4-1-2022

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Purpose. To determine the density variation between (1) the measured density and manually calculated density, (2) density variation of different lots, and (3) density variation of different drug manufacturers in order to support institutions using gravimetric compounding methods.

Summary. Seventeen sterile injectable ingredient (drug) vials frequently used to make compounded sterile products (CSPs) were identified based on the ability to ensure that for each drug there were vials produced by 2 different manufacturers and 2 lots produced by the same manufacturer. Each drug's density was measured using a density meter and by manual calculation using the institution's density formula. Density differences were compared between the 2 different methods. Overall, the average drug density difference between the measured versus calculated density was determined to be 0.022. Further analysis revealed the average difference between the different lot numbers of the same manufacturers was 0.005 for the nonhazardous drugs and 0.0001 for the hazardous drugs. The average difference between the different manufacturers of the same drug was determined to be 0.008 for the nonhazardous drugs and 0.001 for hazardous drugs.

Conclusion. No clinically meaningful difference exists when manually calculating a drug's density compared to measuring a drug's density using a density meter. In addition, there does not appear to be a sizeable density variation between the same drugs in separate lots or produced by different manufacturers.

Keywords: drug compounding, pharmaceutical preparations, specific gravity

Am J Health-Syst Pharm. 2022;79:689-695

The use of intravenous workflow management systems (IVWMSs), including those with capabilities for gravimetric-based verification of compounded sterile products (CSPs), by health-system pharmacies has increased from 8% in 2014 to 36% in 2021.[1] The Institute for Safe Medication Practices (ISMP) "Guidelines for Safe Preparation of Compounded Sterile Preparations" strongly encourage the use of technology-assisted workflow, also known as an IVWMS, with gravimetric capabilities to produce CSPs.[2] Studies have shown that the use of gravimetric IVWMSs has increased the error capture rate in preparation of nonhazardous CSPs, leading to safer and more accurate products.[3,4] Other studies comparing gravimetric IVWMSs to a volumetric-based system in the compounding of hazardous drugs have found that the use of a gravimetric IVWMS produced more accurate products.[5-8]

Gravimetric preparation assures the correct volume and assesses syringe volume consistency and accurate reconstitution. When using gravimetric verification, the ordered dose is compared to the final syringe weight by using a medication's density. One can use a manufacturer-reported specific gravity or calculate the density from the drug label information provided by the manufacturer to the Food and Drug Administration (FDA).[9]

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https://doi.org/10.1093/ajhp/zxab440

Although incorporating gravimetric-based verification improves the safety and accuracy of CSPs, several challenges exist to implementing a gravimetric-based system. One challenge with gravimetric analysis is the limited availability of manufacturer-reported densities for medications used in CSPs.[10] The accuracy of gravimetric compounding is improved with densities that are more accurate. The use of a density meter may financially deter institutions from the use of gravimetric-based verification. However, it is not known if the manually calculated density leads to variation in the gravimetric analysis when compared to density directly measured by a density meter.

Until the FDA requires manufacturers to report drug densities, institutions have to rely on IVWMS vendors to create a density database or create a database on their own, potentially crowdsourcing with peers to obtain all the necessary density information. Currently, it is not known whether there is clinically significant or insignificant density variability in the same drugs produced by different manufacturers or in different lots produced by the same manufacturer. During a gravimetric IVWMS workflow, the system may rely on one density for a given drug, which would not take into account any difference between lots or manufacturers of the same drug if clinically significant differences exist. If the density variability is significant between different lots or manufacturers of the same drug, the specific lot number for each drug and manufacturer would have to be recorded when establishing a density database. Such variances would significantly hinder the creation of such a database, as institutions receive varying products as the institution's primary wholesaler, availability of the drug, and prices change.

To our knowledge, this is the first study to compare the density variations of commonly compounded drugs when measured by a density meter versus manual calculation of density, as well as the first study to quantify the density variation between different lot numbers and manufacturers of the same drug. With this knowledge, institutions can accurately build their drug density database in order to successfully implement gravimetric-based IVWMS.

