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Estimating the refractive index of pharmaceutical solids using predictive methods

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ABSTRACT

Refractive index is a basic physical property of pharmaceutical solids. In this paper, the refractive index values of 424 pharmaceutical solids from the literature were surveyed. It was found that the refractive index values exhibit a normal distribution with an overall mean value of 1.603. The Eisenlohr and Vogel methods developed for organic liquids were employed to estimate the refractive index for pharmaceutical solids. The estimated results were compared with experimentally measured values determined by polarized light microscopy. Both Eisenlohr and Vogel R_D methods agreed very well with the measured mean refractive index values from the literature with an average absolute percent error of 1.22% and 1.25%, respectively. The evaluation for in-house measurements for Pfizer active pharmaceutical ingredients showed larger differences between the calculated and measured values. The results indicate that the Eisenlohr and Vogel R_D methods can provide fast and accurate results for predicting the refractive index of pharmaceutical solids.

1. Introduction

The refractive index is a basic physical property of a crystal material. It is the ratio of the speed of light in vacuum to that in the material. Depending on its symmetry, a crystal may exhibit one, two or three refractive indices (Sirotin and Shaskolskaya, 1975). The refractive index is typically measured using the yellow light of the sodium D line with a wavelength of 589.3 nm at 20 °C (Nelken, 1990). The refractive index is an important parameter for many pharmaceutical applications. For example, the refractive index of a crystalline drug is used in the identification of the drug or its polymorphic forms (Watanabe et al., 1980; Nichols, 1998). It aids determination of molecular structure and weight (Bicerano, 1996). The refractive index is also a key input for accurate particle size determinations using the Mie theory (Jones, 2003). In addition, it is used to predict other properties such as thermal properties (Lisa and Lisa, 2007), surface tension (Pineiro et al., 2000), and solubility parameters (Lawson and Ingham, 1969). Therefore, it is often desirable to obtain the refractive index of pharmaceutical solids during drug research and development.

Although the refractive index of liquids can be easily and rapidly measured using a refractometer (Richardson, 1974), the refractive index determination for solids is more complicated. Traditionally, the refractive index of solids is determined using polarized light microscopy (PLM) by mounting crystals in suitable refractive index liquids on microscope slides (Saylor, 1966). However, it is often difficult to conduct such measurements and it may even be impossible due to lack of a suitable crystal habit or symmetry. Especially in the pharmaceutical industry, the formation of single crystals and use of complex microscope observations are often seen to be unrealistic requirements within laboratories handling a variety of newly discovered active pharmaceutical ingredients (APIs). Furthermore, the measurements are usually time-consuming and labor-intensive. Measurement errors can be large due to the sample nature and analyst handling. As a result, often only one refractive index value is obtained from the measurements for an authentic API sample, leaving uncertainty about the accuracy of the results.

Lack of experimental data for new pharmaceutical compounds leads to the search for empirical methods to estimate the refractive index. Various methods for refractive index estimations have been previously reviewed (Nelken, 1990). Some methods, such as those developed by Eisenlohr (Eisenlohr, 1910; Gold and Ogle, 1969; Nelken, 1990), Vogel (Vogel, 1948; Nelken, 1990), and Hansch et al. (Hansch et al., 1973; Nelken, 1990), used atomic or group contributions to obtain molar refraction. These methods only require structural information, molecular weight and density to calculate the refractive index, and can be carried out by hand computation. They have been shown to give accurate refractive index predictions for organic liquids (Gold and Ogle, 1969; Vogel, 1948 #225, Hansch et al., 1973 #315; Nelken, 1990). A similar approach has also been discussed for inorganic compounds (Korotkov and Atuchin, 2008). Other methods such as Kier and Hall (Kier and Hall, 1976; Nelken, 1990) are based upon molecular structure but involve the use of a connectivity function. In addition, various quantitative

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structure–property relationships (QSPR) have been developed to predict the refractive index of polymers (Xu et al., 2004; Yu et al., 2007). These methods require complicated computation but may provide more accurate results. The different methods apply to different classes of compounds and exhibit different complexity, accuracy and limitation. For their simplicity and applicability to most pharmaceutical solids, the Eisenlohr and Vogel methods are employed in this study to estimate the mean refractive index of the pharmaceutical solids. The calculated values from the predictive methods were compared with the mean refractive index values reported in the literature to evaluate the performance of the methods and the accuracy of in-house measurements.

2. Materials and methods

2.1. Materials

The materials discussed in this paper included pharmaceutical solids reported in the literature (mostly APIs and some excipients) and proprietary Pfizer APIs. A total of 424 pharmaceutical compounds from the literature were surveyed to analyze the distributions of their refractive index values. A subset of 37 of them was employed to evaluate the performance of the predictive methods. The refractive index values of 87 Pfizer APIs were measured in house, and 41 of them were tested against the estimations from the predictive methods.

2.2. Methods

2.2.1. Polarized light microscopy

The refractive index values of the Pfizer APIs were measured using polarized light microscopy (PLM) by mounting the crystalline samples in suitable immersion liquids and making observations of the Becke line. The immersion liquids have known refractive index values ranging from 1.40 to 1.75 with 0.01 intervals. All refractive index values were measured at ~20 °C using the sodium D line. The API samples were authentic development batches without any additional effort to make suitable crystal habit or symmetry for the PLM analysis. It was found that the measurements were very challenging due to irregular crystal habit and poor symmetry. As a result, only one value was obtained for some API samples. For the samples with more than one measured refractive index values, the mean values were reported.

