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Contactless Chemical Analysis of Ternary Multicomponent Tablets by THz Sensing

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Abstract: ***This article presents a contactless method for analyzing ternary mixtures in tablet form using THz sensing. By directly measuring the refractive index at absorption frequencies specific to maltose and glucose, the method enables accurate quantification without the need for uniform sample thickness or advanced chemometric modeling. Testing on 24 mixtures of polyethylene, maltose, and glucose shows that refractive index changes at characteristic peaks are proportional to the target compound's concentration. The findings suggest practical advantages for rapid, non-destructive analysis in industrial settings.***

Keywords: THz time domain spectroscopy, ternary mixtures, sugars analysis, chemical composition, non-destructive testing

1. Introduction

The rapid identification of substances present in mixtures is essential in many fields such as food, safety, pharmacy, the environment and materials science. Methods based on separation, such as gas or liquid chromatography and mass spectrometry, could be considered for industrial processes, but due to the time required for sample preparation, they are not suitable for rapid analysis. Non-contact Raman spectroscopy [1] and Fourier transform infrared spectroscopy (FTIR) are interesting methods for the direct quantification of compounds in complex mixtures. For example, spectroscopic analysis methods have been used successfully for several years to detect and quantify cocaine [2] or microplastics [3] in various environmental compartments in terrestrial or aquatic environments. THz spectroscopic analysis has recently been applied for the non-destructive detection and quantification of complex mixtures [4-5]. However, Raman, FTIR and THz spectroscopy are often combined with chemometric tools. Traditional methods (PLS and N-PLS methods) need to be improved to overcome serious spectral overlaps. A large number of chemometric methods have been compared, including various normalization, dimensionality reduction and prediction models [6-9]. The level of expertise required for these software modelling methods is quite high to allow direct application in the industrial field. Furthermore, all these spectroscopic methods rely on the use of pellets of identical shape and thickness to enable accurate comparison and quantification. This process is time-consuming process for sample preparation. We have already presented new approaches to overcome the interference of thickness variations in order to rapidly evaluate material libraries [10-11]. Here, we present an alternative approach. It uses the strong variation in refractive index at the absorption peak frequencies of maltose and glucose. This article aims to introduce and validate a THz sensing approach for rapid, contactless analysis of ternary mixtures in tablet form, overcoming the need for chemometric methods and sample uniformity.

2. Materials and Methods

Our model is based on a ternary mixture of polyethylene PE, maltose and glucose. Two different thicknesses were evaluated for each of the 24 ternary compositions. Table 1 shows the ratio between the different components in the samples.

Table 1: List of different compositions of ternary mixtures of high-density polyethylene HDPE, maltose and glucose

Relative Compositions			
Sample	PE%	Maltose %	Glucose %
1	20	0	80
2	20	20	60
3	20	40	40
4	20	60	20
5	20	80	0
6	40	0	60
7	40	20	40
8	40	30	30
9	40	40	20
10	40	60	0
11	50	10	40
12	50	20	30
13	50	30	20
14	50	40	10
15	60	0	40
16	60	10	30
17	60	20	20
18	60	30	10
19	60	40	0
20	80	0	20
21	80	5	15
22	80	10	10
23	80	15	5
24	80	20	0

The total amount of PE, maltose and glucose reaches 100% of the composition for each sample. The visual differentiation of mixtures is reported in the triangular diagram (Figure 1).