KEY POINTS

- The use of manually calculated densities is an acceptable alternative to measuring densities with a densitometer when using gravimetric technique in pharmacy compounding.
- Clinically insignificant differences were seen between drug densities of the evaluated samples of the same drug produced in different lots or by different manufacturers.
- The combination of this information could help lead to a shared repository of drug density data among institutions to accelerate the use of gravimetric technique and increase patient safety.

The purpose of this study is to evaluate the density variability when it is manually calculated versus measured directly using a density meter while also comparing the lot and manufacturer density variability of the same drugs.

Study methodology

The study consisted of 2 separate phases: a collection phase and a measurement phase. The collection phase involved the selection and procurement of the study drugs from the primary wholesaler to the institution and regional hospitals. The measurement phase involved determining the density of the included study drugs either by using the density meter or by manual calculation.

Collection protocol. In order to determine the drugs used for measurement, a 1-year purchase history obtained from the primary wholesaler was analyzed. This yielded a list of the top 200 ingredient vials used in routine practice.

Drugs from the top 200 list were selected if they met the following criteria:

- Vial price of $20 or less
- For each study drug, 2 different manufacturers were available and for each manufacturer, 2 different lot numbers were available

Two different densities were collected from the different manufacturers of each drug, and 2 separate densities were collected from the different lots from each of the manufacturers. As a result, there were 4 vials for each drug within the study. A total of 17 drugs that matched the selection criteria were available to be purchased, representing a total of 68 vials, representing 136 measurement samples in total (Table 1).

Measurement protocol. Drugs were separated into hazardous and nonhazardous drugs based on he National Institute for Occupational Safety and Health (NIOSH) list of hazardous drugs.[11] The 17 drugs were examined in the measurement phase. The measurement phase consisted of measuring each vial using the density meter and manually calculating the density, with both procedures performed according to existing institution protocols described in Box 1 and Box 2, respectively.

Density meter. For drugs requiring reconstitution by the user, each drug was reconstituted via gravimetric methods using the institution's gravimetric-based IVWMS (BD Pyxis IV Prep, v. 2.4; Becton, Dickinson and Company, San Diego, CA) according to institutional instructions with either sterile water for injection or 0.9% sodium chloride injection. Hazardous drug measurements were done in an ISO class 5 environment within a biological safety cabinet. Immediately after a drug was reconstituted, density measurements obtained