The literature refractive index values discussed in this paper were also determined by PLM at ~20 °C using the sodium D line (Eisenberg and Schulze, 1970; Watanabe et al., 1980, 1985; Jordan, 1993; Watanabe, 2002). Multiple refractive index values were reported for each compound, often including three principal refractive indices or two key refractive indices. Principal refractive indices (n_a, n_b, and n_c) are associated with principal refractive axes of a crystal. Often the orientation of principal refractive axes needs to be determined for the measurement of principal refractive indices. In some cases, measurements of the principal refractive indices were not easy and may have been impossible, depending on the crystal habit or symmetry. When a couple of refractive indices (n_1 and n_2) measured from the crystals under a PLM are unique and reproducible for a given drug, these data were referred as "key refractive indices" (Watanabe et al., 1980).

2.2.2. Prediction methods

Predictive methods, developed by Eisenlohr and Vogel for organic liquids, were employed to estimate the refractive index of the pharmaceutical solids for the sodium D line at 20 °C. The Eisenlohr and Vogel methods were based on atomic and structural group contributions to molar refraction. Table 1 lists the contributions from each atom or group, R_i, for the Eisenlohr method (Eisenlohr, 1910; Gold and Ogle, 1969; Nelken, 1990). The molar refraction R_D is calculated by the sum of the contributions of the constituent atoms and groups.

Table 1
Atomic and structural contributions to molar refraction for the Eisenlohr method (Eisenlohr, 1910; Gold and Ogle, 1969; Nelken, 1990).

Group	R_i	Group	R_i
—CH_2—	4.618	I	13.9
C	2.418	O (hydroxyl)	1.525
H	1.1	O (ether)	1.643
S as SH	7.69	O (carbonyl)[a]	2.211
S as RSR	7.97	OO (ester)[a]	3.736
S as RCNS	7.91	N (pri-amine)	2.322
S as RSSR	8.11	N (sec-amine)	2.502
F (one F attached to C)	0.95	N (tert-amine)	2.84
F (each F in polyfluorides)	1.1	N (nitrile)[b]	5.516
Cl	5.967	Double Bond	1.733
Br	8.865	Triple Bond	2.398

[a] Includes allowance for double bond.
[b] Includes allowance for triple bond.

$$R_D = \sum_i m_i R_i \quad (1)$$

where m_i is the number of a certain atom or group. The refractive index, n, can then be calculated using the Lorentz–Lorenz equation:

$$n = \sqrt{\frac{M + 2\rho R_D}{M - \rho R_D}} \quad (2)$$

where M is the molecular weight, and ρ is the density. Eq. (2) indicates that the calculation requires molecular weight and density data. The molecular weight can be obtained from the chemical formula. The sources for the density data include the Cambridge Structure Database (CSD, CCDC ConQuest version 1.10), the literature, in-house measurements, and empirical calculations. Details on measurements by helium pycnometry and density calculations using predictive methods have been described elsewhere (Cao et al., 2008).

Vogel revised the atom or group contributions to the molar refraction and added more groups such as phosphates, sulfites, sulfates, nitro compounds, nitrates, and carbonates (Vogel, 1948; Nelken, 1990). The atomic, structural, and group contributions to R_D for the Vogel method are listed in Table 2 (Vogel, 1948; Nelken, 1990). Similarly to the Eisenlohr method, the refractive index can be calculated using Eqs. (1) and (2). In addition, the atom and group refraction coefficients, Mn_i, were given in Table 2 to calculate the refraction coefficient Mn_D and further calculate refractive index by dividing Mn_D by the molecular weight M (Vogel et al., 1952; Nelken, 1990). Note that the density is not required in this calculation. The Vogel methods include two different approaches of using R_D and Mn_D, which are referred as "Vogel R_D" and "Vogel Mn_D" respectively to facilitate the discussion.

$$Mn_D = \sum_i m_i Mn_i \quad (3)$$

$$n = \frac{Mn_D}{M} \quad (4)$$

2.3. Data analysis

To evaluate the performance of the predictive approaches, the calculated refractive index values of 37 pharmaceutical solids were compared with their known values from the literature. Additionally, measured values of the 41 Pfizer APIs were compared with the calculated values from the predictive methods. Various data analyses were used, including percent error (PE), average percent

Table 2
Atomic, structural and group contributions for the Vogel methods (Vogel, 1948; Nelken, 1990).