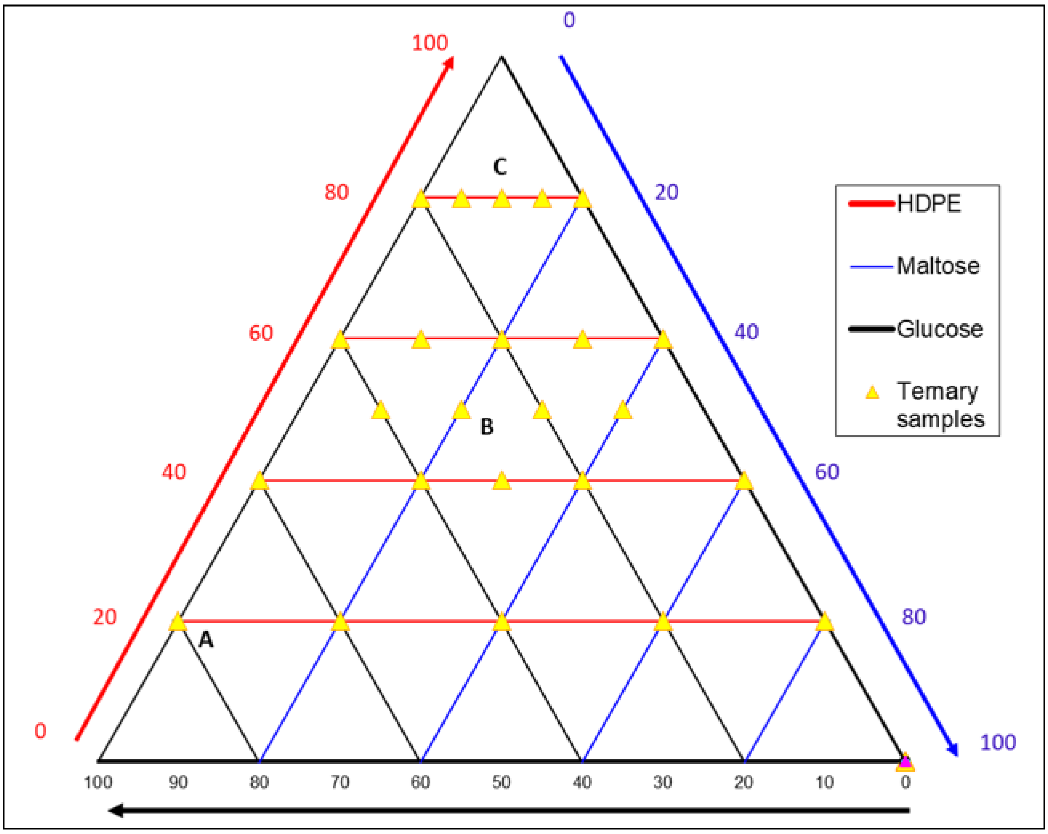

Figure 1: Triaxial representation of the HDPE, maltose and glucose mixtures. The yellow marks indicate the samples used in this study

Each component is represented in the mass percentage graph from 0% to 100%. The vertices of the triangle correspond to 100% of a single component. Binary compositions are indicated along the sides and the various ternary mixtures by the yellow triangle marks. For example, mixture A is composed of 20% polyethylene PE, 0% maltose M and 80% glucose G, mixture B of 50% PE, 20% M and 30% G, and mixture C of 80% PE, 10% M and 10% G respectively. 200 mg of each mixture was used to produce thick tablets with an average thickness of approximately 200 µm, and 100 mg was used for the series of thin tablets with an average thickness of 100 µm. A 3D-printed 24-well plate held the pellets. (Figure 2). Each 8 mm well included a screw and o-ring to secure pellet vertically. The spot size of the THz beam is approximately 5 mm, allowing for the analysis of a large area in the centre of the samples.

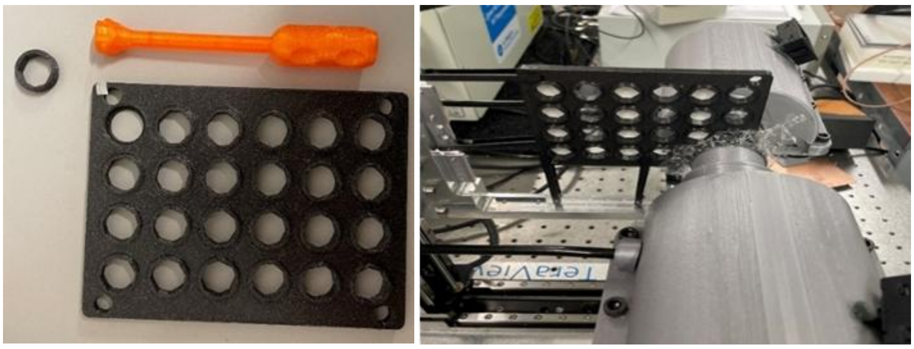

Figure 2: 24-samples holder and vertical positioning between the THz emitter and receiver heads

3. Results

Representative THz spectrums of binary and ternary systems are reported in Figure 3.

