MINI-REVIEW

Quantitative NMR (qNMR) for pharmaceutical analysis: The pioneering work of George Hanna at the US FDA

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Abstract
In the last two decades, quantitative NMR (qNMR) has become increasingly important for the analysis of pharmaceuticals, chemicals, and natural products including dietary supplements. For the purpose of quality control and chemical standardization of a large variety of pharmaceutical, chemical, and medicinal products, qNMR has proven to be a valuable orthogonal quantification method and a compelling alternative to chromatographic techniques. This work reviews a fundamental component of the early development of qNMR, reflected in the pioneering work of the late George M. Hanna during the years between 1984 and 2006 at the US Food and Drug Administration (FDA). Because Hanna performed the majority of his groundbreaking work on a 90-MHz instrument, his legacy output connects with recent progress in low-field benchtop NMR instrumentation. Hanna gradually established the utility of qNMR for the routine quality control analyses practiced in pharmaceutical and related operations well ahead of his peers. His work has the potential to inspire new developments in qNMR applied to small molecules of biomedical importance.

KEYWORDS
enantiomeric purity, qNMR, quality control, quantitative 1H NMR

1 | INTRODUCTION

While most conventional metrological quantification techniques are faced with challenges such as specific response factors and chemical as well as mechanistic considerations, quantitative NMR (qNMR) sets itself apart by being a direct method that only requires complete solubility and the presence of detectable nuclei, such as the most commonly used hydrogens. Today, qNMR has found wide recognition in pharmaceutical analysis, natural product chemistry, metrology, and forensics. It is commonly performed on instruments with magnetic field strengths equivalent to 1H resonance frequencies of 400 MHz or more, and the recent resurgence of benchtop FT-NMR instrumentation adds to the growth of qNMR practitioners.

A pioneer of qNMR, George M. Hanna laid the groundwork for the use of this method in the quality control of pharmaceuticals—in line with his mandate as a scientist at the US Food and Drug Administration (FDA). The qNMR work of his early years, between 1984 and 1998, was carried out on a 90-MHz Varian EM-390 instrument. Only in the year 1999 did he upgrade to a 400-MHz instrument. Figure 1 summarizes four...
milestones of Hanna’s qNMR portfolio of work: his initial qNMR study of dicyclomine in 1984; the combination of identification and quantitation assay by (q)NMR in 1988; in the same year, the concept of quantitating two compounds simultaneously; and the use of qNMR for the analysis of optical purity of an active pharmaceutical ingredient (API). This review connects the steady progression of Hanna’s work by highlighting the major key steps of his output, as well as the relationship to his other published work and contemporary qNMR practice.

As of today, George Hanna’s articles have been cited 300 times in 231 documents. Throughout the years 1984–2020, his articles were cited one to 18 times per year, showing a peak in 2005 with 40 citations, and led to an h-index of 11 to date (www.scopus.com). The moderate h-index and contemporary importance of qNMR in chemical and pharmaceutical analysis indicate how far ahead of his time George Hanna was with his work and that he did not receive adequate credits via citation.

2 | DEVELOPMENT OF QNMR FOR PHARMACEUTICAL QUALITY CONTROL

2.1 | Hanna’s early and low-field years 1984–1998

George Hanna’s first qNMR publication appeared in 1984 and described the NMR spectroscopic evaluation of dicyclomine hydrochloride in different dosage forms.
compound as calibrant, his experimental skills must have been remarkable. The integral of the two overlapping signals of the methyl hydrogens served for quantification of diphenhydramine, while the aromatic signals were used for quantification of the degradation products. A limit of detection (LOD) of 2% of the parent compound could be achieved for the impurities. From a conceptual point of view, this second study extended the analytical scope from identification and quantification of an API to purity determination and stability testing of pharmaceuticals.

These initial two publications were followed 4 years later in 1998 by a report of Hanna and Lau-Cam on the analysis of a carbachol ophthalmic solution.\(^2\) This marks the first reference to the concurrent analysis of complex methylene multiplets, which result from an AA'XX' spin system: Hanna recognized the need to resolve these multiplets qualitatively in order to confirm the identity of the compound (Figure 3). For quantification, however, the three methyl groups of carbachol proved to be more useful, likely due to the fact that excessive total width of the higher order AA'XX' resonances prohibited accurate integration. Acetamide served as an internal standard for this analysis.