Table 1. Drugs Included in Analysis

Drug Name	Concentration, mg/mL[a]	Manufacturer	NDC Number	Lot Number
Acetazolamide	100	West-Ward	00143-9503-01	1801124.1
Acetazolamide	100	West-Ward	00143-9503-01	1601237.1
Acetazolamide	100	Xgen	39822-0190-01	AJ3482
Acetazolamide	100	Xgen	39822-0190-01	AH8249
Azithromycin	100	Fresenius Kabi	63323-0398-10	6118550
Azithromycin	100	Fresenius Kabi	63323-0398-10	6118424
Azithromycin	100	Apotex Corp	60505-6076-04	MT611
Azithromycin	100	Apotex Corp	60505-6076-04	MT709
Cefazolin	330	Novaplus	00143-9262-01	186077.1
Cefazolin	330	Novaplus	00143-9262-01	177046.1
Cefazolin	330	West-Ward Pharmaceuticals	00143-9924-90	188024.1
Cefazolin	330	West-Ward Pharmaceuticals	00143-9924-90	186075.1
Cefoxitin	180	Fresenius Kabi	63323-0342-25	T65L
Cefoxitin	180	Fresenius Kabi	63323-0342-25	EE3V
Cefoxitin	180	WG CriticalCare	44567-0246-25	238C
Cefoxitin	180	WG CriticalCare	44567-0246-25	786J
Ceftriaxone	100	Hospira	00409-7332-11	HR3356
Ceftriaxone	100	Hospira	00409-7332-11	HU0230
Ceftriaxone	100	Sandoz	00781-3209-90	HK2095
Ceftriaxone	100	Sandoz	00781-3209-90	HK2103
Dexamethasone sodium phosphate	4	Fresenius Kabi USA	63323-0165-05	6115812
Dexamethasone sodium phosphate	4	Fresenius Kabi USA	63323-0165-02	6119642
Dexamethasone sodium phosphate	4	Mylan	67457-0423-00	7050833
Dexamethasone sodium phosphate	4	Mylan	67457-0423-00	7050832
Fludarabine	25	Sagent	25021-0242-02	31323090B
Fludarabine	25	Sagent	25021-0242-02	31323090B
Fludarabine	25	Fresenius Kabi	63323-0192-02	6119684
Fludarabine	25	Fresenius Kabi	63323-0192-02	6119685
Fluorouracil	50	Fresenius Kabi	63323-0117-10	6119092
Fluorouracil	50	Fresenius Kabi	63323-0117-10	6118877
Fluorouracil	50	Accord	16729-0276-03	PW03866
Fluorouracil	50	Accord	16729-0276-03	PX02705
Furosemide	10	Hospira	00409-6102-18	W39768
Furosemide	10	Hospira	00409-6102-18	W25774
Furosemide	10	Claris Lifescience	36000-0282-25	A0A0749
Furosemide	10	Claris Lifescience	36000-0282-25	A0B0186
Methotrexate	25	Teva	00703-3671-01	18B08PA
Methotrexate	25	Teva	00703-3671-01	17K22MA

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Table 1. Drugs Included in Analysis

Drug Name	Concentration, mg/mL[a]	Manufacturer	NDC Number	Lot Number
Methotrexate	25	Hospira	61703-0350-37	F104437AA
Methotrexate	25	Hospira	61703-0350-37	E114437AA
Norepinephrine bitartrate	1	Teva	00703-1153-01	31323263B
Norepinephrine bitartrate	1	Teva	00703-1153-01	31323347B
Norepinephrine bitartrate	1	Claris Lifescience	36000-0162-01	17367C
Norepinephrine bitartrate	1	Claris Lifescience	36000-0162-01	17348D
Olanzapine	5	American Regent	00517-0955-01	702600
Olanzapine	5	American Regent	00517-0955-01	804200
Olanzapine	5	Sandoz	00781-3159-72	NU812
Olanzapine	5	Sandoz	00781-3159-72	NU810
Ondansetron	2	West-Ward	00641-6078-01	037415
Ondansetron	2	West-Ward	00641-6078-01	117318
Ondansetron	2	Hospira	00409-4755-18	X11950
Ondansetron	2	Hospira	00409-4755-18	W71681
Paclitaxel	6	Hospira	61703-0342-50	E026865BA
Paclitaxel	6	Hospira	61703-0342-50	F026865AA
Paclitaxel	6	Fresenius Kabi	63323-0763-50	8780026A01
Paclitaxel	6	Fresenius Kabi	63323-0763-50	8780059A01
Potassium chloride	2 mEq/mL	Hospira	00409-6651-19	89-446-DK
Potassium chloride	2 mEq/mL	Hospira	00409-6651-19	90-460-DK
Potassium chloride	2 mEq/mL	APP Pharmaceuticals	63323-0965-20	6015562
Potassium chloride	2 mEq/mL	APP Pharmaceuticals	63323-0965-20	6017003
Vancomycin	50	Athenex	70860-0105-20	YV746
Vancomycin	50	Athenex	70860-0105-20	163708
Vancomycin	50	Hospira	00409-4332-01	841653A
Vancomycin	50	Hospira	00409-4332-01	781903A
Vecuronium	1	Sun Pharma Global	47335-0931-40	JKS0398A
Vecuronium	1	Sun Pharma Global	47335-0931-40	JKS0478A
Vecuronium	1	Teva	00703-2914-01	31324476B
Vecuronium	1	Teva	00703-2914-01	31324532B

[a]All concentrations expressed as mg/mL unless otherwise indicated.

using a density meter (Mettler Toledo DA-100M Density Meter; Mettler Toledo, Columbus, OH) were collected. Density measurements were examined using the institution's protocol (shown in Box 1). Each vial's density was measured twice (to account for same-sample variances) using the density meter and, in some instances, 3 times; where there was a difference, the 2 or 3 values were averaged for the final analysis. Two different densities were collected for the products for different manufacturers of each drug, and 2 separate densities were collected for the different lots of each of the manufacturers. In the end, there were 8 different density measurements of each study drug.

