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Use of prediction methods to estimate true density of active pharmaceutical ingredients

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Abstract

True density is a fundamental and important property of active pharmaceutical ingredients (APIs). Using prediction methods to estimate the API true density can be very beneficial in pharmaceutical research and development, especially when experimental measurements cannot be made due to lack of material or sample handling restrictions. In this paper, two empirical prediction methods developed by Girolami and Immirzi and Perini were used to estimate the true density of APIs, and the estimation results were compared with experimentally measured values by helium pycnometry. The Girolami method is simple and can be used for both liquids and solids. For the tested APIs, the Girolami method had a maximum error of −12.7% and an average percent error of −3.0% with a 95% CI of (−3.8, −2.3%). The Immirzi and Perini method is more involved and is mainly used for solid crystals. In general, it gives better predictions than the Girolami method. For the tested APIs, the Immirzi and Perini method had a maximum error of 9.6% and an average percent error of 0.9% with a 95% CI of (0.3, 1.6%).

Keywords: Density; Prediction; Active pharmaceutical ingredient; Helium pycnometry; Mathematical model

1. Introduction

The true density refers to mass of solid material divided by its exact volume without porosity. The true density is an important parameter in pharmaceutical research into the behavior of pharmaceutical solids. For example, it plays a critical role in determination of powder porosity (Sun, 2005a), particle mechanical properties (Heckel, 1961; Sun, 2005b), powder fluidization (Hedden et al., 2006) and suspension settling (Geng and Kuznetsov, 2005). These influences can be directly related to formulation development of solid or suspension dosage forms.

Although density data can be found in references for many compounds, it is unavailable for compounds that are newly synthesized during pharmaceutical research and development. Previous studies have shown that measurements from helium pycnometry can give the closest approximation to the true density (Viana et al., 2002). However, sometimes such measurements may not be conducted due to lack of the material or because the compound is very potent and has handling restrictions. Additionally, helium pycnometry has its limitations when used for channel hydrates and other systems containing loosely bound solvents because the volatile water or solvents will alter the helium pressure and introduce measurement errors (Sun, 2004). In these cases, density prediction methods may be very helpful. If the predictions give reasonably accurate results, they may be very beneficial to pharmaceutical research and development to save time and material.

There are various methods for density prediction or calculation that have been previously reviewed (Lyman et al., 1990; Piacenza et al., 2002). Some methods, such as Fedors (1974), Exner (1967), Girolami (1994) and Stine (1981), used atomic or group increment procedures to obtain molar volume of a molecule. Other methods, such as Kitaigorodski (1973), Cady (1979) and Immirzi and Perini (1977), considered volume contributions not only from the molar volume by group increments but also from the free space due to crystal packing. Additionally, the true density for crystals can be calculated based on their crystal structures determined by X-ray crystallography (Richards and Lindley, 2006), but this procedure is not common because X-ray crystallography is not a routine technique. Different methods may apply to different classes of compounds and exhibit different complexity, accuracy and limitation. In this paper, for

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practical applications, we choose two prediction methods, Girolami and Immirzi and Perini, and describe how to use them to estimate the true density of active pharmaceutical ingredients (APIs) based on their molecular weight, formula or bonding structure.

2. Materials and methods

2.1. Materials

The APIs discussed in this paper included Pfizer compounds synthesized over a few decades. A total of 83 APIs were tested to evaluate the performance of the prediction methods. Although the exact structures of the compounds are not disclosed, the majority of compounds have "the rule of 5" characteristics (Lipinski et al., 1997). The category and molecular weights of the tested APIs are listed in Table 1, including 41 free forms and 42 salts/hydrates of 14 different kinds with molecular weights from 179 to 1029.

2.2. Methods

2.2.1. Helium pycnometry

Experimental density values of the Pfizer APIs were measured using a Micromeritics AccuPyc 1330 helium pycnometer (Norcross, GA, USA). Helium pycnometry is the most commonly used method to give the closest measurements for powder true density. In this method, the difference in helium pressure before and after loading sample is measured to calculate the sample volume. Helium penetrates into smallest pores and crevices and permits to approach the real volume of the sample. During the test, the helium pressure was set to be 21 psi with a purging time of ~15 min. The measurements were conducted in a controlled environment with a temperature of 20 °C and a relative humidity of 50%. For each measurement, 3–5 g sample was used. Replicates were run for each sample to ensure good reproducibility with a standard deviation less than 0.01 g/cm^3, and the average was reported.