In the same year, Hanna and Lau-Cam extended the analytical use of qNMR to the simultaneous determination of quinidine and dihydroquinidine sulfate in quinidine tablets.\(^3\) The structural difference of these two compounds lies in the chemical bond order between H-10 and H-11: a double bond in quinidine and a single bond in dihydroquinidine, which translates into an effect on the integral of the resonance of the vicinal H-9. As summarized in Figure 4, in quinidine samples free of dihydroquinidine, the integral of H-9 was equal to that of H-10, whereas an increase in the signal integral of H-9 could be observed in the presence of dihydroquinidine, as both molecules contributed to the same signal. Thus, the difference between the integrals of the H-9 and H-10 resonances could be used as an indirect assessment of the integral value for the H-9 signal of dihydroquinidine.

Further impurity profiling studies followed. A 1993 study described the solution of furosemide\(^6,7\) samples in D\(_2\)O-NaOD, a solvent mixture that allowed the separation of the resonances of furosemide and its degradation product, 4-chloro-5-sulfamoylanthranilic acid (CSA). The mean standard deviation (SD) recovery values of furosemide and CSA from 10 synthetic formulations were 99.6 (SD 0.8%) and 98.9 (SD 1.7%), respectively. A subsequent publication\(^8\) reported the detection and quantification of the ethylene glycol dimethacrylate dimer as an impurity in the methyl methacrylate monomer by qNMR. The resonances for the methylene hydrogens of ethylene glycol dimethacrylate at 3.7 ppm were used for quantitation, and the LOD for the dimer content was less than 1%.
advantage of this method was that it did not require any sample preparation and limited exposure to the relatively toxic compounds.

In a 1996 study, Hanna and Lau-Cam developed a qNMR method for the detection of diatrizoate meglumine or the combination diatrizoate meglumine and diatrizoate sodium in commercial solutions for injection. The internal standard, sodium acetate, was added to the injectable solution and diluted with D2O. The drug content from the 1H NMR spectrum was calculated based on the integral values for the –N–CO–CH3 hydrogens of diatrizoic acid at 2.23 ppm, the N–CH3 hydrogens of meglumine at 2.73 ppm, and the CH3 hydrogens of sodium acetate at 1.9 ppm. The recovery was 100.3 (SD 0.55%) for diatrizoic acid and 100.1 (SD 0.98%) for meglumine, which was determined from 10 synthetic mixtures. In addition to being able to simultaneously analyze diatrizoic acid and meglumine, the method could be used to identify diatrizoate meglumine and its individual molecular components.

Hanna published the first report of the assessment of optical purity by qNMR in 1989. He achieved this goal with the help of chiral lanthanide shift reagents for the enantioselective analysis of the antipodes of tranylcypromine. As indicated in Figure 5, the cyclopropyl methine hydrogen adjacent to the amine group experienced the largest lanthanide-induced chemical shift difference. Thus, the enantiomeric purity and percent composition could be calculated from the relative intensities of the shifted signals. A series of subsequent papers applied the chiral lanthanide chemical shift method to other APIs.

### 2.1.1 Indacrinone

A qNMR method for the quantitative determination of optical purity of indacrinone was described in a 1989 study: Hanna converted the S(+-) and R(−) enantiomers to their methyl ester derivatives, then added the chiral europium(III) or praseodymium(III) shift reagents Tris [3-(heptafluoropropylhydroxymethylene)-D-camphorato] praseodymium(III) (Pr(hcf)3) and Tris [3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) (Eu(hcf)3) (2:1) to their solution in CCl4 and HCl. The optical purity was calculated from the

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**FIGURE 3** In 1988, Hanna made first reference to complex methylene 1H multiplets, in this case due to AA’XX’ spin systems, and the need to resolve the coupling pattern for an unambiguous structure elucidation on the example of carbachol in ophthalmic solution. The 9H N–CH3 integral was used for quantification. This figure uses elements of the original fig. 1 from Hanna and Lau-Cam with permission from the publisher.
relative intensities of the resonance signals for the methyl groups at position C-2 of the indanone ring, which become diastereomeric in the complex with the chiral reagent. Mean recoveries of $S$$(+)$-indacrinone from synthetic enantiomeric mixtures were 99.75 ($n = 6$, SD 0.63%) for the europium(III) and 100.01 (SD 0.55%) for the praseodymium(III) reagents.