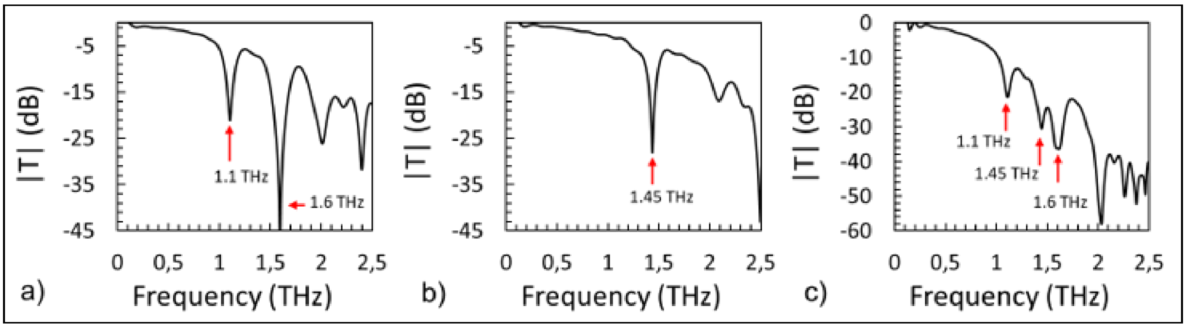

Figure 3: Typical THz transmission spectrum of two binary mixtures 20% HDPE-80 % maltose-0% glucose (a); 20% HDPE-0 % maltose-80 % glucose (b) and a ternary system 20% HDPE-40% maltose-40% glucose (c).

In the binary system a) (20% HDPE-80 % maltose-0% glucose) peaks corresponding to maltose absorption are detected at 1.1 THz and 1.6 THz. A characteristic absorption peak for glucose (mixture b) is detected at 1.45 THz. In the ternary spectrum c) (20% HDPE-40% maltose-40% glucose), the corresponding peaks for maltose and glucose are clearly differentiated.

In addition to spectral representation of data, it also possible to extract from the raw data the refractive index for each sample. When THz pulse propagates through the sample under test, it is delayed, attenuated and distorted due to the refractive index, absorption coefficient and dispersion of the material that constitutes the sample, respectively. By comparing the pulse transmitted through the sample with the one in absence of sample (reference) one gets the information concerning the material itself. Indeed, the complex transmission coefficient $\tilde{T}$ of the sample is given in the frequency domain by the ratio of the Fourier transform of the transmitted pulse with sample over the reference one. The modulus $|\tilde{T}|$ and the phase φ_T of the complex transmission coefficient, both depend on the refractive index n and the absorption coefficient □ of the material that constitutes the sample [12]:

$$|\tilde{T}| = \frac{4\sqrt{n^2+\kappa^2}}{(n+1)^2+\kappa^2}\, e^{-\frac{\alpha}{2}d} \tag{1.a}$$

$$\varphi_T = -\left[\tan^{-1}\left(\frac{\kappa}{n}\right) + \tan^{-1}\left(\frac{2(n+1)\kappa}{\kappa^2-(n+1)^2}\right) + \frac{2\pi f d}{c}\,(n-1)\right] \tag{1.b}$$

where k = □*c/(4*□*f)* is the extinction coefficient of the material, c is the light velocity in void and f the considered frequency. By numerically solving the above set of non-linear equations, n and □*=4*□*f*□*/c* are extracted together with the sample thickness d [13] over the available THz range. The upper frequency of the THz bandwidth is limited by the absorption coefficients of the samples under test, which prevent any THz characterization above 2 THz.

Tablets under test are measured 10 times. Based on the previous equations the effective refractive index of each tablet has been calculated and the average values are reported on Figure 4 for different mixture compositions (samples 1, 5, 6, 10, 15, 19, 20 and 24 in Table 1).