Table 1
Compound categories used for evaluation of two density prediction methods

Number of compounds	83
Range of molecular weight	179–1029 100–500 (71%) 500–700 (24%) >700 (5%)
Number of free forms	41
Number of salts	41
Benzenesulfonate	1
Benzoate	2
Citrate	3
Ethylenediamine	1
HCl	16
K	1
Lactate	2
Maleate	1
Mesylate	6
Na	3
Tosylate	1
Succinate	1
Tartrate	3
Number of hydrates	1

Table 2
Relative volumes for different atoms used in the Girolami (1994) method

Element	Relative volume
H	1
First short period, Li–F	2
Second short period, Na–Cl	4
First long period, K–Br	5
Second long period, Rb–I	7.5
Third long period, Cs–Bi	9

2.2.2. Prediction methods

Two density prediction methods, Girolami and Immirzi and Perini, are discussed here and applied to estimate the true density of APIs.

Girolami developed a simple "back of the envelope" method for estimating the densities and molecular volumes of liquids and solids (Girolami, 1994). The equations were derived from the van der Waals radii of different atoms. Each atom was given a relative volume, v_j, as listed in Table 2. Note that the simplification of adopting a common van der Waals radius for the elements in the same period was made to deduce the relative volumes for different elements. The sum of the relative volumes of the constituent atoms, V_s, can be calculated using the following equation, where m_j is the number of a certain element.

$$V_s = \sum_j m_j v_j \quad (1)$$

The volume of a molecule in cubic Angstroms can be given by $6.40V_s$ for solids (Pauling, 1960), and the density ρ for solids can be calculated by

$$\rho = \frac{M\ (\mathrm{g\,mol^{-1}})(10^{24}\ \mathrm{angstrom^3/cm^3})}{(6.022 \times 10^{23})(\mathrm{mol^{-1}})(6.4V_s)(\mathrm{angstrom^3})} = \frac{M}{3.85V_s} \quad (2)$$

where M is the molecular weight, and the result is expressed in g/cm^3. Although corrective factors such as hydrogen-boding groups and rings were discussed in the method for certain classes of liquids (Girolami, 1994), for simplicity, those corrective factors were not used in this study to estimate API density because they might not suitable for solid APIs and would make the method more complicated.

The Immirzi and Perini method was developed based on data for over 500 organic crystalline compounds with molecular weights ranging from 50 to 1000. To account for the empty space in an organic crystal, the method used atomic volumes based upon the number of other atoms bonded to the specific atom. For example, carbon may bond to 2, 3, or 4 other atoms, oxygen to 1 or 2, and nitrogen to 1, 2 or 3 (Immirzi and Perini, 1977; Lyman et al., 1990). The additivity of the Immirzi and

Table 3
Volume increments (v_j, angstrom^3) for common elements and ions used in the Immirzi and Perini method

Element or ion	v_j
–H	6.9
=C=	15.3
–C≡	15.3
	13.7
	11.0
O=	14.0
–O–	9.2
N≡	16.0
=N–	12.8
	7.2
S	23.8
–F	12.8
–Cl	26.7
–Br	33.0
–I	45.0
H_2O	21.5
Benzene frame (carbons only)	75.2
Naphthalene frame (carbons only)	123.7
Non-aromatic rings (5 or 6 member rings, rough est.)	−3.0
O–H···O hydrogen-bond (–COOH)	−2.6
N–H···O hydrogen-bond (–CONH– or –$CONH_2$)	−2.8
N–H···N hydrogen-bond	−0.3
Cl^-	28.9
Br^-	39.3
I^-	56.6
Na^+	13.6
K^+	27.3
Rb^+	34.1

Note: Different coordination numbers are considered for C, N, and O. Source: Immirzi and Perini (1977). Reprinted with permission from the International Union of Crystallography.

Perini method can be expressed using the following equation

$$V_s = \sum_j m_j v_j \quad (3)$$

where V_s is the calculated crystal volume for a single molecule (angstrom^3/molecule), m_j is the relative stoichiometric multiplicities and v_j is the volume increments of elements or ions (angstrom^3).

Table 3 lists the v_j values for common elements and ions. Once V_s is determined, the following equation can be used to calculate the solid density ρ.

$$\rho = \frac{1.660M}{V_s} \quad (4)$$

where M is the molecular weight of the compound, and the result is expressed in g/cm^3. Both methods predict density at room temperature, thus the predictions can be compared with the values measured by helium pycnometry.