Manual calculation of densities. The density of each study drug was manually calculated according to institutional

Box 1. Institutional Protocol for Calculating Densities by Density Meter

1. Place the drying tube in the opening of the pump box.
2. Insert one of the sample inlet/outlet tubes in the sample outlet and route its other end to a waste beaker.
3. Turn on the instrument.
4. Rinse the measurement tube with a syringe containing 10 mLofethanol. Slide the tube of the air pump over the sample inlet to dry the measurement tube. Do this by pressing the PUMP key. An asterisk shows that the pump is active. The instrument itself checks when the measurement tube is dry and then switches off automatically.
5. Enter the temperature for which you plan to measure your sample. Do this by pressing FUNC, then "arrow up" or "arrow down" repeatedly until "Function 1 Meas. Parameter" appears. Press ENTER. Use the arrows to set the temperature, then press ENTER to confirm.
6. Determine the factor of the measurement tube. Press the CALIB key. After the instrument measures the density of air, "Set Water" will be displayed. Inject distilled, degassed water into the sample inlet using a syringe and press CALIB. If the instrument correctly displays the density of water, return to initial position by pressing RESET. Correct densities of water at various temperatures are listed on page 13 of the instrument manual. If the difference between the measured and the listed value is greater than 0.001 g/cm^3, check whether the measurement tube is clean and repeat the calibration.
7. Press the FUNC key, then press "up" or "down" arrow repeatedly until "Function 0 Sample No. Clear" appears. Press ENTER. This sets the sample number for the next measurement to 1.
8. Press RESET to obtain initial display.
9. Repeat step 4 and inject the sample using a syringe.
10. Press the MEAS key.
11. "Measurement" flashes until the value is stable, then the result flashes until you press RESET.
12. Enter densities up to the thousandths place (eg, 1.001 g/mL).

protocol, as seen in Box 2. For manual calculations the following formula for density was used:

$$Density = \frac{\begin{array}{c}\text{Total Ingredient Mass} \\ (\text{active} + \text{inactive}) \\ + \text{Diluent Mass}\end{array}}{\text{Final Volume}}$$

Results

Density meter versus manual calculation. A total of 17 drugs were included within the study, as seen in Table 1. Thirteen of the study drugs were classified as nonhazardous and 4 were classified as hazardous. A total of 68 density measurements were included in the analysis. The average difference between the density measured using the density meter and the manually calculated density was determined to be 0.0217. This equates to an average difference of 1.66%.

Lot variation. For nonhazardous drugs, the average difference between the different lot numbers of the same manufacturer was determined to be 0.0005. For hazardous drugs, the average difference between the different lots of the same manufacturer was determined to be 0.0001.

Manufacturer variation. For nonhazardous drugs, the average difference between values for products of different manufacturers of the same drug was determined to be 0.0008. For hazardous drugs, the average density difference between values for 2 different manufacturers of the same drug was determined to be 0.001. Full data can be seen in Appendix 1.

