

# Batch-Specific Discrimination using Nuclear Quadrupole Resonance Spectroscopy

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## Abstract

In this paper, we report on the identification of batches of analgesic paracetamol (acetaminophen) tablets using nitrogen-14 Nuclear Quadrupole Resonance Spectroscopy ( $^{14}\text{N}$  NQR). The high sensitivity of NQR to the electron charge distribution surrounding the quadrupolar nucleus enables the unique characterization of the crystal structure of the material. Two hypothesis were tested on batches of the same brand; the within the same batch variability and the difference between batches that varied in terms of their batch number and expiry date. The multivariate analysis of variance (MANOVA) did not provide any within-batches variations, indicating the natural deviation of a medicine manufactured under the same conditions. Alternatively, the statistical analysis revealed a significant discrimination between the different batches of paracetamol tablets. Therefore, the NQR signal is an indicator of factors that influence the physical and chemical integrity of the material. Those factors might be the aging of the medicine, the manufacturing or storage conditions. The results of this study illustrate the potential of NQR as promising technique in applications such as detection and authentication of counterfeit medicines.

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## Introduction

At present, the crime of counterfeit pharmaceuticals is threatening public health globally. Drug counterfeiting may result in drug resistance or even death, as well as loss of consumer confidence and a serious threat to the economy of the pharmaceutical industry. The nature and extent of this industrialized problem varies between countries, with a greater trend in developing regions with weak regulatory oversight.<sup>1</sup> Unfortunately, due to lack of accurate sources of information, reliable statistics describing the degree of this problem are not available, but all indicators show that this problem is severe.<sup>1,2</sup> Estimates of the magnitude of the problem refer to 10% of counterfeit drugs worldwide, with this percentage fluctuating from country to country.<sup>1,3</sup> According to the World Health Organization (WHO), the online market also poses a great danger to patient's health, with up to 50% of medicines purchased from the internet possibly being counterfeit.<sup>1,3,4</sup> Incidents have also been reported from the Pharmaceutical Security Institute, indicating an alarming increase throughout the last couple of years.<sup>2</sup> Counterfeiters target not only life-saving and expensive lifestyle medicines such as fat reduction pills and hormones but also low cost products such as simple painkillers and antibiotics.<sup>5</sup>

The WHO definition refers to a counterfeit medicine as a "product that is deliberately and

fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Those may include products with the correct active ingredients, or with the wrong ingredients, without active ingredients, with insufficient active ingredients, or with fake packaging”.<sup>3</sup> Substandard products also pose an additional threat. The WHO describes those medicines as substances produced without a deliberate misrepresentation, but as low quality products with wrong dosage of active pharmaceutical ingredient (API) that do not meet the quality assurance standards, or being degraded due to bad storage conditions.<sup>6,7</sup> Initial testing for detection of counterfeit drugs is visual inspection, with pharmaceutical companies developing methods to protect their products such as holograms, unique packaging and printing. Several studies report cases of fake packaging, indicating the necessity of additional sophisticated analytical techniques for the detection and identification of the contents of the pharmaceutical products.<sup>6</sup> Analytical approaches such as Raman spectroscopy, thin-layer chromatography, near-infrared spectroscopy, and mass spectroscopy have been used for the chemical analysis of drugs.<sup>1,8-10</sup>

Nuclear Quadrupole Resonance (NQR) spectroscopy is a radio-frequency (RF) technique that examines uniquely polycrystalline compounds containing quadrupolar nuclei whose spin quantum number is greater than a half, such as  $^{14}\text{N}$  and  $^{35}\text{Cl}$ .<sup>11</sup> Different from Nuclear Magnetic Resonance (NMR), no static magnetic field is required for NQR. The signal generation is based on the interaction of the electric quadrupole moment, which is a property of the sample, with the electric field gradient (EFG) from the surrounding charges in the crystal.<sup>11,12</sup> As a consequence, NQR is highly sensitive to dynamical alterations within the crystal, with an EFG and frequency content that is characteristic for the material under study.<sup>12</sup> Several studies proposed the application of NQR in the determination of solid crystalline and polymorphic forms, as well as the versatility in the detection and authentication of pharmaceuticals.<sup>7,12-16</sup> Notably, NQR can generate signals