2.3. Data analysis

To evaluate the two predictive approaches, various methods of data analysis were used, including percent error (PE), average percent error (APE) and its 95% confidence interval (CI), and root average square error (RASE). PE, APE, and RASE were determined as follows:

$$\text{PE} = \frac{\text{Predicted} - \text{Measured}}{\text{Measured}} \times 100\% \quad (5)$$

$$\text{APE} = \frac{\sum \text{PE}}{N} \quad (6)$$

$$\text{RASE} = \sqrt{\frac{\sum (\text{Predicted} - \text{Measured})^2}{N}} \quad (7)$$

3. Results and discussion

The experimentally measured density values by helium pycnometry were assumed to be sufficiently accurate and were used as references for judging the accuracy of the two predictive approaches. This was verified by comparing the experimental density data for 39 samples (31 Pfizer internal compounds and 8 common APIs) to the values determined from single X-ray crystallography from the Pfizer Crystal Structure Database (PCSD) or Cambridge Crystal Structure Database (CCSD, Cambridge Crystallographic Data Centre, Cambridge, UK). The structure data was mined using ConQuest version 1.9 (Cambridge Crystallographic Data Centre, Cambridge, UK). Note that the two sets of data were obtained at similar temperatures (room temperatures) to avoid effects of thermal expansion on density (Hancock and Rowe, 1998; Sun, 2007). Fig. 1 shows a plot of measured values versus data from X-ray crystallography, and Table 4 lists examples for some common APIs (part of the data points in Fig. 1). Compared with the density values obtained from X-ray crystallography, the measured values have an average percent error (APE) of −0.3% with a 95% CI of (−0.7, 0.1) and a root average square error (RASE) of 0.015 g/cm^3. The close agreement between the two sets of data confirmed that the measured density values were suitable for use as references.

For the APIs tested in this paper, almost all compounds are non-hydrates (only one was hydrate) and the water content of non-hydrates was normally controlled at a level of less than

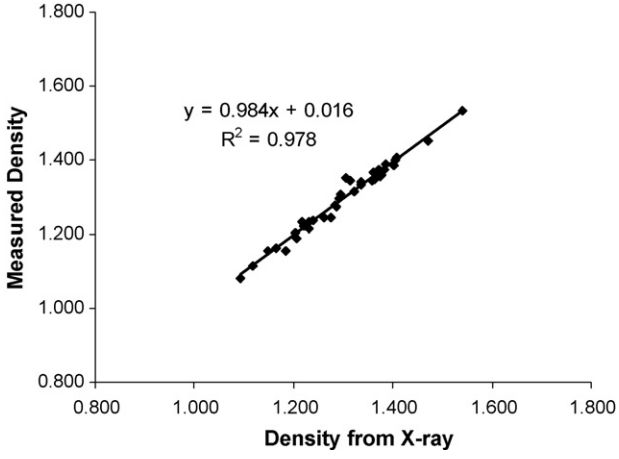


Fig. 1. Density values (g/cm^3) for 39 APIs: measured by helium pycnometry vs. determined by X-ray crystallography.

Table 4
Measured density values (g/cm^3) by helium pycnometry and values determined by X-ray crystallography from Cambridge Crystal Structure Database (CCSD) for some common APIs

Compounds	Measured values	X-ray data	CCSD reference code	Temperature (K)
Acetaminophen (form I)	1.295	1.293	HXACAN01	295
Benzocaine	1.189	1.207	QQQAXG01	295
Ibuprofen (RS)	1.116	1.119	IBPRAC	295
Indomethacin (form γ)	1.374	1.372	INDMET	295
Ketoprofen	1.279	1.284	KEMRUP	295
Lidocaine hydrochloride monohydrate	1.202	1.204	LIDOCN	295
Niacinamide	1.385	1.403	NICOAM02	295
Phenacetin	1.237	1.238	PYRAZB21	298

1% during the manufacturing process. Therefore, it is reasonable to assume that the water content had a very minor impact on the helium pycnometry measurements here. In addition, the particle size distribution (PSD) can affect the measurements of helium pycnometry because different particle sizes may introduce different porous structures and thus result in different measurements. The PSD data for about 50% of the tested compounds collected from a Sympatec laser diffraction spectrometer showed the volume mean diameters ranging from 3 to 50 μm, which are small enough to neglect the potential effect on density measurement. Additionally, survey for the measured density values of different lots of a same compound with different PSDs showed that the PSD had no significant impact on the measurements. For example, two Ibuprofen lots with different volume mean diameters of 91 and 26 μm were examined. Our measurements from helium pycnometer were 1.117 and 1.115 g/cm^3 with a difference in the instrument error range.

