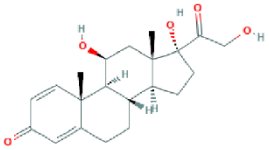
Phenobarbital



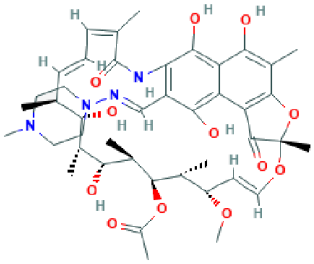
Piracetam



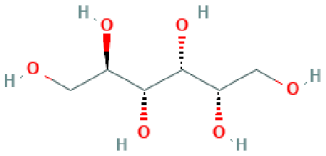
Praziquantel



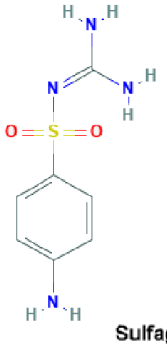
Prednisolone



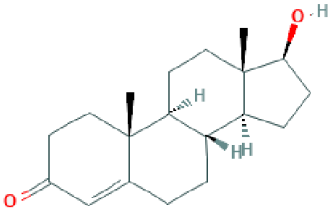
Rifampicin



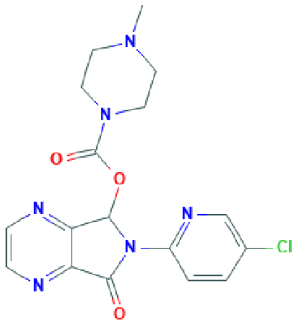
Sorbitol



Sulfaguanidine



Testosterone



Zopiclone

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