from the majority of pharmaceutical products, as approximately 50% of isotopes in the periodic table contain quadrupolar nuclei.<sup>13</sup> As the magnitude of the NQR spectral lines are proportional to the number of quadrupolar nuclei within the compound, the signals can be quantitatively providing evidence of the amount of the API within the sample.<sup>12,15</sup> NQR is a non-invasive and non-destructive method, with the RF radiation passing through materials such as plastic and cardboard without attenuation, eliminating the need to remove the medicine from its packaging.<sup>13</sup> Furthermore, no special sample preparation is required; signals can easily be acquired from medicines in the form of pills, capsules or powder, within their packets, blister packs or small bottles. The absence of a magnet makes NQR a relatively inexpensive technique, suitable for field applications. However as with all analytical methods, NQR also has some limitations. The occurrence of spurious signals, mainly generated from piezoelectric materials, may cause signal contamination; however, phase cycling pulse sequences are developed to largely eliminate those effects prolonging the experimental duration for a more accurate and precise detection of the NQR signal characteristics. Improvements in experimental techniques help to reduce those limitations.<sup>12,14</sup> Furthermore, advanced and robust statistical signal processing algorithms have been developed to improve the detection and classification of the NQR signals.<sup>17,18</sup> In this work, the common NQR signal detectors based on approximate maximum-likelihood approaches are used to estimate unique parameters of the signal echo train, as well as perform RF interference mitigation.<sup>18</sup>

The overall strategy for the authentication of counterfeit drugs is complicated. The so-called ‘high-quality’ counterfeit medicines pose a significant alert, since they may contain the correct composition, but possibly differ in terms of excipients, ingredients and manufacturing conditions. NQR has been proved to be an effective indicator of important structural information of the solid-state environment of the different crystal forms (polymorphs) due to the sensitivity from changes in the electron charge distri-

bution surrounding the quadrupolar nucleus.<sup>19</sup> A considerable line broadening is generally observed in NQR signals, originating from crystal defects or impurities existing in the material.<sup>7,12,14</sup> This aspect is directly correlated with the characterization of the physical and chemical properties, or similarly, the ‘stability’ of the drug. Consequently, this can be influenced by the manufacturing conditions and processing (e.g. pressure) of the drug, the aging factor, the environmental storage conditions such as the temperature and humidity.<sup>12,19</sup> Several studies have addressed the effect of those factors on the NQR resonance frequency and relaxation time constants.<sup>7,12,16,20,21</sup> In real applications, a database should contain statistically efficient ‘fingerprints’ of the API and discrete formulations of each medicine. This includes different medicines, or medicines of the same formulation but produced by a different pharmaceutical company. Unfortunately, the detection can be greatly limited by the batch-to-batch variation observed in the genuine medicine and within the same batch, which is mainly concerned in the presence of ‘high quality’ fake products. Furthermore, an experimentalist should consider the variation within drugs with a long shelf life. An example is paracetamol tablets with a typical shelf life of about three years.<sup>22</sup> As mentioned above, the stability of the medicine is influenced by several factors, therefore, a fingerprint generated say during the first year of the medicine may not be a reliable evidence of its characteristics until the end of its self life. In this paper, we report on an NQR study performed on different batches of paracetamol tablets from the same manufacturing company, in order to identify any differences in their physical integrity. The two main hypothesis to be tested are (a) the within-batches and (b) the batch-to-batch variability.