The true densities of the 83 Pfizer APIs were calculated using both Girolami and Immirzi and Perini methods. Table 5 shows an example of how the calculations are conducted for Phenacetin using Eqs. (1)–(4) and Tables 2–3. The calculations of both methods are quite simple, especially the Girolami method. More importantly, the calculated values, 1.194 from Girolami and 1.244 from Immirzi and Perini, were very consistent with the values determined by helium pycnometry (1.236) and X-ray crystallography (1.238).

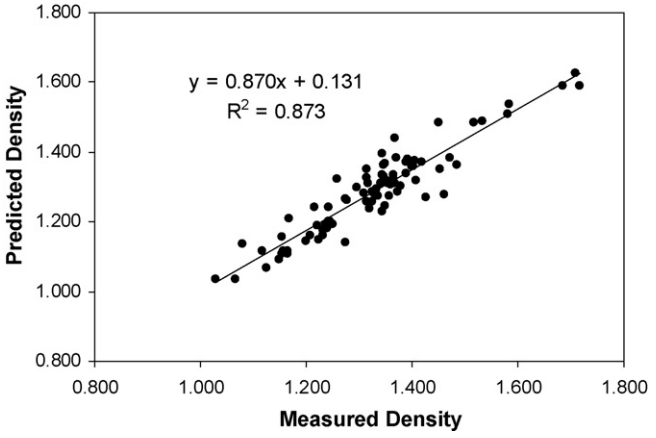
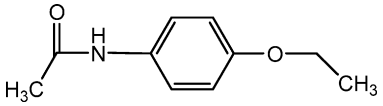


Fig. 2. Predicted vs. measured density values (g/cm^3) using Girolami method for 83 APIs.

To evaluate the performance of the two methods, the calculated density values were compared with the measured values. Plots of predicted versus measured density values are shown in Fig. 2 for the Girolami method and Fig. 3 for the Immirzi and Peniri method. The results from both methods are summarized in Table 6. As seen in Figs. 2–3 and Table 6, both methods agreed well with the measured values, but the prediction results from the two methods were shown to be significantly different by a statistical *t*-test. Overall, the Immirzi and Perini method gave more accurate and precise predictions than the Girolami method.

Table 5
Use of two prediction methods to calculate the true density for phenacetin

Formula	$C_{10}H_{13}NO_2$
Molecular weight	179.22
Bonding structure	
Measured density (g/cm^3)	1.237
Prediction from Girolami method (g/cm^3)	13 H, 10 C, 1 N and 2 O. Use Table 2 and Eqs. (1) and (2): $V_s = 13 \times 1 + 13 \times 2 = 39$ and $\rho = (M/3.85V_s) = (179.22/(3.85 \times 39)) = 1.194$
Prediction from Immirzi and Perini method (g/cm^3)	13 H—, 1  , 3  , 1 O═, 1 O—, 1  , 1 benzene ring, and 1 —CONH group. Use Table 3 and Eqs. (3) and (4): $V_s = 13 \times 6.9 + 1 \times 13.7 + 3 \times 11.0 + 1 \times 14.0 + 1 \times 9.2 + 1 \times 7.2 + 1 \times 75.2 - 1 \times 2.8 = 239.2$ and $\rho = (1.660M/V_s) = ((1.660 \times 179.22)/239.2) = 1.244$

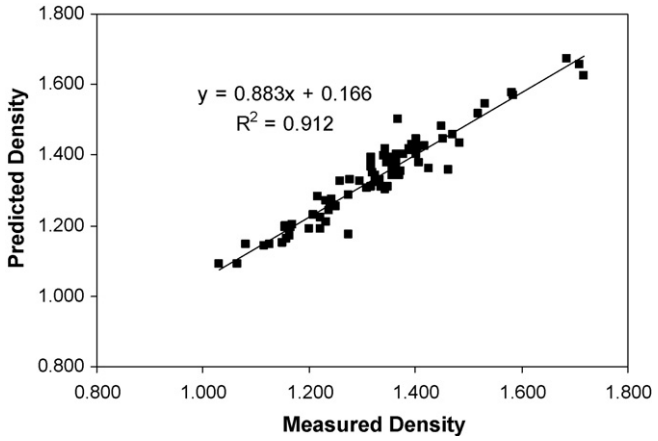


Fig. 3. Predicted vs. measured density values (g/cm^3) using Immirzi and Perini method for 83 APIs.

