PHARMACY PRACTICE

Refractometric Screening of Oral Syringes

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INTRODUCTION

Preventing and detecting dispensing errors is a common goal of every pharmacy department and every pharmacy based quality assurance program. Numerous checking procedures have been devised for checking dispensed medication. An optimum checking procedure would be quick, simple, and accurate. However, most testing procedures which are quick (visual inspection) are not accurate and more accurate or specific tests are not quick (liquid chromatography). In 1987, Meyer et al[1] described the use of refractometry in the quality assurance of pediatric parenteral nutrient solutions. This procedure is rapid, simple, and inexpensive and can be applied to a wide array of drugs in solution.

Refractometry is based on the refractive index (RI) measurement of different media, and is specified RI (t, λ). The RI is characteristic of a molecule in solution and changes with both temperature (t) and wavelength (λ). The refractive index is generally estimated at 20°C ± 0.5 and is referenced to the D line of sodium (λ = 589.3 nm). Since drugs in solution will have different refractive index measurements, a refractometer can be used to qualitatively identify syringe contents. It can be part of a quality assurance program of solutions prepared according to good manufacturing practice.[3]

Most applications, described to date, have been used to reduce drug diversion involving narcotics[4] or controlled substances,[5-8] but it has also been used in the quality assurance of pediatric parenteral nutrient solutions,[1] anaesthetics and other drugs.[9]

Refractometry can also be used to decrease the risk of patients receiving adulterated products. Prior to this study, the pharmacy of Brabois Adultes Hospital dispensed every oral solution and some syrups in unit-dose oral 1, 3, and 5 mL syringes or 30 mL vials to wards without any quality control testing.

The objective of this study was to evaluate the feasibility of refractometric testing of oral syringes in order to detect packaging errors before dispensing. To realise this objective, reference refractive indices were determined for solutions from original vials and daily refractometric quality control was completed for one year.

METHODS

Calibration and use of refractometer

Each day before being used, the hand-held refractometer with thermometer (Model R5000; Atago, Japan) was calibrated with distilled water. A small drop (100-150 μL) of the test solution was placed on a designated window (main prism) of the instrument and covered with the sub prism. The eyepiece was directed to a light source, and the reading was taken as the boundary between the dark background and the bright background against the calibrated scale. The scale ranged from 1.333 to 1.520. Using an adjustment screw, the reading for distilled water was set at 1.333 each day. Following each measurement the refractometer window was rinsed with several drops of water and methanol successively to remove water-soluble and fat-soluble residues, respectively. Then the prism surface was dried with a non-abrasive wipe.

Sixty-four of the most commonly dispensed oral solutions at the Brabois Adultes Hospital were selected for the study. Reference values were estimated for solutions from commercially available medications. The refractive index of each solution was read three times for each lot and the mean RI was calculated for temperatures between 20°C and 28°C. This mean value for each temperature was used as a limit of the reference range in the quality assurance program. One person performed all the refractometer readings so that inter-operator variability was eliminated in this study. Each measurement takes approximately one and one-half minutes. This time includes the time to complete the refractometric reading, record the results, and clean the refractometer.

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Daily Testing Program

All oral drops were contained in syringes (1, 3 or 5 mL) or in vials (30 mL). Some syrups were contained in vials (30 mL). During the first six months of the program, three unit-dose solutions were randomly and analysed each day. The technician preparing the solutions did not know which syringes were taken for quality control. Refractometry values of well mixed tested solutions were compared with the range obtained from reference solutions. When a RI value of a sample syringe did not agree with the expected reference value, the remaining syringes with the same drug and the commercially available multi-dose vials were tested.

As a result of three errors found in the first six months, daily quality control was extended to all oral syringes in the second six months of the program.

RESULTS

Reference RI values

Since RI measurements are sensitive to temperature, the reference range was determined for each drug at both 20°C and 28°C (Table I). This table shows both the generic and the proprietary names of the drugs in France and in Canada.[11-13]

Over the first six-month period of the program, 428 RI measurements were carried out. On three occasions, the refractive index reading obtained from the solution in a syringe was outside the predicted range. Two drugs were involved. Valium® (diazepam: RI at 1.407 instead of 1.400-01.403) and Théralène® (trimaprazine: two incidents - RI at 1.443 and 1.442 instead of 1.410-1.413).

Due to these incorrect results, daily quality control was extended to all oral syringes for another six months. During the second six months, 2,400 samples were analysed. No errors were revealed during this daily systematic analysis.