Group	R_i	Mn_i	Group	R_i	Mn_i
CH_2	4.647	20.59	NCS (in isothiocyanates)	15.615	93.11
H (in CH_2)	1.028	−2.56	Carbon–carbon double bond	1.575	−6.07
C (in CH_2)	2.591	25.71	Carbon–carbon triple bond, terminal	1.977	−12.56
O (in ethers)	1.764	22.74	CN (in nitriles)	5.459	36.46
O (in acetals)	1.607	22.41	Three-carbon ring[a]	0.614	−4.72
CO (in carbonyls)	4.601	42.41	Four-carbon ring[a]	0.317	−4.67
CO (in methyl ketones)	4.758	42.42	Five-carbon ring[a]	−0.19	−4.56
COO (in esters)	6.2	64.14	Six-carbon ring[a]	−0.15	−3.53
OH (in alcohols)	2.546	23.94	CO_3 (carbonates)	7.696	86.35
CO_2H	7.226	63.98	SO_3 (sulfites)	11.338	118.09
Cl	5.844	50.41	NO_3 (nitrates)	9.03	87.59
Br	8.741	118.07	SO_4 (sulfates)	11.09	138.86
I	13.954	196.27	PO_4 (orthophosphates)	10.769	139.74
F	0.81	21.84	CH_3	5.653	18.13
NH_2 (in primary aliphatic amines)	4.438	22.64	C_2H_5	10.3	38.72
NH (in secondary aliphatic amines)	3.61	23.34	C_3H_7n	14.965	59.25
NH (in secondary aromatic amines)	4.678	29.52	C_3H_7i	14.975	58.95
N (in tertiary aliphatic amines)	2.744	24.37	C_4H_9n	19.585	79.81
N (in tertiary aromatic amines)	4.243	30.23	C_4H_9i	19.62	79.54
NO (nitroso)	5.2	43.14	C_4H_9s	19.42	80.21
O–NO (nitrite)	7.237	62.27	C_5H_{11}n	24.25	100.46
NO_2 (nitro)	6.713	65.61	C_5H_{11}i (from the synthetic alcohol)	24.195	100.3
N·NO (nitrosoamine)	7.85	69.67	C_5H_{11}i (from fermentation alcohol)	24.28	100.21
S (in sulfides)	7.921	52.86	C_6H_{13}n	28.855	121.1
S_2 (in disulfides)	16.054	106.52	C_7H_{15}n	33.55	141.75
SH (in thiols)	8.757	50.2	C_8H_{17}n	38.135	162.43
CS (in xanthates)	13.07	77.2	C_3H_5 (allyl)	14.52	57.6
SCN (in thiocyanates)	13.4	88.9	C_6H_5 (Benzene ring missing one H)	25.359	122.03

[a] Assume to apply to 3-, 4-, 5- and 6-member rings.

error (APE), average absolute percent error (AAPE), and root mean square error (RMSE). The APE indicates prediction accuracy, while the AAPE and RMSE indicate prediction precision. The PE, APE, AAPE, and RMSE were determined as follows:

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

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

$$\text{AAPE} = \frac{\sum |\text{PE}|}{N} \quad (7)$$

$$\text{RMSE} = \sqrt{\frac{\sum (\text{Predicted} - \text{Measured})^2}{N}} \quad (8)$$

3. Results

3.1. Survey of literature refractive index values

The refractive index data of 424 pharmaceutical solids from the literature were surveyed (Eisenberg and Schulze, 1970; Watanabe et al., 1980, 1985; Jordan, 1993; Watanabe, 2002). There were a total of about 1200 individual refractive measurements (n_1, n_2, n_a, n_b, and n_c) that ranged from 1.40 to 2.00 with a mean of 1.606 and a standard deviation of 0.082. About 50 compounds had both key and principal indices. Fig. 1 shows the distribution of all individual values, similar to a normal distribution with the same mean and standard deviation. Only 73 (~6%) refractive index measurements are below 1.50 but greater than 1.40, while 163 (~14%) refractive measurements are above 1.70 but less than 2.00. The majority of the measurements (~80%) are in the range of 1.50–1.70, and ~49% are in the range of 1.55–1.65. A spike is observed in the refractive index interval of 1.73–1.74, corresponding to 41 measurements mainly for n_2 or n_c.

More than 98% of the surveyed compounds had two or three refractive index values, and only 7 compounds had one refractive index value. The mean value, standard deviation (STD), and maximum refractive index difference (max–min) were calculated for each compound. For the compounds with only one refractive index value, the value was used as the mean, and STD and max–min are zero. Fig. 2 shows the distribution of the mean refractive index values with an overall mean refractive index of 1.603 and a standard deviation of 0.053. The distribution agrees well with a normal distribution with the same mean and standard deviation, as shown in Fig. 2. The mean refractive index values of all surveyed compounds are in the range of 1.45–1.80, but only 8 compounds (~2%) are in the range of 1.45–1.50 and 15 compounds (~4%) are in the range of 1.70–1.80. The majority of the compounds (~94%) have mean refractive index values in the range of 1.50–1.70, and ~64% compounds have mean refractive index values in the range of 1.55–1.65. The STDs of the 424 compounds ranged from 0 to 0.34, but about 80% compounds have STDs ≤0.1, and about 53% compounds have STDs ≤0.05. The max–min values ranged from

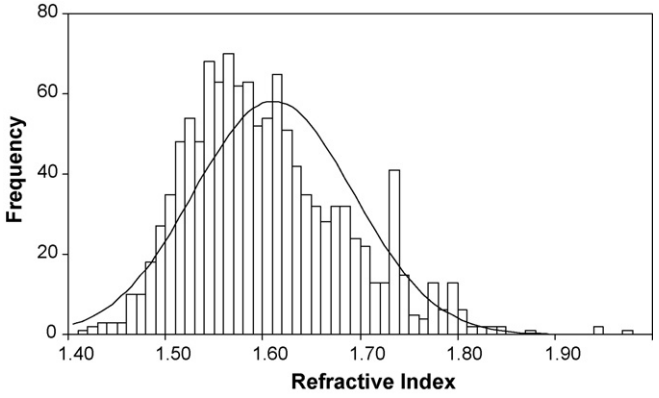


Fig. 1. Frequency distribution of ~1200 individual refractive index values of 424 pharmaceutical compounds from the literature. The solid line is the normal distribution with a mean of 1.606 and a standard deviation of 0.082.