Table 6
Summary and comparison of the two methods in density prediction results

	Girolami	Immirzi and Perini
R-squared value	0.08728	0.9118
PE < −5%	20 compounds (24%)	3 compounds (4%)
PE within 5%	61 compounds (74%)	71 compounds (86%)
PE > 5%	2 compounds (2%)	9 compounds (10%)
Maximum error	−12.7%	9.6%
PE within 2%	17 compounds (20%)	43 compounds (52%)
PE within 1%	12 compounds (14%)	27 compounds (33%)
APE (%)	−3.0%	0.9%
95% CI of APE	(−3.8, −2.3%)	(0.3, 1.6%)
RASE (density unit, g/cm^3)	0.063 g/cm^3	0.041 g/cm^3

Note: PE, Percent error; APE, average percent error; CI, confidence interval; RASE, root average square error.

Specifically, from the Immirzi and Perini method, approximately 86% of the predictions were within 5% of the measured values, and 52% of the predictions were within 2%, and 33% of the predictions were within 1%. The maximum error was 9.6%. This method had an APE of 0.9% with a 95% CI of (0.3, 1.6%) and a RASE of 0.041 g/cm^3. For comparison, from the Girolami method, approximately 74% of the predictions were within 5% of the measured values, and 20% of the predictions were within 2%, and only 14% of the predictions were within 1%. The maximum error was −12.7%. This method had an APE of −3.0% with a 95% CI of (−3.8, −2.3%) and a RASE of 0.063 g/cm^3. Although both Girolami and Immirzi and Perini methods were based on the van der Waals molecular volume, the Immirzi and Perini method was more accurate because it included corrective terms for the proper stoichiometric coefficient, hydrogen-bond formation, ring formation and ring fusion (Immirzi and Perini, 1977).

3.1. Effect of counter ion

As listed in Table 1, the 83 compounds included about 50% of free form APIs and 50% salts. The accuracy of the two methods applied to different types of APIs was evaluated. Similar data analysis conducted for free forms or salts alone indicated that the APEs for the free forms and salts were not significantly different using either method. When using the Girolami method, the APE was determined to be −2.9% with a 95% CI of (−4.0, −1.9%) for the free forms and −3.1% with a 95% CI of (−4.2, −2.1%) for the salts. With the Immirzi and Perini method, the APE was determined to be 1.1% with a 95% CI of (0.2, 2.0%) for the free forms and 0.8% with a 95% CI of (−0.2, 1.7%) for the salts.

3.2. Effect of density magnitude

The APIs tested in this study had measured density values ranging from 1.030 to 1.717 g/cm^3, where 12 compounds (15%) had density values >1.000 but <1.200 g/cm^3 (in the density region of (1.000, 1.200)), 7 compounds (8%) had density values >1.500 but <1.800 g/cm^3 (in the density region of (1.500, 1.800)), and 64 compounds (77%) had density values ≥1.200 but ≤1.500 g/cm^3 (in the density region of [1.200, 1.500]). An analysis was conducted for the three density regions to evaluate if the prediction methods exhibited different performance in different regions. As listed in Table 7, for the Girolami method, there was no significant differences among the three density regions, but the method appeared to give best predictions in (1.000, 1.200). In contrast, the Immirzi and Perini method was most accurate in [1.200, 1.500], and it also gave better predictions in this region than the Girolami method. A survey of density measurements by helium pycnometry for a total of ∼200 APIs indicated that about 85% of the compounds had density values in the range of [1.200, 1.500], suggesting that APIs most often have true density values in this range (Hancock et al., 2003). Therefore, it can be concluded that the Immirzi and Perini method would likely give better predictions than the Girolami method when used for typical APIs.