DISCUSSION

All measurements in this study used well mixed solutions. Bardas et al[7] have found that refractometric discrepancies were often caused by analysis of non-homogenous drug solutions. With non-homogeneous solutions, there may not be a sharp interface between light and dark fields in the refractometer, and a precise reading of the refractive index may be difficult.

Our results suggest that refractometer readings are sufficiently reproducible to provide reliable measurements for a wide range of drug solutions currently used in hospitals. Our experience with various lots of the same product further suggests that the variability among lots is low ($\pm$ 0.001 units). However, Cheung et al[5] have reported that equivalent-concentrations of the same drug in solutions produced by different manufacturers do not have the same refractive index. Thus, pharmacists should not extrapolate the RI values for one manufacturer's drug preparation to another.

A narrow RI range is more useful in a quality control screening procedure such as this, since similar refractive indices can be obtained with different drug solutions. In certain cases, RI measurements were slightly different for different concentrations of the same drug solution, for example, with Neuleptil 1 and 4% (Table I). However, it is not always possible to differentiate one drug from another, if they have similar RI ranges. There were several overlaps in RI measurements, which limits the use of this method for drug identification. Some drug solutions with the same refractive index are presented in Table II. We have found that a range greater than 0.003 units is not sufficiently selective, although, for most drugs the variation in the interval was small. Of the 64 drugs analysed, 45 had an interval of less than or equal to 0.002 units, and 12 had an interval equal to 0.003 units. Of the remaining seven, four drugs had a range of 0.004 units and three had a range of 0.005 units (Table I). Duxil®, which is a white opaque suspension, gave one of the widest intervals of 0.005 units. The best refractometric readings are obtained with clear and transparent solutions.

Since this test is not specific. If the RI reading is not as expected, this indicates that the solution is not the one indicated on label. However, if the RI reading is as expected, this indicates that the drug in solution may be either the correct drug solution or another solution with the same RI value. Nevertheless, we observed three incorrect values (one with Valium® and two with Théralène®) during the first six months, each indicating a packaging error.

Hand-held refractometry appears to be a useful tool for pharmacists in monitoring the appropriate labelling of drugs in solution. Little training is required, and the amount of sample required per test is only about 100 mL. The screening procedure is simple, fast (one and one half minutes per test), and inexpensive. However, this test is not specific. Different drugs may have the same refractive indices. Nevertheless, the use of such a screening procedure increases the pharmacist's ability to determine if a syringe is correctly labelled. Refractometry of oral syringes has improved the pharmacy department's quality assurance program, reducing the risk of a patient receiving the wrong medication.

REFERENCES:

1. Meyer GE, Novielli KA, Smith JE. Use of refractive index measurement for quality assurance of pediatric nutrient solution. *Am J Hosp Pharm* 1987; 44: 1617-20.
2. Pharmacopée Française. Xème édition, Moulins-lès-Metz: Maisonneuve, 1982.
3. Ministère des affaires sociales et de l'intégration. Bonnes Pratiques de Fabrication. Paris: Direction des journaux officiels, 1992 (Bull off n°91/17bis).
4. Mac Donnell N, Leister K. A rapid method for detecting tampering with injectable narcotics. Proceedings of the American

Society of Hospital Pharmacists Midyear clinical meeting 1989; 24 P-300D:107.
5. Gill DL Jr, Goodwin SR, Knudsen AK, et al. Refractometer screening of controlled substances in an operating room satellite pharmacy. *Am J Hosp Pharm* 1990; 47: 817-8.
6. Cheung JF, Chong S, Kitrenos JG, et al. Use of refractometers to detect controlled-substance tampering. *Am J Hosp Pharm* 1991; 48: 1488-92.
7. Frankenfield DL, Johnson RE. Refractometry of controlled substances. *Am J Hosp Pharm* 1991; 48: 2129-30.
8. Bardas SL, Ferraresi VF, Liebermann SF. Refractometric screening of controlled substances used in operating rooms. *Am J Hosp Pharm* 1992; 49: 2779-81.
9. Donnelly AJ. Refractometry in an operating room pharmacy. *Am J Hosp Pharm* 1990; 47: 1753-4.
10. Product Monograph Atago Model R5000 Refractometer Bioblock Scientific, Illkirch-Graffenstaden, France, 1994.
11. Reynold JEF, ed. Martindale: The Extra Pharmacopoeia. 30th ed London: *The Pharmaceutical Press*, 1993.
12. Vidal®. 70ème éd. Paris: OVP éditions du Vidal®, 1994.
13. Compendium of Pharmaceutical Specialities. 29th ed. Ottawa (Ontario) Canada: *Canadian Pharmaceutical Association* 1995.