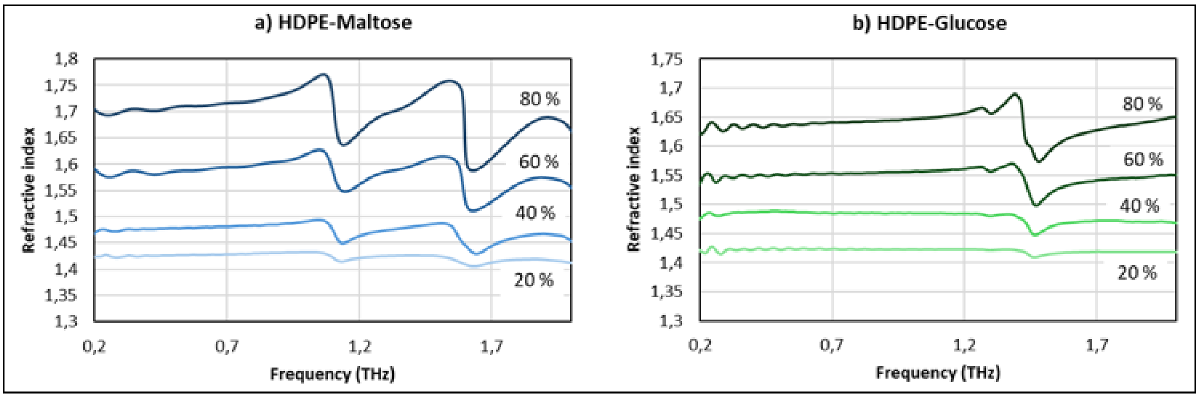

Figure 4: Effective refractive indices versus frequency, extracted from a) HDPE-maltose and b) HDPE-glucose pellets for different mass proportions of maltose and glucose respectively.

For binary systems, the refractive index below 0.8 THz changes linearly with proportions of polyethylene, maltose and glucose. Measuring the refractive index could therefore be used as a simple method to determine the ratio of glucose or maltose. However, this direct approach can not be applied to ternary systems. Indeed, as illustrated by Figure 5, below 0.8 THz, it not possible, for example, to differentiate mixtures 40% maltose - 10% glucose (sample 14) and 30% maltose - 20% glucose (sample 13) or even the mixtures 20% maltose - 30% glucose (sample 12) and 10% maltose - 40% glucose (sample 11).

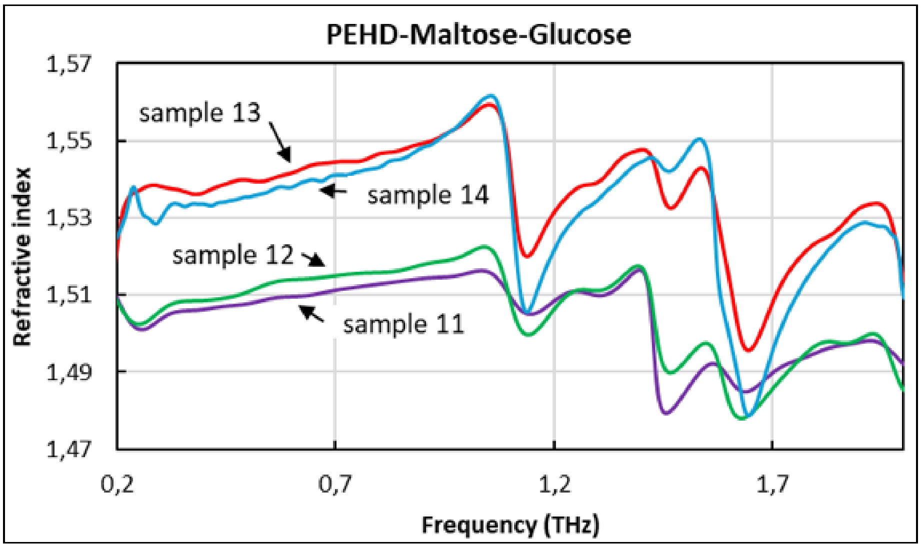

Figure 5: Effective refractive indices versus frequency, extracted from ternary systems: sample 11 (10% maltose - 40% glucose), sample 12 (20% maltose - 30% glucose), sample 13 (30% maltose - 20% glucose) and sample 14 (40% maltose - 10% glucose)

To overcome this issue, we propose a different approach based on the variation of the effective refractive index of the mixture in vicinity of the absorption lines of the maltose and glucose. Indeed, there is a variation of the refractive index at the frequency of absorption for both maltose and glucose. The amplitude of the variation in refractive index around an absorption peak is related to the amplitude of absorption and therefore to the respective quantities of maltose or glucose.

