Relationship between Refractive Index and Dry-Substance Content for Lactulose Syrups

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Abstract □ The relationship between the refractive index and the dry substance content of lactulose syrups of different compositions was investigated. It was found that, for a concentration range of 55–75% of dissolved carbohydrates, the sucrose tables can be used after correction by a factor of 0.97.

Keyphrases □ Lactulose—determination of dry substance, refractive index-dry-substance content relationship □ Refractive index-dry-substance content, lactulose syrups

Lactulose (4-*O*-β-D-galactopyranosyl-D-fructofuranose) is a synthetic disaccharide which is primarily used for the treatment of constipation (1), portal systemic encephalopathy, and hepatic coma (2). The drug, prepared by a base-catalyzed isomerization of lactose, known as the Lobry de Bruyn-Alberda van Ekenstein rearrangement, is commonly marketed as an aqueous syrup. This syrup also contains small amounts of lactose and other carbohydrates formed during the isomerization process (3).

Lactulose, lactose, and galactose can be analyzed by specific chromatographic (4, 5) or enzymatic methods (6); however, suitable methods are not available to determine each of the other sugars. The total weight of the other sugars can be determined from the difference between the amount of the analyzed compounds and the total weight of solid material dissolved in the syrup. Our problem, therefore, was to find a method to determine the amount of carbohydrates present in the lactulose syrup.

Several methods for dry-substance determination of sugars are known and have recently been critically discussed (7). Drying procedures at temperatures of >100°C are not reliable for lactulose syrup because of the possible decomposition of labile carbohydrates and the loss of water by dehydration reactions. Freeze-drying procedures are also unsatisfactory because water is not completely removed from the amorphous or syrupy residue and the remaining water must be determined by a different method. An indirect method for the determination of the dry substance content is by measuring the water content using the Karl Fischer method (8). This method, however, requires special equipment and is time consuming. The dry-substance content of sugar solutions is frequently determined by means of refractometry (9) or densimetry (10). Refractive index measurements, in particular, are easily and accurately accomplished and would be the method of choice provided that the relationship between dry-substance content and refractive index is known. For aqueous sucrose solutions, correlation tables (Brix values) are readily available (9, 11, 12) and are included in the refractive index measuring scale. Refractive index data have also been published for aqueous solutions of other common sugars such as glucose (12), fructose (11), lactose (13, 14), and maltose (9) and for different types of syrups (12, 15–17); however, no data were available for lactulose. Therefore, we have investigated the refractive index-dry-substance relationship for lactulose syrups with different compositions.

Table I—Results for the Solutions of Pure Lactulose in Water

Real Dry Substance, %	°Brix at 20°C	Factor[a]
54.37	55.95	0.972
55.72	57.10	0.976
60.99	62.63	0.974
61.72	63.88	0.966
67.96	70.85	0.959
67.99	70.03	0.971
74.53	76.85	0.970
75.10	77.28	0.972
Mean		0.970

[a] The amount of real dry substance/dry substance from refraction.

Table II—Results for the Solutions of an Artificial Mixture of Pure Lactulose, Lactose, and Galactose

Real Dry Substance, %	°Brix at 20°C	Factor[a]
54.74	56.40	0.971
61.95	63.78	0.971
67.47	69.38	0.972
74.55	76.60	0.973
Mean		0.972

[a] The amount of real dry substance/dry substance from refraction.

EXPERIMENTAL SECTION

Apparatus—Refractive indices were measured on a refractometer[1] thermostated at 20 ± 0.1°C[2]. The water content in the dry substance was determined automatically[3]. For freeze-drying procedures, a self-made laboratory freeze-drier was used. The condenser was cooled with solid carbon dioxide in acetone.

Chemicals—Lactulose, the analytical reference standard, had a purity >99.5% and a water content of 0.23% (recrystalized from methanol). The α-D-lactose monohydrate[4] had a purity of >99.5% and the α-D-galactose[5] had a purity of >99%.

Preparation of Sugar Solutions—Eight solutions of pure lactulose in water were made by weight in the range of 55–75% (Table I). Then, an artificial mixture containing lactulose (89.9%), lactose (4.5%), and galactose (5.6%) was prepared. Four solutions were made by weight in the range of 55–75% by dilution of this mixture with water (Table II).