Table I. Range of refractive indices of oral solutions

Proprietary Names (France) [1]	Proprietary Names (Canada) [1,2]	Generic Name	Range of RI
Alcaphor	NA	trometamol citrate sodium citrate dipotassium citrate	1.385-1.387
Artane 0.4%	Artane 0.04%	benhexol HCl;	1.407-1.409
Atarax 0.2%	Atarax 0.2%	hydroxyzine HCl;	1.438-1.440
Bisolvon 0.2%	NA	bromhexine HCl;	1.334-1.335
Célestène 0.05%	Celestone Soluspan 0.6% (I)	betamethasone	1.438-1.441
Dédrogyl 0.015%	NA	calcifediol	1.430-1.433
Dépakine 20%	Depakine 5%	sodium valproate	1.364-1.366
Digoxine Nativelle 0.005%	Lanoxin 0.005%	digoxin	1.379-1.380
Dihydroergotamine Sandoz 0.2%	(DHE)-Sandoz 0.1%(I)	dihydroergotamine mésylate	1.397-1.398
Dipipéron 4%	NA	pipamperone HCl;	1.342-1.344
Dogmatil 0.5%	NA	sulpiride	1.345-1.346
Droleptan 2%	Inapsine 0.25% (I)	droperidol	1.341
Duphalac 66%	Cephulac 66%	lactulose	1.460-1.461
Duxil	NA	almitrime, raubasine	1.412-1.417
Effortil 0.75%	NA	etilefrine HCl;	1.334-1.335
Flunaxol 4%	Flunaxol 2 & 10% (I)	flupenthixol HCl;	1.360-1.361
Génatropine 0.13%	NA	atropine oxyde	1.342-1.344
Génésérine3 0.3	NA	eserine oxyde	1.338-1.339
Haldol faible 0.05%	NA	haloperidol	1.333 - 1.334
Haldol fort 0.2%	Haldol 0.2%	haloperidol	1.333-1.334
Heptamyl 30%	NA	heptaminol HCl	1.384-1.385
Hydrosol Polyvitaminé	High potency multivitamin / mineral	vitamin A B1 B2 B5 B6 PP C D2 and E	1.424-1.425
Imodium 0.02%	Imodium 0.02%	loperamide HCl;	1.422-1.424
Iskédyl	NA	raubasine, dihydroergocristine mésylate	1.370-1.371
Kaneuron 5%	NA	phenobarbitone caffeine crataegus passion flower	1.397-1.399
L-Thyroxine 0.015%	Tabs only	thyroxine sodium	1.414-1.419
Largactil 4%	Largactil 0.5 & 2%	chlorpromazine HCl;	1.412-1.415
Laroxyl 4%	Elavil 0.2%	amitriptyline	1.389-1.393

Table I. Range of refractive indices of oral solutions — *Continued*

Proprietary Names (France) [1]	Proprietary Names (Canada) [1,2]	Generic Name	Range of RI
Lasilix 1%	Lasix 1%	frusemide	1.382-1.384
Loxapac 2.5%	Loxapac 2.5%	loxapine	1.415-1.418
Ludiomil 2%	Tabs only	maprotiline HCl;	1.386-1.387
Lysanxia 1.5%	NA	prazepam	1.432-1.436
Majeptil 4%	Majeptil Tabs only	thioproparezine mesylate	1.410-1.413
Melleril 4%	Melleril 3% solution	thioridazine HCl	1.384-1.387
Melleril 0.2%	Mellaril 0.2% susp	thioridazine HCl	1.404-1.405
Méthergin 0.025%	NA	methylergometrine maleate	1.353-1.354
Moditen fort 4%	Moditen 0.05%	fluphenazine HCl;	1.451-1.453
Neuleptil 1%	Neuleptil 1% drops	pericyazine	1.403-1.406
Neuleptil 4%	NA	pericyazine	1.405-1.408
Nootropyl 20%	NA	piracetam	1.433-1.435
Nozinan 4%	Nozinan 4% drops Nozinan 0.5% liquid	methotrimeprazine	1.407-1.411
Orap 0.25%	Orap 0.25%	pimozide	1.380
Piportil 4%	Piportil 4%	pipothiazine	1.420-1.421
Pragmarel 2.5%	NA - tabs only	trazodone HCl;	1.408-1.411
Primpéran 0.26%	Maxeran 0.26%	metoclopramide HCl;	1.334
Quitoxin 1%	Sinequan Tabs only	doxepin	1.425-1.427
Rivotril 0.25%	Rivotril 0.25%	clonazepam	1.430-1.433
Silomat 6%	NA	clobutinol HCl;	1.370-1.371
Solupred 0.1%	NA	prednisolone sodium metasulphobenzoate	1.395-1.396
Stérogyl 0.05%	Drisdol 8,288 UI/mL	ergocalciferol	1.362-1.363
Surbronc 0.6%	NA	ambroxol HCl;	1.392-1.393
Surmontil 4%	Surmontil 4%	trimipramine mesylate	1.415-1.416
Tanakan 4%	NA	Ginkgo biloba	1.366-1.367
Tementil 4%	Stemetil 0.1%	prochlorperazine mesylate	1.408-1.409
Tercian 4%	NA	cyamemazine	1.423-1.427
Terfluzine 4%	Stelazine Tabs only	trifluoperazine HCl;	1.396
Théralène 4%	Panectyl 0.05%	trimaprazine tartrate	1.410-1.413
Un alpha 300 mg/ml	NA	alfacalcidol	1.406-1.411
Valium 1%	Valium NLA,Tabs only	diazepam	1.400 - 1.403
Vasobral	NA	dihydroergocrypine mesylate caffeine	1.355-1.356
Vastarel 2%	NA	trimetazidine	1.347
Vitamin K1 2%	Vitamin K1, 0.2 & 1%	phytomenadione	1.342-1.343
VogalËne 0.4%	NA	metopimazine	1.408-1.409
Zaditen 0.02%	Zaditen 0.02%	ketotifene fumarate	1.428-1.430