For quantification we calculated the refractive index variation Δn_1 around the maltose absorption peak at 1.1 THz (i.e difference between refractive index values at frequency f_1 = 1.03 THz before the peak of absorption and at f_2 = 1.17 THz after the peak absorption). In the same way, Δn_2 was evaluated around the glucose absorption peak at 1.45 THz, by subtracting the refractive index at f_4=1.5 THz with the one at f_3= 1.36 THz, as indicated on figure 6.

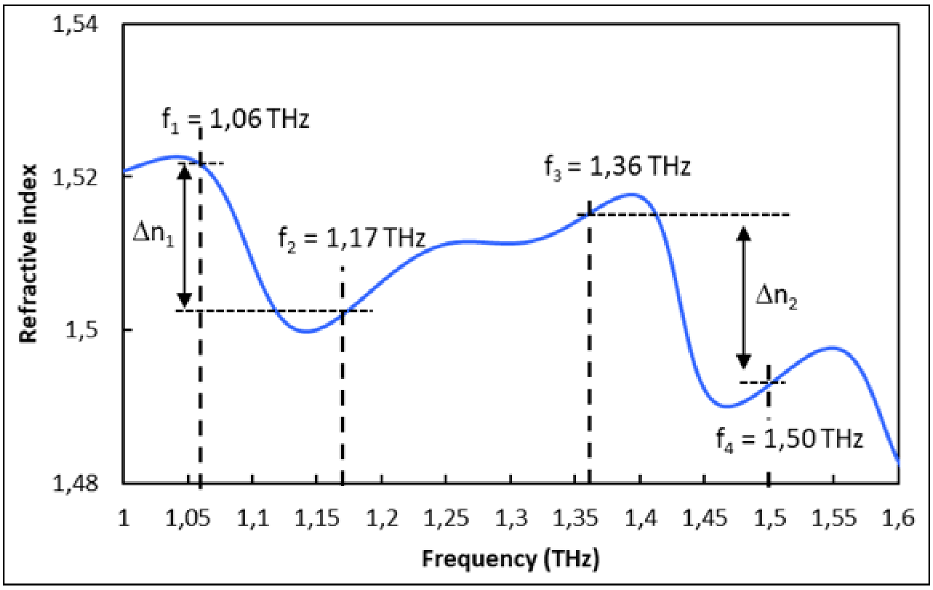

Figure 6: Methodology applied to calculate refractive index variation Δn_1 and Δn_2

The variation in refractive index Δn_1 for different percentage of maltose in ternary mixture pellets is reported on Figure 7 for the two sets of pellets of different thickness (100 µm-thick ones and 200 µm-thick ones).

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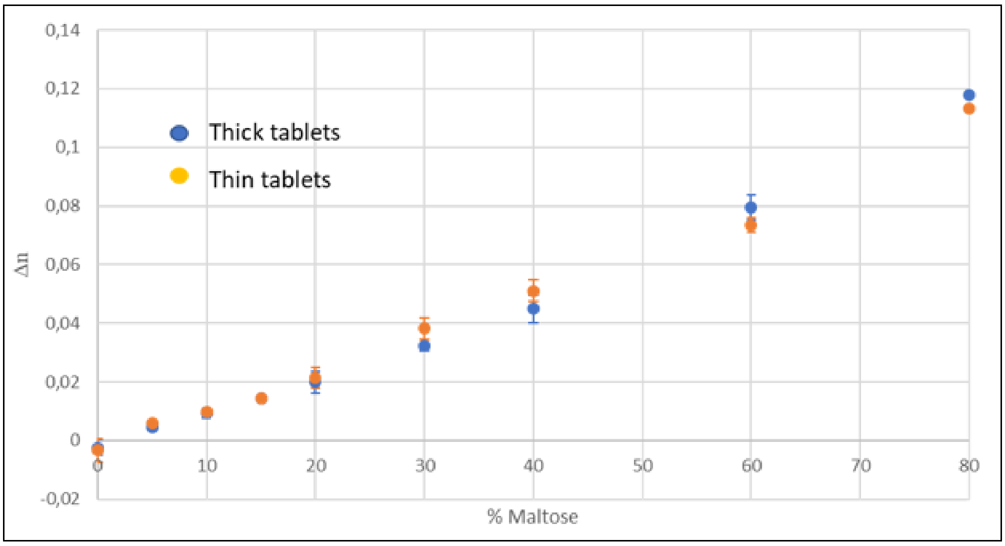