2.1.2 Tramadol and timolol maleate

The two studies from 1989 and 1995 compare the applicability of the two lanthanide shift complexes, (Pr(hcf)$_3$) and (Eu(hcf)$_3$), for the purpose of measuring the enantiomeric purity of the compounds tramadol$^{[1[10]}$ and timolol maleate.$^{[11]}$ Optimal experimental conditions were established by evaluating the interactions of solvents, substrate concentrations, and the concentration of the chiral lanthanide shift reagent complexes. Larger induced shifts and enantiomeric shift differences were achieved in both cases with Pr(hcf)$_3$. Enantiomeric compositions of tramadol were calculated from the shift differences in the tramadol methoxy group, leading to the determination of enantiomeric purities of up to 98.5%. The timolol maleate composition was determined based on the enantiomeric C(CH$_3$)$_3$ hydrogens, and the analysis of six synthetic mixtures led to a recovery rate of $R$$(+)$-timolol of 99.5% (SD 1.17%).

2.1.3 Carprofen

Another study from 1989 described carprofen$^{[12]}$ derivatized into its still enantiomeric methyl esters...
dissolved in CDCl₃ and then complexed with (Eu(hfc)₃). Determination of the enantiomers was based on the relative intensities of the α-methyl hydrogens. The mean recovery for the six determinations of S(+)−carprofen from the semisynthetic enantiomeric mixtures was 99.3% (SD 1.7%).

2.1.4 | Methylphenidate

A 1990 publication reported how the optical purity and absolute configuration of threo-methylphenidate could be determined with the chiral solvating agents (R)(−)− and (S)(−)-2,2,2-trifluoro-1-(-9-anthryl)ethanol. Enantiomeric resonances of threo-methylphenidate[13] were effectively resolved in CDCl₃. Optical purities were determined from the intensities of the methyl ester resonances. In addition, the enantiomeric configuration could be derived from the relative field positions of these resonances via studies of molecular models. The mean recovery rate for the (2S,2′S)(−)-threo-enantiomer was 99.9 (SD 0.6%). This approach was superior to the use of chiral Eu(III) shift reagents as it depended less on highly pure reagents and solvents. It also did not require strictly anaerobic working conditions.

2.1.5 | Chlorpheniramine

A study from 1993 described a qNMR spectroscopic method to quantify chlorpheniramine[14] maleate in tablet and injection dosage forms by simultaneous identification of the analyte without the need for a pure standard. The free base formed from chlorpheniramine in aqueous solutions was extracted into CHCl₃, and, as a more convenient sample preparation method, the maleate salt was extracted into CHCl₃. tert-Butyl alcohol was chosen as internal standard for its isolated singlet signal, and CDCl₃ was used as a solvent. The integrals of the signals at 2.18 ppm (singlet, 6H) and between 1.95 and 2.70 ppm (multiplet, 4H) were used for quantitation. Quantification of commercial tablets and injections by the elaborated qNMR method ranged from 99.8% to 100.3% for tablets and from 99.7% to 100.2% for injections. These results correlated closely with those obtained by RP-HPLC.

2.1.6 | Ephedrine

Moving to natural products, a 1995 study described the enantiomeric purity analysis of the Ephedra alkaloids (−)-ephedrine, (+)-pseudoephedrine, and (+)-norephedrine.[15] Determination of diastereomeric cross-contamination of ephedrine and pseudoephedrine, and measurement of the concentrations of these alkaloids in the presence or absence of (+)-norephedrine was achieved using the integrals for the −CHO hydrogens following addition of a trace of DCl. Mean recovery rates for ephedrine and pseudoephedrine from their respective synthetic mixtures were 99.9 (SD 0.6%) and 99.6 (SD 0.8%) of the added portion. Recovery for pseudoephedrine from diastereomeric mixtures with ephedrine...
was more than 99.4 (SD 0.7%) of the added portion, with an LOD of 1.92%. Mean recovery of (+)-norpseudephedrine from mixtures with ephedrine and pseudoephedrine was more than 99.7 (SD 2.5%) of the added portion, with an LOD of 1%.

### 2.1.7 Ibuprofen

In 1997, Hanna published on the enantiomeric composition of ibuprofen[6] using chiral europium(III) lanthanide chelation in CCl₄ after converting the enantiomers into methyl esters. Analysis of the synthetic enantiomeric mixtures correlated with the known masses of each enantiomer present in the mixtures. Analysis of 10 samples with quantitation based on the f-methyl hydrogens or ester methyl hydrogens led to average recovery rates of 99.39 (SD 0.92%) and 99.42 (SD 0.6891%) of (S)-(+)−ibuprofen, respectively.

Within the 15 years from his first published qNMR work, Hanna gradually moved from quantification to purity determination, stability testing, and simultaneous determination, to the determination of enantiomeric purity in pharmaceutical samples. Collectively, he thereby established an orthogonal analytical methodology rivaling the conventional colorimetric, titrimetric, and IR spectroscopic methods. The proof-of-concept analytes he chose were all active pharmaceutical entities with a common structural motif; notably, all of them contained tertiary or quaternary amines.