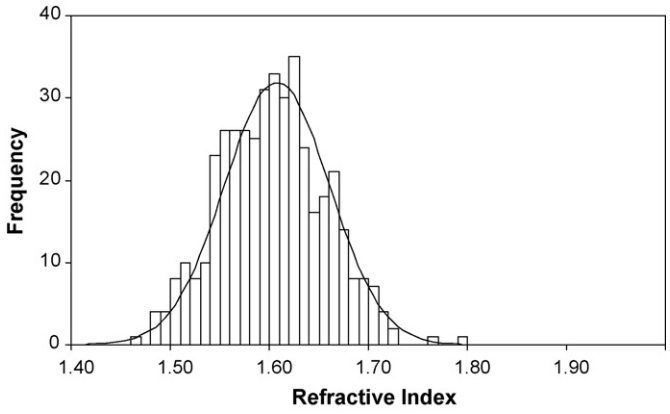


Fig. 2. Frequency distribution of mean refractive index values of 424 pharmaceutical compounds from the literature. The solid line is the normal distribution with a mean of 1.603 and a standard deviation of 0.053.

0 to 0.48, but about 83% compounds have max–min values ≤0.2 and about 56% compounds have max–min values ≤0.1. The STD and max–min of multiple refractive index measurements for each compound indicates the possible difference of a single measured refractive index value from the mean. In summary, more than 50% of the compounds have mean refractive index values of 1.55–1.65 with standard deviations ≤0.05 and max–min values ≤0.1.

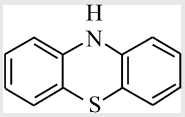
3.2. Calculations and literature values

The refractive index values of 37 pharmaceutical solids were calculated using the Eisenlohr and Vogel methods. The 37 compounds were selected based on which region their mean refractive index value fall in. From Section 3.1, the mean refractive index values of all surveyed 424 compounds were in the range of 1.45–1.80, and most were in 1.55–1.65. The 1.45–1.80 range was subdivided to three regions, 1.45–1.55, 1.55–1.65, and 1.65–1.80, and 10–15 compounds were randomly selected from each region to ensure the sampling was representative to the whole range of 1.45–1.80. Table 3 shows an example of how the calculations are conducted for Phenothiazine using Eqs. (1)–(4) and Tables 1–2. The calculations of both methods are quite simple, especially the Eisenlohr method. The calculated values, 1.771 from Eisenlohr and 1.776 from Vogel R_D, were very consistent with the mean measured value of 1.765 from the literature (Watanabe, 2002). However, the calculated value of 1.615 from the Vogel Mn_D method was largely different from the mean measured value.

To evaluate the performance of the predictive methods, the calculated values of the 37 compounds were compared with mean refractive index values collected from the literature. Table 4 summarizes collected density data, measured and calculated refractive index values. The density data were obtained from the CSD, the literature, in-house measurements by helium pycnometry, and calculations using the Immirzi and Perini method (Immirzi and Perini, 1977; Lyman et al., 1990; Cao et al., 2008). The density values from the CSD were determined by X-ray crystallography at room temperature, representing the true density of the crystals. A previous study has shown that the predicted density agrees well with measurements and X-ray data (Cao et al., 2008). All 37 compounds have either two or three refractive index values. The mean refractive index values ranged from 1.45 to 1.80 with 10–15 compounds at each range of 1.45–1.55, 1.55–1.65 and 1.65–1.80. The 37 compounds were selected to cover the refractive index range for typical pharmaceutical solids as surveyed in the previous section. Additionally, the overall mean of the measured refractive index values of the 37 compounds is 1.604, about same as the overall mean of 1.603 for all survey literature compounds, suggesting well-representative sampling.

Fig. 3 shows plots of the refractive index calculated from the Eisenlohr and Vogel methods versus measured mean values from the literature. Linear fittings were performed for the data points (dotted lines). For comparison, a solid line was drawn to represent the perfect match between the calculated and measured values. Table 5 summarizes the analysis results for the predictive methods. Both Eisenlohr and Vogel R_D plots show good linear correlations with slopes of 0.93 and 0.89, and fitting coefficients (R^2) of ~0.9. The Eisenlohr method shows an APE of 0.10%, an AAPE of 1.22%,

Table 3
Use of prediction methods to calculate the refractive index for Phenothiazine.