Discussion

This study is the first to our knowledge that compared measured densities to manually calculated densities in order to advance the practice of using gravimetric technique. Our findings suggest that there was a clinically insignificant difference, as demonstrated by the minute difference in a given drug's density measured using a density meter compared to values measured using the formula. While there is no known density variation that would lead to inaccurate final compounded products, it is reasonable to suggest that the average density difference of 0.0217 would not lead to clinically significant differences in patient outcomes. With the knowledge gained in our study, we believe that when a manufacturer does not report a drug's density, an institution may use a manually calculated density when using gravimetric technique to prepare a CSP. Another barrier to the use of a density meter is the requirement of training staff on how to use the machine. Using a calculated density when the manufacturer has not reported a density will allow an institution to save money by forgoing the initial cost of a density meter as well as associated maintenance fees and drug waste associated with use of the density meter. These findings may allow more institutions to confidently implement gravimetric compounding workflow for as many products as possible.

A common question that arises when implementing gravimetric technique is if there is a density difference in using the same drugs but with different lots, or the same drug with different manufacturers. When finding a density with a density meter, there could be differences between values for the same drug and different manufacturers or even in different lots of the same drug produced by the same manufacturer. A difference amongst

Box 2. Institutional Protocol for Manually Calculating Densities

For drugs already in solution:

1. Go to DailyMed website (administered by US National Library of Medicine) and type in the National Drug Code number of the product.
2. Go to the "Description" section of DailyMed entry.
3. Look for paragraph describing the contents of each mL.
4. Write out the mass of active ingredient in each mL.
5. Write out the mass of inactive ingredient in each mL. Do not include any ingredients listed at the bottom of the description that "may have been added to adjust pH."
6. Determine total volume of the product to calculate total mass of active and inactive ingredient.
7. Add the mass of all ingredients and convert to grams.
8. Calculate the volume of the diluent in the product using the equation: Total volume – (0.7 X mass of ingredients) = diluent volume
9. Multiply diluent volume by 0.997 to get mass of diluent.
10. Add mass of ingredients to the mass of diluent.
11. Divide mass by volume of product to get density.

For drugs to be reconstituted:

1. Multiply the volume of sterile water for injection (SWFI) to be added by 0.997 and add this mass in grams to the mass of the powder.
2. Divide this total mass (in grams) by the volume of SWFI used to reconstitute (in mL).

manufacturers and/or lots of the same manufacturer would require a significant increase in the drug database maintenance. Up until now, it has been assumed by health-system leaders that drugs, regardless of manufacturer or lot, have the same density. Our study compares the differences of measured densities between the same drug produced by different manufacturers, as well as differences in density values for drugs produced by the same manufacturer but in different lots. Our results indicate that within the samples of hazardous and nonhazardous drugs evaluated, there was only a marginal difference between different lots produced by the same manufacturer. The results also indicated that there was a clinically insignificant difference in the measured densities of similar hazardous and nonhazardous drugs that are produced by different manufacturers. Institutions often set the IVWMS to an acceptability threshold of ±5% of the intended dose. The 1.66% average difference seen in this study is within the accepted tolerance of ±5%. The results of this study indicate that only 1 entry per drug needs to be entered into a gravimetric drug database, regardless of lot number or drug manufacturer.

In order to ensure the accuracy of the database, an independent double check of the manually entered density is recommended. An important benefit of using gravimetric methods is to improve patient safety through improved accuracy, so ensuring the density is entered correctly into the system is equally important.

A limitation of this study is that there is not a known density difference that would yield clinically significant results. However, based on the minute differences in densities reported, it is reasonable to predict there would not be a difference in the final compounded product when verification is performed using a gravimetric technique.

Conclusion

There is a clinically insignificant difference measured density and calculated density when performing gravimetric technique. A minor difference is seen in drug densities of the same drug produced in different lots or by different manufacturers. While density data may appear to hinder adoption of gravimetric verification in pharmacy compounding, confidence in manual calculations plus a shared repository of drug density data among institutions may accelerate developments in this important area of patient safety.

Disclosures

The institution received a grant from Becton, Dickinson and Company (BD) to perform this study. Dr. Amerine has served as a consultant for BD. Dr. Johnson and Dr. Gehrig are employees of BD.

Previous affiliations

At the time of writing Dr. Pansour and Dr. Higgins were PharmD students at UNC Eshelman School of Pharmacy and Dr. Pyle was affiliated with UNC Health.

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