## Experimental

**Test Samples.** Analgesic paracetamol (acetaminophen) tablets were purchased and tested at the  $\nu_+$  NQR spectral line, 2.5624 MHz at 283 K. No sample preparation was

required for the experiments. Six batches of the same brand were purchased from a London shop, such that they differed in terms of their expiry date and batch number. Note that all batches were analyzed prior to their expiry date. In order to test the first hypothesis, five samples per batch were compared to determine significant variations between samples of the same batch. Furthermore, for the batch-to-batch variability, the six different batches were analyzed and compared.

**NQR spectrometer.** A Tecmag pulsed RF spectrometer was used, along with a Tomco RF power amplifier. The Tecmag TNMR software was used to generate the pulse sequences as well as extracting the acquired signals for a further signal processing in Matlab and R statistical software, controlled via a PC. The blister packs were inserted in a cylindrical fixed pitch coil (inductance  $L = 34\mu\text{H}$ ). The coil was immersed in silicon oil bath within the probe, in order to control and stabilize the temperature during the measurements. In addition, an infrared temperature sensor was manually designed and placed inside the probe, in order to record any significant temperature fluctuations. The temperature was kept monitored within  $283 \pm 0.5$  K.

## Results and discussion

**Spectral analysis.** The  $^{14}\text{N}$  NQR signals were acquired using a pulsed spin locking (PSL) sequence, which consists of a series of refocusing RF pulses,  $\theta_{\pm 90^\circ}^r$ , phase shifted by  $90^\circ$  with respect to the first preparatory pulse,  $\theta_0^p$ , separated by the pulse spacing  $\tau$ , as

$$\theta_0^p - \tau - (\theta_{\pm 90^\circ}^r - \tau - \theta_{\pm 90^\circ}^r)_n \quad (1)$$

where  $n$  denotes the number of NQR echoes in the echo train. The PSL parameters,  $\tau$  spacing, RF pulse width and  $n$ , were 1033  $\mu\text{s}$ , 60  $\mu\text{s}$  and 1024 respectively. In order to enhance the signal-to-noise ratio (SNR), 32 scans were applied. The SNR is here defined as the ratio of the power of the noise free signal,  $\sigma_s^2$ , and the power of the noise,  $\sigma_w^2$ .<sup>17,18</sup> The SNR of the measurements is computed to be  $-24 \pm 2$  dB.

Table 1: MANOVA: within batches comparison.

Batch Label	Source	Statistic	F	Pr(>F)	
1	Samples	W	0.9916	0.2704	0.8466
		P	0.0084	0.2704	0.8466
2		W	0.9408	2.0113	0.1175
		P	0.0591	2.0113	0.1175
3		W	0.9929	0.2258	0.8783
		P	0.0071	0.2258	0.8783
4		W	0.9721	0.9170	0.4357
		P	0.0278	0.9170	0.4357
5		W	0.9858	0.4606	0.7104
		P	0.0142	0.4606	0.7104
6		W	0.9639	1.1991	0.3144
		P	0.0361	1.1991	0.3144

W = Wilk's  $\lambda$ ; P = Pillai's Trace  
 '\*\*\*' p<0.001; '\*\*' p<0.01; '\*' p<0.05; ' ' p<0.1

The NQR spectra were analyzed using the recently presented NQR data model.<sup>23,24</sup> The echo train structure of the signal generated by the PSL sequence has been modeled as a sum of exponentially damped sinusoidal echoes.<sup>17,23</sup> In comparison with the conventional Fourier Transform analysis, this approximate maximum-likelihood detector exploits the full echo train structure of the signals, providing estimates of characteristic parameters. The improved model introduces an amplitude modulation function of the NQR spectral lines, by incorporating the dependency of the resonance frequency on the material's temperature.<sup>23</sup> This dependency strongly affects the detection performance in the cases where the temperature of the material is not perfectly known, leading to inaccurate knowledge of the quadrupolar frequency. That is, significant variations in the signal intensity may result when the quadrupolar frequency does not match the excitation frequency of the RF pulses, a condition known as off-resonance effects.<sup>23,24</sup> In the case of paracetamol, the temperature coefficient is +0.069 kHz/K (Figure S-1, Supporting Information), therefore, no significant off-resonance effects occur; in fact the expected frequency uncertainty is about  $\pm 0.035$  kHz for a temperature drift of  $\pm 0.5$  K during the measurements. The NQR signal is typically described by a set of time constants which are characteristic to the material under study. These are the spin echo decay time,  $T_{2e}$ , and the spin-phase memory