Formula	$C_{12}H_9NS$
Molecular weight	199.27
Bonding structure	
Density (g/cm^3)	1.387[a]
Refractive index	1.765[b]
Eisenlohr	12C, 9H, 1N (sec-amine), 1S as RSR, and 6 double bonds Use Table 1 and Eqs. (1) and (2): $R_D = 12 \times 2.418 + 9 \times 1.1 + 1 \times 2.502 + 1 \times 7.97 + 6 \times 1.733 = 59.786$ $n = \sqrt{\frac{M + 2\rho R_D}{M - \rho R_D}} = \sqrt{\frac{199.27 + 2 \times 1.387 \times 59.786}{199.27 - 1.387 \times 59.786}} = 1.771$
Vogel R_D	1S, 1NH, $2C_6H_5$ (benzene ring missing one H), a six-member ring, and subtracting 2H Use Table 2 and Eqs. (1) and (2) $R_D = 1 \times 7.921 + 1 \times 3.61 + 2 \times 25.359 + 1 \times (-0.15) - 2 \times 1.028 = 60.043$ $n = \sqrt{\frac{M + 2\rho R_D}{M - \rho R_D}} = \sqrt{\frac{199.27 + 2 \times 1.387 \times 60.043}{199.27 - 1.387 \times 60.043}} = 1.776$
Vogel Mn_D	Use Table 2 and Eqs. (3) and (4) $Mn_D = 1 \times 52.86 + 1 \times 23.34 + 2 \times 122.039 + 1 \times (-3.53) - 2 \times (-2.56) = 321.85$ $n = \frac{Mn_D}{M} = \frac{321.85}{199.27} = 1.615$

[a] From Cambridge Structure Database (reference code: PHESAZ).
[b] Mean measured refractive index value (Watanabe, 2002).

Table 4
Calculated and literature reported refractive index values for 37 pharmaceutical solids.

Compound	Density	CSD code, reference, or note for density	n_a or n_1	n_b or n_2	n_c	Reference for n	Mean	Eisenlohr	Vogel R_D	Vogel Mn_D
Acetaminophen	1.293	HXACAN01	1.581	1.643	1.705	Jordan (1993)	1.643	1.613	1.614	1.538
Alpha Lactose monohydrate	1.547	Lide (2007–2008)	1.520	1.553		Watanabe (2002)	1.537	1.549	1.552	1.517
Amobarbital	1.167	Craven and Vizzini (1969)	1.471	1.538		Watanabe (2002)	1.505	1.510	1.510	1.482
Anthralin	1.433	ANTHLN	1.580	1.690	1.800	Eisenberg and Schulze (1970)	1.690	1.692	1.697	1.599
Ascorbic acid	1.652	Lide (2007–2008)	1.478	1.670		Watanabe et al. (1985)	1.574	1.571	1.574	1.525
Benzocaine	1.207	QQQAXG01	1.538	1.567		Watanabe (2002)	1.553	1.573	1.576	1.514
Benzoic acid	1.266	Lide (2007–2008)	1.504	1.618	1.700	Watanabe (2002)	1.607	1.588	1.591	1.523
Caffeine	1.230	Lide (2007–2008)	1.470	1.688		Watanabe (2002)	1.579	1.541	1.554	1.529
Carbamazepine	1.343	CBMZPN	1.589	1.750		Watanabe (2002)	1.670	1.713	1.717	1.603
Cocaine	1.250	Hrynchuk et al. (1983)	1.502	1.581		Watanabe (2002)	1.542	1.571	1.585	1.527
Danthron	1.586	INDANT	1.790	1.800		Eisenberg and Schulze (1970)	1.795	1.731	1.730	1.567
Digitoxin	1.285	Cao et al. (2008), a	1.522	1.557		Jordan (1993)	1.540	1.560	1.564	1.536
D-Mannitol	1.489	Lide (2007–2008)	1.520	1.555	1.558	Watanabe (2002)	1.544	1.551	1.551	1.523
Erythromycin	1.212	Cao et al. (2008), a	1.493	1.501		Watanabe (2002)	1.497	1.533	1.551	1.474
Ethionamide	1.272	Cao et al. (2008), a	1.570	1.790		Watanabe (2002)	1.680	1.698	1.710	1.648
Glucose	1.520	Ferrier (1960)	1.528	1.558		Watanabe (2002)	1.543	1.536	1.541	1.547
Griseofulvin	1.460	GRISFL03	1.650	1.672		Watanabe et al. (1985)	1.661	1.610	1.615	1.517
Hydralazine hydrochloride	1.479	HYDLAZ01	1.528	1.803	1.850	Jordan (1993)	1.727	1.754	1.750	1.579
Ibuprofen	1.119	IBPRAC	1.522	1.572	1.644	Jordan (1993)	1.579	1.566	1.570	1.500
Indomethacin	1.372	INDMET	1.550	1.750		Watanabe (2002)	1.650	1.624	1.648	1.618
Lidocaine	1.133	Cao et al. (2008), a	1.486	1.694		Jordan (1993)	1.590	1.600	1.601	1.500
Meprobamate	1.257	Cao et al. (2008), a	1.515	1.544		Watanabe (2002)	1.530	1.531	1.532	1.457
Metharbital	1.288	MDEBAR	1.529	1.533	1.590	Watanabe (2002)	1.551	1.551	1.550	1.494
Niacin	1.469	NICOAC02	1.424	1.717	1.790	Watanabe (2002)	1.644	1.683	1.676	1.599
Nystatin	1.267	Cao et al. (2008), a	1.553	1.513		Watanabe (2002)	1.533	1.560	1.565	1.533
Phenacetin	1.238	PYRAZB21	1.518	1.574	1.750	Watanabe (2002)	1.614	1.608	1.611	1.506
Phenothiazine	1.387	PHESAZ	1.610	1.734	1.950	Watanabe (2002)	1.765	1.771	1.776	1.615
Picrotoxin	1.454	Cao et al. (2008), a	1.520	1.552	1.565	Watanabe (2002)	1.546	1.562	1.570	1.562
Piroxicam Form I	1.471	Vrecer et al. (2003), a	1.464		1.950	Jordan (1993)	1.707	1.699	1.695	1.589
Probenecid	1.312	b	1.550	1.600		Watanabe et al. (1985)	1.575	1.569	1.609	1.504
Quinine	1.222	Cao et al. (2008), a	1.596	1.624	1.689	Watanabe (2002)	1.636	1.626	1.652	1.578
Salicylic acid	1.443	Lide (2007–2008)	1.550	1.740		Watanabe (2002)	1.645	1.628	1.631	1.539
Sorbitol	1.488	b	1.510	1.540		Watanabe (2002)	1.525	1.551	1.551	1.523
Sulfamerazine Form I	1.335	Sun (2004)	1.568	1.657	1.687	Watanabe (2002)	1.637	1.660	1.642	1.646
Sulfathiazole Form I	1.500	SUTHAZ01	1.674	1.685	1.786	Eisenberg and Schulze (1970)	1.715	1.736	1.715	1.616
Urea	1.330	Roberts et al. (1990)	1.484	1.602		Eisenberg and Schulze (1970)	1.543	1.518	1.509	1.460
Urethan	1.150	Bracher and Smallj (1967)	1.420	1.471	1.515	Eisenberg and Schulze (1970)	1.469	1.453	1.455	1.409