3.3. Effect of molecular weight

The studied APIs had molecular weights ranging from 179 to 1029. The data was analyzed in three different molecular weight regions (<300, 300–600, and >600) to evaluate if the predictions differ at different regions, as listed in Table 8. Among the three

Table 7
Analysis of density region on predictions of the two methods

Measured density region	Number of compounds in the region	Girolami method		Immirzi and Perini method	
		APE (%)	95% CI	APE (%)	95% CI
(1.000, 1.200)	12	−1.8	(−3.7, 0.2%)	2.6	(1.0, 4.3%)
[1.200, 1.500]	64	−3.1	(−4.0, −2.3%)	0.9	(0.2, 1.6%)
(1.500, 1.800)	7	−4.4	(−7.0, −1.8%)	−1.4	(−3.5, 0.8%)

Table 8
Analysis of molecular weight on predictions of the two methods

Molecular weight region	Number of compounds in the region	APE from the Girolami method (%)	APE frome the Immirzi and Perini method (%)
(100, 300)	7	−1.4	2.8
[300, 600]	67	−3.2	0.9
(600, 1100)	9	−3.3	2.8

regions, the Girolami method appeared to give best estimations for the APIs with molecular weights less than 300. This is probably because the Girolami method used here does not include corrective factors and smaller molecules (less molecular weight) usually involve fewer corrections. In contrast, the Immirzi and Perini method appeared to give best estimations for APIs with molecular weights of 300–600. Additionally, Table 8 shows that most APIs (81%) had molecular weights between 300 and 600. Although both methods gave good predictions in this region, again the Immirzi and Perini method showed a better accuracy.

Overall, both methods agree well with the measured values. They offer different advantages that may be applied for different situations. The Girolami method is simple and quick as it only requires the formula (the number of each atom) for the calculations. It can be used for any compounds including both liquids and solids. The Immirzi and Perini method is more complex compared to the Girolami method because it requires the bonding structure for the calculations. It can be applied to crystals with elements H, C, O, N, S, F, Cl, Br, I, Na, K and Rb, which include most pharmaceutical solids. The predictions from the two methods are significantly different statistically. On average, the Girolami method underestimates the true density values by 3.0%, while the Immirzi and Perini method overestimates the true density values by 0.9%. However, if corrective factors are introduced to both methods by adding 3.0% to the Girolami calculated values or subtracting 0.9% to the Immirzi and Perini calculated values, the two methods will have non-significantly different, unbiased predictions comparing with the measured values. After the corrections, Eqs. (2) and (4) may be revised to (8) and (9) respectively, resulting an APE of −0.1% with a 95% CI of (−0.9, 0.6%) for the adjusted Girolami method and an APE of 0.0% with a 95% CI of (−0.6, 0.7%) for the adjusted Immirzi and Perini method. Note that these corrective factors are based on the limited results for tested APIs and may need further verification.

$$\rho = \frac{M}{3.85V_s} \times (100\% + 3.0\%) = \frac{M}{3.74V_s} \quad (8)$$

$$\rho = \frac{1.660M}{V_s} \times (100\% - 0.9\%) = \frac{1.645M}{V_s} \quad (9)$$

There are certainly limitations for the two methods. For example, the use of the two methods to macromolecules such as proteins, polymers and excipients are not considered and may need to be evaluated differently. In addition, both methods are based only on the van der Waals molecular volume and do not consider important factors such as the crystallinity or conformation of the materials. Therefore, the effect of polymorphism is not taken into account in the predictions. Usually polymorphism may cause true density to differ in the second decimal place. For example, two polymorphs of sulfamerazine have true density values of 1.335 and 1.415 g/cm^3 (Sun and Grant, 2001); two polymorphs of aspartame hemihydrate have density values of 1.492 and 1.464 g/cm^3 (Leung et al., 1998). Other restrictions for the Immirzi and Perini method include that (Immirzi and Perini, 1977): (1) compounds not solid at room temperature, or having structural disorder are excluded; (2) compounds containing molecules of solvent (solvates) are excluded, except for water; (3) only the elements H, C, O, N, S, F, Cl, Br, I, Na, K and Rb are considered; (4) cyclic compounds are limited to benzene and naphthalene derivatives.

4. Conclusions

Two empirical density prediction methods, developed by Girolami and Immirzi and Perini, were applied to APIs including free forms and various salts/hydrates. Both methods agreed well with the measured values by helium pycnometry. The Girolami method is very simple and can be used for any compounds, while the Immirzi and Perini method is more involved but gives a greater accuracy than the Girolami method. This study has shown that both methods can be used to predict the true density for APIs with an average percent error less than 5%.

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