decay time  $T_2^*$ .<sup>17</sup> For simplicity, the sinusoidal echo damping constant,  $\beta_k = D_w/T_{2,k}^*$ , and the echo train damping constant,  $\eta_k = D_w/T_{2e,k}$ , of the  $k^{th}$  spectral line are introduced in the NQR data model, with  $D_w$  denoting the spectrometer dwell time.<sup>17,18,23</sup> For each batch, five samples were analyzed to test variation within the batch. The NQR spectra were repeated 20 times per sample during different times and days. Due to the prolonged duration of each experiment, the number of repetitions was limited. Using the aforementioned signal data model, a maximum-likelihood approach is applied to estimate the unknown parameters  $\beta$ ,  $\eta$ , and the magnitude scaling due to the SNR,  $\rho$ .

**Statistical analysis** Both of the proposed hypothesis were tested using MANOVA.<sup>25-27</sup> The first hypothesis tests the within-batch variability; that is, the null hypothesis states that the three-dimensional mean vector of  $\beta$ ,  $\eta$ , and  $\rho$  is the same for each of the five samples in each batch. The vector of the five samples was set as the categorical variable, thus, one-way MANOVA was performed. In order to test the hypothesis, two statistical test criteria were applied. Those include the Wilks' Lambda ( $\lambda$ ) and Pillai's Trace statistical tests. Table 1 summarizes the MANOVA results for each of the six different batches (sample size per batch  $N=100$ ; five samples of the same batch per 20 repeats each)). For each of the two test criteria, the corresponding F-statistic and probability values

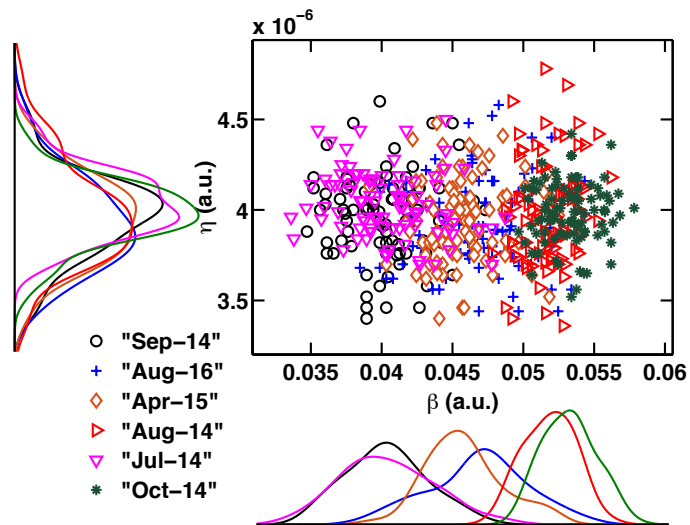


Figure 1: Scatterplot with marginal histograms of  $\beta$  with respect to  $\eta$  variable for the six different batches of paracetamol.

Table 2: MANOVA: between batches comparison.

Source	Statistic	F	Pr(>F)
batch categ.	W 0.1982	78.094	$2.2e^{-16}$ ***
	P 0.8345	41.158	$2.2e^{-16}$ ***

W = Wilk's  $\lambda$ ; P = Pillai's Trace  
 (\*\*\*)  $p < 0.001$ ; (\*\*\*)  $p < 0.01$ ; (\*)  $p < 0.05$ ; ( ' )  $p < 0.1$

Table 3: Univariate ANOVAs between batches comparison – Wilk's  $\lambda$ .