a: the density was calculated based on the method in the reference; b: the density was measured in house by helium pycnometry.

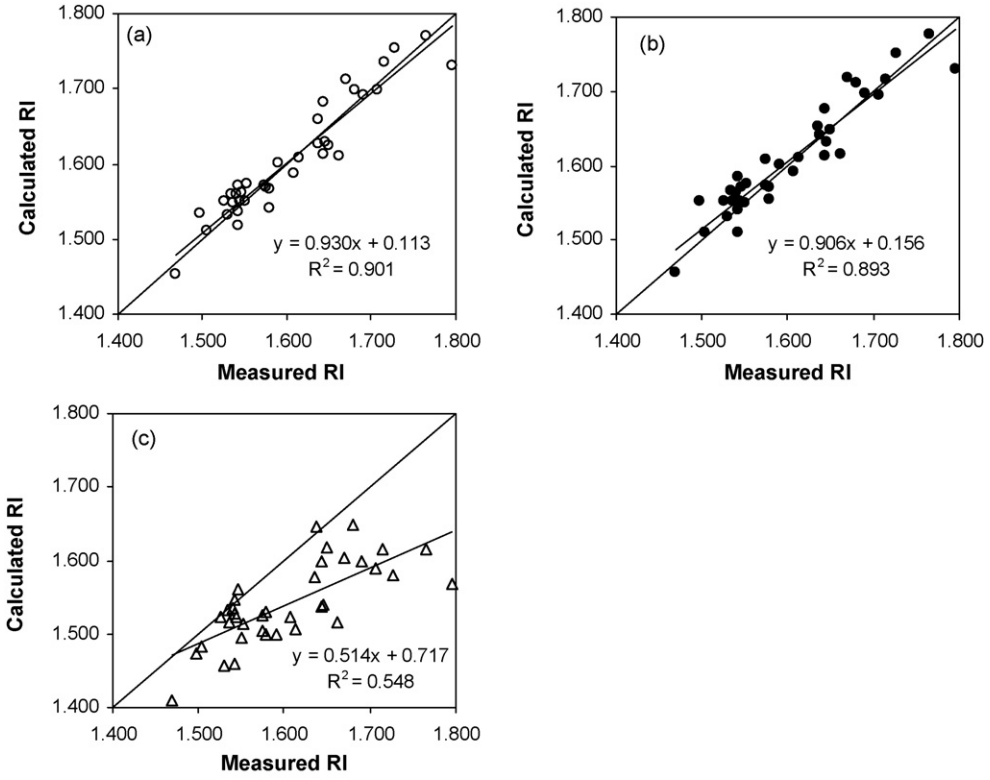


Fig. 3. Calculated refractive index values from (a) Eisenlohr, (b) Vogel R_D, and (c) Vogel Mn_D versus measured values for the 37 literature pharmaceutical solids.

a RMSE of 0.024, while the Vogel method shows an APE of 0.36%, an AAPE of 1.25%, and a RMSE of 0.026. Specifically, all samples showed differences not more than 4% between the measured and calculated values, and more than 80% samples showed differences not more than 2.0%. The results clearly indicate that the calculated refractive values from both Eisenlohr and Vogel R_D methods agree very well with the mean measured values. The error analysis for the 95% confidence intervals indicates that the Eisenlohr and Vogel R_D methods are not significantly different. It is obvious that the Vogel Mn_D method did not give satisfactory estimations against the measured values. The plot shows poor correlation between the calculated and measured values. An APE of −3.85% and an AAPE of 3.95% from Vogel Mn_D are significantly different from the errors from Eisenlohr and Vogel R_D, indicating much larger differences between the calculated and measured values. In addition to the comparison with the mean refractive index, the calculated values were also compared with individual principal indices (n_a, n_b and n_c) or key indices (n_1 and n_2). Much larger differences between the calculated and individual values were observed than between the calculated and mean values. Therefore, the calculated values are the best estimations for the mean refractive index values.