Another set of sugar solutions was prepared with four samples of lactulose syrup which were freeze-dried. The amorphous residue was kept at 70°C for 2 h. From the residue of each batch, four solutions in water were made by weight in the range of 55–75%. Since it was not possible to obtain a water-free residue, a correction was made for the remaining water determined with the Karl Fischer titration (in the four batches these values were 0.93, 0.98, 0.21, and 0.20%, respectively) (Table III).

[1] Zeiss Opton Abbe refractometer.
[2] Colora Ultra Thermostat K5.
[3] Metrohm Karl Fischer Automat E547.
[4] 0138; Baker.
[5] 1564; Baker.

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Table III—Results for Lactulose Syrups with Known Dry-Substance Content after Freeze-Drying

Real Dry Substance, %		°Brix at 20°C	Factor[a]
Batch 1	54.62	56.40	0.968
Batch 2	54.19	55.80	0.971
Batch 3	54.92	56.53	0.975
Batch 4	54.86	56.18	0.977
Batch 1	61.56	63.53	0.969
Batch 2	61.45	63.58	0.966
Batch 3	62.08	63.60	0.976
Batch 4	61.89	63.38	0.977
Batch 1	67.22	69.53	0.967
Batch 2	67.13	69.25	0.969
Batch 3	67.93	69.73	0.974
Batch 4	68.03	69.63	0.977
Batch 1	74.13	76.60	0.968
Batch 2	74.42	76.83	0.969
Batch 3	74.56	76.10	0.980
Batch 4	74.86	76.38	0.977
Mean[b]			0.973

[a] The amount of real dry substance/dry substance from refraction. [b] Mean of four batches.

Table IV—Mean results for 26 Batches of Lactulose Syrup and 61 Batches of Formulated Product

	Dry Substance, %[a]	°Brix at 20°C	Factor[b]	*SD* of Factor
Lactulose syrup	70.719	72.877	0.970	0.0085
Formulated product	67.072	68.884	0.974	0.010

[a] Using Karl Fischer titration. [b] The amount of real dry substance/dry substance from refraction.

Table V—Correction Factors for Dry-Substance Determination using Sucrose Brix Values for Refractive Index Measurements at 20°C (9, 11, 12)

Product	Correction Factor			Ref.
	30% d.s.	50% d.s.	70% d.s.	
Lactose	0.969	—[a]	—[a]	13, 14
Maltose	0.979	0.981	—[a]	9
Glucose	1.010	1.015	1.021	12
Fructose	1.013	1.016	1.021	11
HFCS (42)[b]	1.010	1.014	1.018	15–17
CS (42)[c]	0.969	0.970	0.971	12, 15–17
CS (70)[d]	0.988	0.991	0.994	12, 15–17

[a] No data available due to low solubility. [b] High fructose corn syrup, 42% fructose. [c] Corn syrup, acid conversion, 42 D.E. [d] Corn syrup, dual conversion, 70 D.E.

Samples of 26 production batches of lactulose syrup and 61 batches of formulated product[6] were analyzed for dry substance using the Karl Fischer titration and the refractive index (Table IV).

RESULTS AND DISCUSSION

The relationship between the real dry-substance content of lactulose solutions and the dry substance obtained from the refraction and sucrose index (°Brix), is expressed as: real dry substance/dry substance from refraction. From the refractive index-dry-substance relationship, as given for various sugars in the literature, correction factors can be calculated for sucrose dry-substance values.

Table V gives the results for solutions of some common carbohydrates and syrups at three different concentrations. It appears that the factor for the aqueous sugar solutions varies between 0.969 for lactose and 1.021 for glucose and fructose. The mean factor we found in all our experiments was within this range.

It may be concluded from Tables I and II that the factor for pure lactulose, or for lactulose mixed with lactose and galactose, will be ~0.97 for solutions of 55–75% of dry-substance content. Almost the same values were found for lactulose syrups of different compositions. Thus, the presence of other carbohydrates in lactulose syrup does not significantly influence the refractive index. The dry-substance content of lactulose syrups can, therefore, be determined easily and accurately by refractometry using sucrose-dry-substance or Brix values after correction by a factor of 0.97.

[6] Duphalac; the lactulose content is 667 g/L according to the label claim.

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