Variabes	F	Pr(>F)
$\rho$	1.2765	0.2725
$\eta$	2.5776	0.0256*
$\beta$	364.28	$2.2e^{-16}$ ***

(\*\*\*)  $p < 0.001$ ; (\*\*\*)  $p < 0.01$ ; (\*)  $p < 0.05$ ; ( ' )  $p < 0.1$

are shown. In conducting the hypothesis test, the  $p$ -values are compared with the threshold value,  $\alpha$ ; that is, the probability of rejecting the null hypothesis when it is actually true. The level of statistical significance is associated with the number of asterisks in Table 1. The observed  $p$ -values related with the statistical test criteria do not attain a statistically significant difference in the variables between the five samples. This applies for all the six batches, which, as mentioned before, differ mainly in terms of their expiry date and batch number. As expected, the null hypothesis fails to be rejected in this case for a significance  $\alpha$  level 0.1 ( $p$ -values  $> 0.1$ ). In fact, the outcome indicates the existence of the natural variation of a pharmaceutical product, which was produced under the same manufacturing conditions and processes.

Next, we assess possible differences in the three-dimensional variable mean vector for the six batches; that is, the batch-to-batch variability is examined. One-way MANOVA is performed using the “batch category” as the categorical variable for a sample size  $N = 600$ . We begin by illustrating the data graphically. Figure 1 indicates a two-dimensional scatter-plot of the  $\beta$  and  $\eta$  variables, along with the corresponding marginal histograms for the six different batches (Figure S-2 and Table S-1, Supporting Information, for the scatter-plot matrix and descriptive statistics of the three variables respectively). Here, the batches are denoted according to their expiry date for clarification. In comparison with the echo train damping parameter  $\eta$ ,  $\beta$  seems to show an evidence of discrimination between the six batches. The outcome of the one-way MANOVA for the two statistical test criteria, Wilks'  $\lambda$  and Pillai's Trace, is highlighted in Table 2. The null hypothesis states that the means of the six different batches are equal. The results indicate that the  $p$ -values associated with both of the test criteria is very small ( $p = 2.2e^{-16}$ ), with a significant discrimination even for a significance level  $\alpha = 0.001$ ; therefore, the null hypothesis is rejected for this value of  $\alpha$ . In order to locate the parameter influencing this variability, univariate ANOVAs are applied on each of the three variables and the results are shown in Table 3 using the Wilk's  $\lambda$  as the statistical test

Table 4: Tukey’s post-hoc test for the  $\beta$  variable.

Expiry Date	Mean difference	CI	Pr
Aug-14 – Apr-15	0.0059	0.0048 – 0.0071	0.0000
Aug-16 – Apr-15	0.0009	-0.0001 – 0.0021	0.1486
Jul-14 – Apr-15	-0.0054	-0.0066 – -0.0043	0.0000
Oct-14 – Apr-15	0.0074	0.0062 – 0.0085	0.0000
Sep-14 – Apr-15	-0.0055	-0.0066 – -0.0043	0.0000
Aug-16 – Aug-14	-0.0050	-0.0061 – -0.0038	0.0000
Jul-14 – Aug-14	-0.0144	-0.0126 – -0.0103	0.0000
Oct-14 – Aug-14	0.0014	0.0002 – 0.0026	0.0074
Sep-14 – Aug-14	-0.0115	-0.0126 – -0.0103	0.0000
Jul-14 – Aug-16	-0.0064	-0.0076 – -0.0053	0.0000
Oct-14 – Aug-16	0.0064	0.0052 – 0.0076	0.0000
Sep-14 – Aug-16	-0.0065	-0.0077 – -0.0053	0.0000
Oct-14 – Jul-14	0.0128	0.0117 – 0.0174	0.0000
Sep-14 – Jul-14	-0.0000	-0.0012 – 0.0011	0.9354
Sep-14 – Oct-14	-0.0129	-0.0140 – -0.0117	0.0000