Table 5
Summary and comparison of the refractive index predictions from the three methods for 37 literature pharmaceutical solids.

Methods	Eisenlohr	Vogel R_D	Vogel Mn_D
APE (%)	0.10	0.36	−3.85
95% CI (%)	(−0.39, 0.59)	(−0.16, 0.87)	(−4.85, −2.86)
AAPE (%)	1.22	1.25	3.95
95% CI (%)	(0.93, 1.50)	(0.92, 1.58)	(3.00, 4.90)
RMSE	0.024	0.026	0.082
95% CI (%)	(0.018, 0.029)	(0.019, 0.031)	(0.059, 0.100)
PE NMT 2%	84%	81%	35%
PE NMT 4%	100%	100%	65%

Note: PE = percent error; APE = average percent error; AAPE = average absolute percent error; CI = confidence interval; RMSE = root mean square error; NMT = not more than.

3.3. Calculations and in-house measurements

A similar evaluation was conducted for the Pfizer APIs. The overall mean measured refractive index of the 87 APIs was determined to be 1.598, similar to the overall mean value of 1.603 for the surveyed literature compounds. A subset of 41 APIs was selected with a similar sampling procedure described in Section 3.2, and the refractive index calculations were conducted for the 41 APIs. The density values used for the calculations were measured by helium pycnometry or predicted using the Immirzi and Perini method (Cao et al., 2008). The calculated refractive index values were then evaluated against the measured ones, as plotted in Fig. 4. Table 6 summarizes the analysis results. The APEs are 2.51% for

Table 6
Summary and comparison of the refractive index predictions from the three methods for the 41 Pfizer APIs.

Methods	Eisenlohr	Vogel R_D	Vogel Mn_D
APE (%)	2.51	2.98	−2.97
95% CI (%)	(1.24, 3.78)	(1.45, 4.51)	(−4.62, −1.32)
AAPE (%)	3.77	4.46	4.92
95% CI (%)	(2.85, 4.68)	(3.33, 5.58)	(3.81, 6.02)
RMSE	0.074	0.089	0.099
95% CI (%)	(0.053, 0.090)	(0.065, 0.108)	(0.076, 0.118)
PE NMT 2%	49%	27%	24%
PE NMT 5%	71%	73%	59%

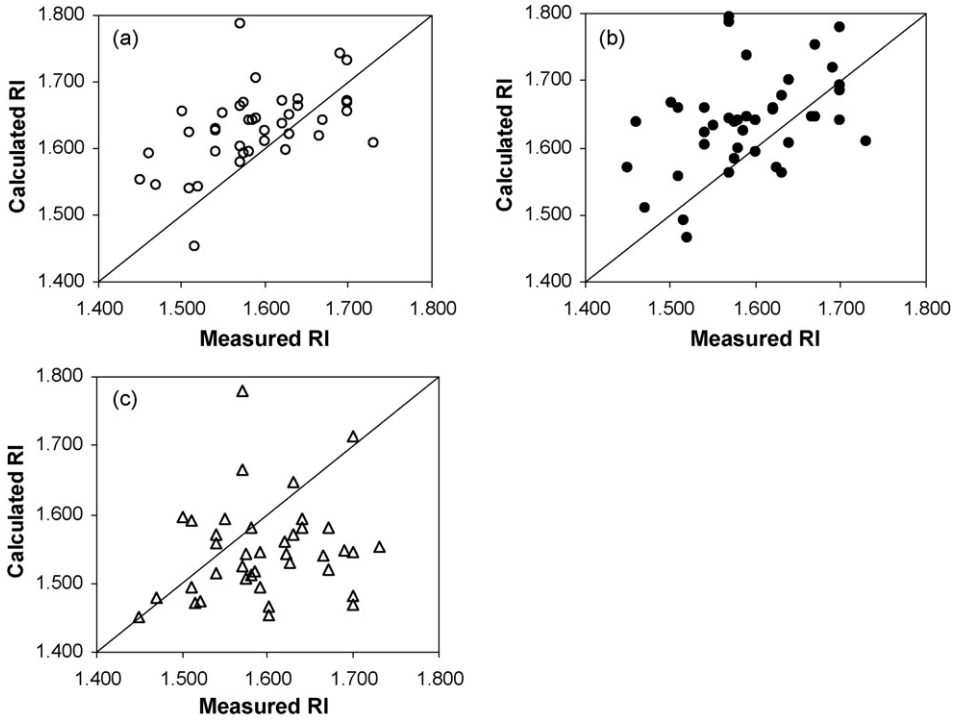


Fig. 4. Calculated refractive index values from (a) Eisenlohr, (b) Vogel R_D, and (c) Vogel from Mn_D versus measured values for the 41 Pfizer APIs.