Figure 7: Variation □n_1 for different % of maltose in ternary mixtures for thick (blue dots) and thin (yellow dots) tablets

Two main information could be extracted: a) the refractive index variation □n_1 is linearly proportional to the percentage of maltose and similar values were measured for both thick and thin tablets, b) □n_1 is only sensible to the amount of maltose and is practically not affected by the composition of the rest of the tablet (i.e % of PE and glucose), indicating that there is no matrix interference using this new approach.

Similar conclusions were obtained for the glucose quantification (Figure 8). However, below 10% of glucose, one can see an interference with the maltose composition, this could be explained by the proximity of the maltose absorption peak at 1.6 THz with the glucose absorption peak at 1.45 Hz.

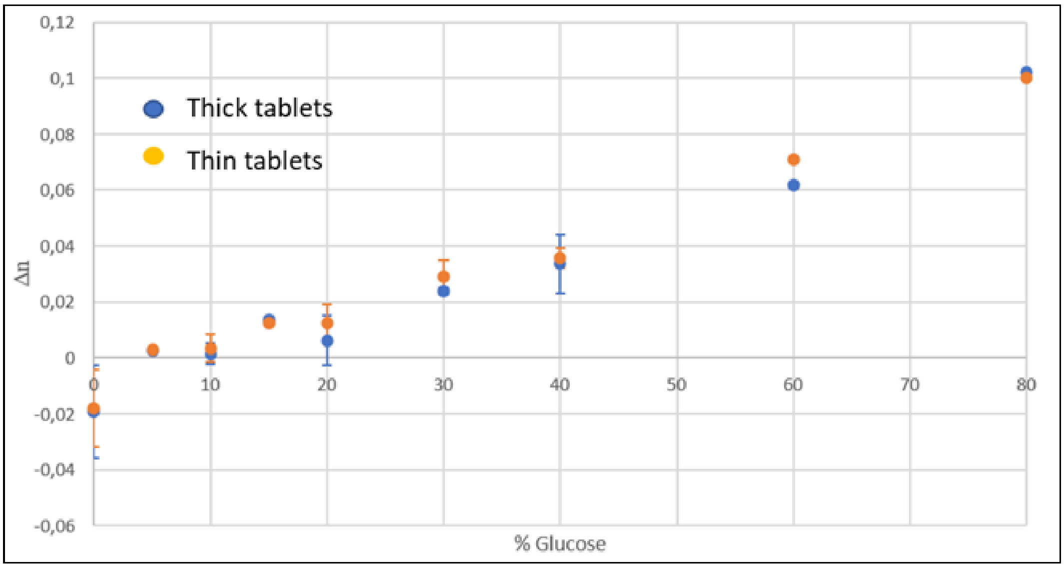

Figure 8: Variation □n_2 for different % of glucose in ternary mixtures for thick (blue dots) and thin (yellow dots) tablets

The Teraview THz equipment can be only applied for vertical evaluation of samples/ this is not useful to analyse tablets moving on horizontal conveyor for instance. Thus, we also applied this new approach to a Toptika system allowing horizontal position for tablets thanks to a transmission analysis from top to down. However, the THz spot for this equipment is around □m thus really smaller than the spot applied for the Teraview system. This could be a problem in case of heterogeneous tablets. Thus 16 different areas were analysed for each tablet. Similar results were obtained indicating a homogeneous repartition of the three components into tablets. The average of the 16 measurements for each sample was calculated and applied to equations to obtain corresponding refractive index and variation of refractive index at different frequencies.