criterion. In comparison with the  $\eta$  and  $\rho$  variables, the outcome is highly significant for the sinusoidal damping  $\beta$  variable with  $p < 0.001$  indicating a great effect on the difference between the six batches. After obtaining a significant outcome, we further investigate the effect of the  $\beta$  variable on the multiple comparisons of all pairs of levels of the batch category factor, in order to test which means differ. Here we test the hypothesis that the pairwise combinations are equal using the Tukey’s post-hoc statistical test. A significance level  $\alpha = 0.05$  was used to construct the hypothesis test. Table 4 shows the outcome of the Tukey’s post-hoc test that includes the mean differences of all the combinations, the adjusted confidence intervals ( $CI=100(1 - \alpha)$ ) and the corresponding probability values. Figure S-3 in Supporting Information represents the results graphically. For the combinations, Aug-16/Apr-15 and Sep-14/Jul-14, we fail to reject the null hypothesis since  $p > 0.05$ . The  $p$ -values for all the other pairs show evidence of significant differences for  $\alpha = 0.05$ .

The statistical analysis of the NQR spectra shows a good evidence of significant discrimination between the different batches. As previously discussed, NQR is sensitive in alterations in the electric charge distribution around the nucleus, thus providing useful information about the crystal structure of the material. The NQR signal parameters can guide one to characterize the physical and chemical integrity of

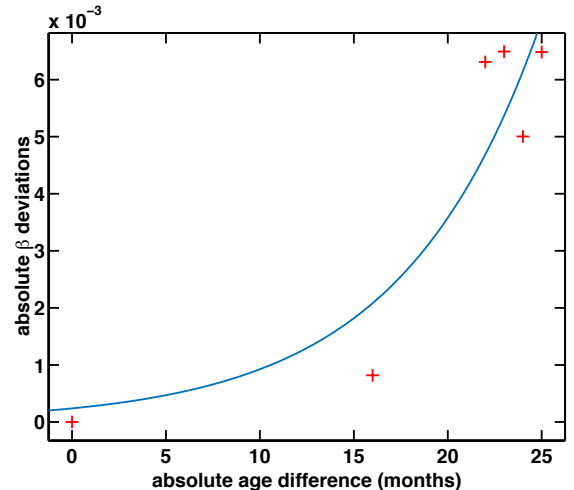


Figure 2: Absolute age difference versus the associated absolute  $\beta$  deviations from the reference/newest batch (red crosses). For illustration purposes, a possible exponential fit is shown (blue curve).

the substance under study. The differences in the batches may be influenced by a list of factors. Those may be the manufacturing processes, the aging or storage conditions. NQR is not a clear indicator of the factor causing those crystal structure variations. However, since we know that the batches have a different expiry date, one may want to test how the most discriminating factor,  $\beta$ , changes with respect to the aging factor. From Figure 1, the estimated  $\beta$  parameters of the recently purchased batch with expiry date August 2016, lie within the  $\beta$  parameters of the “older” batches. If one thinks of the ‘Aug-16’ batch as the age reference point, the deviations of all the other batches

from the newest one can be computed. Figure 2 illustrates the absolute age deviations – in units of months – of all the batches with respect to the reference (newest) batch, as a function of the analogous deviations of the  $\beta$  variable. Despite the fact that the number of points is small, there is a correlation between the absolute  $\beta$  deviations with respect to the absolute age differences that could perhaps be modeled as an exponential decay. For purpose of illustration, this is shown in Figure 2. The  $\beta$  variable could possibly be an indicator of the age of the medicines. For a complete and more accurate conclusion, more batches at a wider range of expiry dates should be analyzed. The results of this study strongly suggest that such a study would be worthwhile.