Eisenlohr, 2.98% for Vogel R_D, and −2.97% for Vogel Mn_D, the AAPEs for all methods are between 3.70% and 5.00%, and the RMSEs are between 0.070 and 0.100. This error analysis indicates a larger difference between the calculated and measured values exists for the Pfizer APIs than for the surveyed literature compounds. The calculated values from the Eisenlohr and Vogel R_D methods were not significantly different from each other but were often larger than the measured ones, while the values calculated from Vogel Mn_D were smaller than the measured in most cases. However, there were still a large proportion of the samples that showed a close agreement between the measured and calculated values from the Eisenlohr and Vogel R_D methods. Specifically, for the Eisenlohr method, about 46% samples exhibited differences between the calculated and measured values of not more than 2.0%, while about 71% samples showed differences of not more than 5.0%. Similarly, for the Vogel R_D method, about 73% samples showed differences between the calculated and measured values of not more than 5.0%.

4. Discussion

Evaluation of the literature data clearly indicates that the Eisenlohr and Vogel R_D methods each give accurate estimations of the mean refractive index of pharmaceutical solids. Both methods provide similar accuracy, but the Eisenlohr method offers the advantages of being simple and quick. It was found during the computation that the Eisenlohr method can be at least two times faster than the Vogel method. Therefore, when applicable, the Eisenlohr method is preferred for refractive index predictions. However, the Vogel method can apply to more classes of compounds such as phosphates, sulfites, sulfates, nitro compounds, nitrates, and carbonates.

Based on Eq. (2), errors from density values can directly affect the calculation accuracy of both Eisenlohr and Vogel R_D methods. To analyze the error propagation from density, the derivative of n versus ρ is taken, and the relationship between change in n (Δn) and change in ρ ($\Delta\rho$) can be established.

$$\frac{\Delta n}{\Delta \rho} = \frac{3c}{2(c-\rho)^2\sqrt{\frac{c+2\rho}{c-\rho}}} \tag{9}$$

where c is the ratio of M to R_D. To estimate Δn from $\Delta\rho$, c and ρ values will be needed. From the calculations using both Eisenlohr and Vogel R_D methods, it was found that the c values typically ranged from 3.5 to 3.9 with an average value of ~3.7. For most pharmaceutical solids, the density is typically in the range of 1.200–1.500 (Cao et al., 2008; Hancock et al., 2003). For the 37 literature compounds, the average density is about 1.35. Therefore, the values of 3.7 and 1.35 are used for c and ρ in Eq. (9) to determine the relationship between Δn and $\Delta\rho$.

$$\Delta n \approx 0.6\Delta\rho \tag{10}$$

This relationship means that if a 5% error in density determination will translate into a ~3% error in refractive index calculation. The 3% error for a refractive index value of 1.60 would be ~0.05. Therefore, the error in density has significant impact on the predication accuracy for the refractive index. Specifically, when the density is calculated from the Immirzi and Perini method, a 2–3% absolute percent error is observed (Cao et al., 2008). This density error translates into a ~1.5% absolute percent error in refractive index calculations, which is similar to what observed from both Eisenlohr and Vogel R_D methods. In summary, this error propagation analysis suggests that the predicted density data are suitable for use in the refractive index calculations when X-ray data and measurements are not available.

It is not surprising to see larger differences between the calculated and measured values for some Pfizer APIs than for the surveyed literature compounds. Several possible factors can contribute to the larger differences between calculated and measured values for these samples. Firstly, sample characteristics such as chemical structure, polymorphism, crystal habit, particle size, or API purity may have been less well controlled for the exploratory

drug candidates. This could potentially increase the error in either the refractive index predictions and/or measurements. Secondly, about 40% tested Pfizer APIs had calculated density, while all tested literature compounds had X-ray or pycnometry density values. As discussed above, error from density calculation can be propagated to refractive index predictions. Thirdly, since about 25% of the tested 41 Pfizer APIs had only one refractive index from the measurements, it is possible that those measurements were not truly representative of the mean refractive index values of the APIs. For the surveyed literature compounds, when individual refractive index values such as n_a or n_c were evaluated against the calculations, larger errors were also observed compared to when using the mean values. Additionally, the analysis for the STDs and max–min showed the possible variation of a single refractive measurement can be easily as large as 0.1 from the mean value. However, there was no obvious difference in the accuracy of the prediction for Pfizer API samples with one or more than one refractive index value, possibly due to limited sample size. Overall, since the analysis for the surveyed literature pharmaceutical compounds indicate that the predictive Eisenlohr and Vogel R_D methods give accurate refractive index estimations, we believe that the use of these two predictive methods for the authentic APIs is generally accurate and reliable. Furthermore, the use of the predictive methods can eliminate the time-consuming and labor-intensive laboratory measurements. This could be of benefit, for example, for pharmaceutical applications such as particle size analysis, where the mean refractive index is required for laser diffraction measurements using the Mie theory (Jones, 2003).

5. Conclusions

This study has shown that the refractive index of pharmaceutical solids can be estimated by the predictive methods developed by Eisenlohr and Vogel. When compared with measured values, the estimated results from the Eisenlohr and Vogel R_D methods show absolute percent errors less than 1.5%. The evaluation for in-house measurements for Pfizer APIs showed larger differences between the calculated and measured refractive index values due to difficulties in the measurements. The results indicate that the Eisenlohr and Vogel R_D methods can provide fast and accurate results for predicting the refractive index.

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