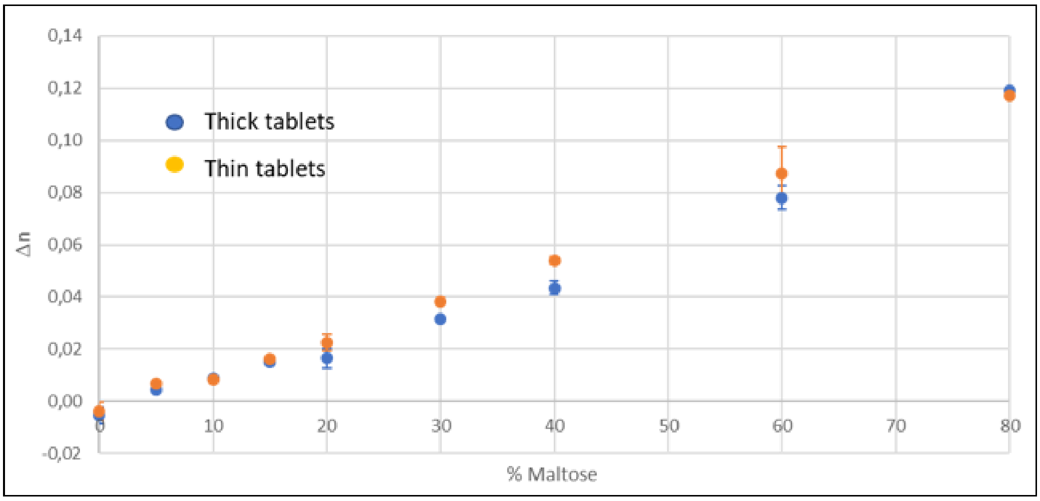

Figure 9: Variation □n_1 for different % of maltose in ternary mixtures for thick (blue dots) and thin (yellow dots) tablets, using the horizontal Toptika system and 16 spatial distributions of analysis for each tablet.

Figure 9 clearly indicates that the new approach could be effectively applied to differentiate tablets in horizontal position, according to their relative amount of maltose. Similar results were obtained for glucose quantification, with the same limitation than the Teraview system for % of glucose lower than 10%.

In order to decrease the time for quantification we also investigated a single small spot in the centre of each tablet. The same precision was obtained for the quantification of maltose and glucose than the previous analysis, both for thick and thin tablets (Figure 10). This represent a key point for fast analysis in industrial process.

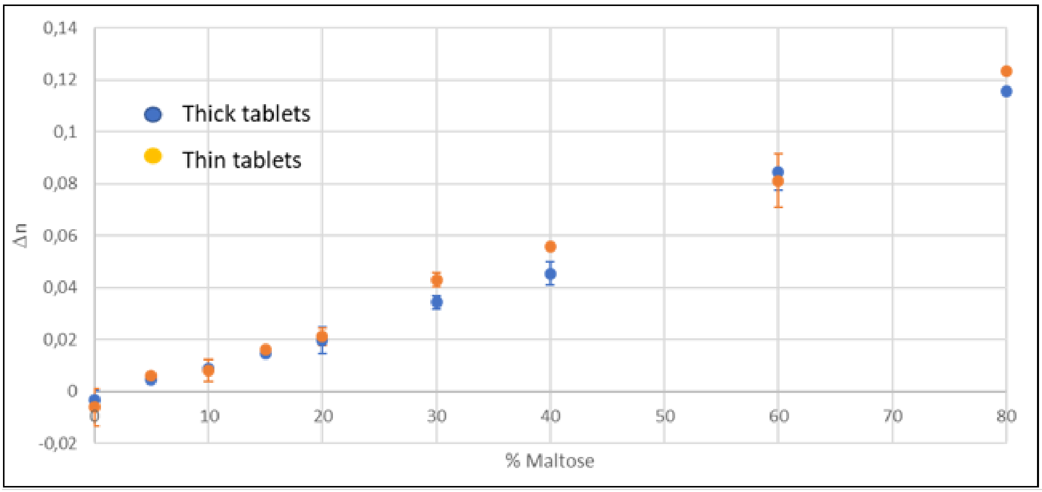

Figure 10: Variation □n_1 for different % of maltose in ternary mixtures for thick (blue dots) and thin (yellow dots) tablets, using the horizontal Toptika system for single spot analysis.

4. Conclusions

In conclusion we report here a new approach to quantify ternary mixtures, based on the variation of the refractive index in the corresponding area of peak absorption for both maltose and glucose. This approach could be applied for thick or thin tablets. This represents a potential for application in industry process, without any expertise in chemometrics analysis or any soft modelling software.

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Data Availability Statement: Data are available on demand to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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