1. Proprietary names are provided because Cheung et al[5] have reported that equivalent concentrations of solutions produced by different manufacturers may not have the same RI.
2. Where Canadian formulations of identical or similar strength are available the Canadian proprietary name is provided. Where an oral liquid formulation is not available in Canada the proprietary name and strength of an injectable formulation is given followed by the designation (I). When only tablets are available, this is identified by "Tabs only" and where a medication is unavailable in Canada this is indicated by NA. Where a product has recently been discontinued (no longer available), this is identified with "NLA".

Table II. Oral solutions with similar refractive indices

R1	Proprietary Names (France)
1.333	Haldol faible - Haldol fort
1.334	Primpéran - Haldol faible - Bisolvon - Effortil - Haldol fort
1.335	Bisolvan - Effortil
1.342 and 1.343	Vitamin K1 - Dipipéron - Génatropine
1.344	Dipipéron - Génatropine
1.366	Dépakine - Tanakan
1.370 and 1.371	Silomat - Iskédyl
1.380	Orap - Digoxine
1.384	Lasilix - Heptamyl - Melleril drops
1.385	Heptamyl - Melleril drops - Alcaphor
1.386 and 1.387	Melleril drops - Alcaphor
1.392 and 1.393	Surbronc - Laroxyl
1.396	Solupred - Terfluzine
1.403	Neuleptil 1% - Valium
1.404	Melleril syrup - Neuleptil 1%
1.405	Neuleptil 1% - Neuleptil 4% - Melleril syrup - Eludril
1.406	Un alpha - Neuleptil 1% - Neuleptil 4%
1.407	Un alpha - Nozinan - Neuleptil 4%- Artane
1.408	Pragmarel - Vogalène - Nozinan - Artane - Un alpha - Neuleptil 4% - Tementil
1.409	Un alpha - Pragmarel - Tementil - Nozinan - Vogalène - Artane
1.410 and 1.411	Un alpha - Pragmarel - Théralène - Nozinan - Majeptil
1.412	Majeptil - Duxil - Largactil - Théralène
1.413	Majeptil - Duxil - Largactil - Théralène
1.414	Duxil - Largactil - L Thyroxine
1.415	Largactil - Duxil - Surmontil - Loxapac - L Thyroxine
1.416	Largactil - Surmontil - Loxapac - L Thyroxine - Duxil
1.417	Duxil - L Thyroxine - Loxapac
1.418	L Thyroxine - Loxapac
1.423	Tercian - Imodium
1.424	Tercian - Hydrosol Polyvitaminé - Imodium
1.425	Quitoxin - Tercian - Hydrosol Polyvitaminé
1.426 and 1.427	Tercian - Quitoxin
1.430	Dédrogyl - Rivotril - Zaditen
1.431	Dédrogyl - Rivotril
1.432	Dédrogyl - Rivotril - Lysanxia
1.433	Dédrogyl - Lysanxia - Nootropyl - Rivotril
1.434 and 1.435	Lysanxia - Nootropyl
1.438 and 1.440	Atarax - Célestène