In NQR, the SNR increases with more signal averages; more precisely, the SNR is proportional to the square root of the number of scans used in the pulse sequence. It is highly important to address that the choice of SNR will determine how well defined the cluster separation will be. The higher the SNR, the less ‘spread’ and more accurate the estimated parameters will be. One way to theoretically determine the variance of the estimated parameters is to compute the Cramér-Rao lower bound (CRLB).<sup>23,28</sup> The CRLB computes the lower bound on the least achievable variance of any unbiased estimator. One may use the CRLB as a test of how optimal an estimator performs. Figure 3 illustrates the estimated  $\beta$  versus  $\eta$  variables for the two batches Sep-14 and Oct-14, and their corresponding CRLB ellipsoids. The ellipsoids simply indicate that approximately 99% of the data are expected to lie within these margins. As shown, the experimental results show a good correlation with their associated CRLB ellipsoids (SNR = -24 dB). The theoretical CRLB is highly correlated with the SNR.<sup>23,28</sup> The higher the SNR, the tighter the ellipsoids would be, and vice versa. Analogously, the more scans used during an experiment, the less spread the measurements would be. Therefore, one may need to acquire more signal averages to achieve a greater discrimination between the medicines under study, however, at the expense of prolonged experimental durations. In Figure 3, the

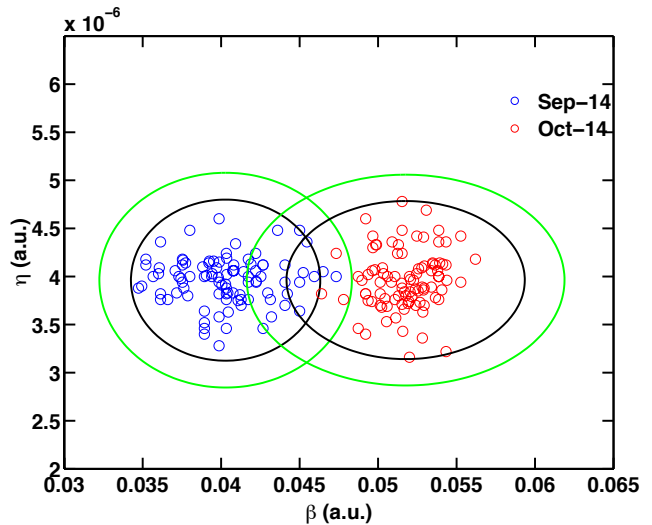


Figure 3: Scatterplot of  $\beta$  versus  $\eta$  variables for two batches (Sep-14 and Oct-14), along with their corresponding CRLB ellipsoids for two values of SNRs.

CRLB ellipsoids for a lower SNR (SNR = -30 dB) is computed in order to highlight how the degree of overlap will affect the discrimination of the two batches.

## Conclusions

In this study, different batches of analgesic paracetamol tablets were analyzed using NQR, in order to test and compare their physical and chemical integrity. The first hypothesis was to test the within-batches variability of samples of exactly the same batch. One-way MANOVA revealed no significant differences between the samples; the variability observed may be an evidence of the natural variation within one medicine. In the second hypothesis, batches of different expiry dates and batch numbers were compared. The statistical analysis indicate a significant discrimination - even at 99.9% confidence interval - between the paracetamol batches, mainly affected by the echo damping constant,  $\beta$ . The signal parameters are characteristic to the material under study, and may reveal important information about its crystal structure and chemical properties. From our results, the echo damping constant  $\beta$  could be an indicator of the aging effects on the different batches. A wider range of batches from more brands should be collected and analyzed to en-



hance our results. Additionally, an analytical technique should be applied in order to chemically determine the factors responsible for the variation.

Previous studies highlight the potential of  $^{14}\text{N}$  NQR in the detection and identification of pharmaceutical substances. It has been shown that  $^{14}\text{N}$  NQR can distinguish between medicines of the same formulation and different brands and could potentially be employed in investigating the factors influencing the physical integrity of pharmaceutical materials.

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**Supporting Information Available:** Additional information as noted in text. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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# Graphical TOC Entry