### 2.2 Recent QNMR methodology that connects to Hanna’s work

The methodology as it was established by Hanna et al. in the 1980s is still successfully applied, and even newly suggested, for the analysis of specific pharmaceutics and in forensic sciences. Examples from 2019 and 2020 demonstrate not only the topicality of the method but also how far in advance Hanna’s early reports have been. For instance, the increasing complexity of the illicit drug, 3,4-methylenedioxymethamphetamine (MDMA, aka ecstasy) is challenging the routinely used chromatographic methods. The usefulness of qNMR as a replacement method was very recently demonstrated on a 500-MHz instrument and suggested for the quantification of seized samples from night clubs by Naqi et al.[16] Considering the availability of high-resolution benchtop NMR instruments, this also opens opportunities for field work.

In a very similar manner as Hanna and Lau-Cam reported in their initial qNMR studies about the quantification of diphenhydramine and dicyclomine in 1984 and carbachol in 1988, in a 2019 study, Qin et al. proposed the quantitative determination and validation of topiramate API and its tablet formulation by qNMR.[17] The purity of topiramate in tablets was determined with qNMR on a 400-MHz instrument, and the results turned out to be consistent with those of the traditional pharmacopeial HPLC method. Another recent study from 2020 by Nasr and Shalan describes the use of qNMR at 400 MHz to analyze three anti-hepatitis drugs.[18] Daclatasvir was analyzed by quantitative ¹H NMR, and a ¹⁹F NMR method was used to determine sofosbuvir and ledipasvir in both bulk drugs and tablet dosage forms. The reported methods are described as “easy, rapid and precise with respect to other analytical techniques.” Guimaraes et al. recently suggested the use of 400-MHz qNMR to analyze liposome-encapsulated drugs.[19] The encapsulation process usually leads to a mixture of encapsulated and free active ingredients. Assessing the concentration of a drug encapsulated in liposomes by use of traditional UV/Vis methods is problematic when the maximum absorbances of the drug and the components of the formulation are similar. The authors demonstrated the superiority of qNMR as a direct method for the quantification of the encapsulated drugs with the hydrophilic compound methotrexate disodium salt and the more hydrophobic tamoxifen.

The usefulness of qNMR in pharmaceutical applications similar to those developed by Hanna was demonstrated in another very recent study by Samuels and Wang on two ionic compounds prepared as salts with counter ions.[20] Their quantification is generally challenging due to their aggregation tendency, low solubility, and signal drift. Two hydrochloride salts, an endo-drug substance and its exo-isomer, were successfully analyzed by qNMR at 600 MHz. The analysis requires in situ neutralization of the HCl salt and subsequent solubilization of the organic free base. While the identity of these two drugs is not disclosed, the method is described as “simple, cost-effective, and reliable”—attributes that echo well with Hanna’s publications.

A 2019 study by Babenko et al. describes a qNMR method for the quantification of saccharides used in dry-powder inhalation (DPI) formulations.[21] Saccharide deposition in the lungs is generally undesirable in DPI use, and the particle size distribution of the aerosolized dry powders dispersed from a DPI is commonly studied using an in vitro impactor. The newly developed qNMR method reliably quantifies pulmonary deposition of unwanted saccharides in samples generated by the in vitro impactor experiment. All three saccharides could be quantified using the newly developed 600-MHz qNMR method. Considering that Hanna and Lau-Cam
established quantitative $^1$H NMR as an analytical tool for quality control for pharmaceuicals already in the 1980s and relied solely on a 90-MHz instrument, it is surprising that qNMR as a method has yet to keep up with pace of the development of both high-end (400 to 900+ MHz) and benchtop (100 MHz and below) instrumentation that is routinely used today.

### 2.3 Hanna's later and high-field years

The International Conference of Harmonization Q3A tripartite guideline entitled “Impurities in New Drug Substances” was recommended for adoption by the regulatory agencies of the European Union, Japan, and the United States in 1995. Identification of recurring impurities with an abundance of 0.1% or larger thereby became a requirement. In 1997, the USP 23 added Supplement 6, “Other Impurities,” which stated that, if an impurity is present, but the monograph assay does not detect it, the impurity should have the amount and identity stated on the label. If the unlabeled impurity exceeds a content of more than 0.1%, the substance violated USP requirements.

In response to these new guidelines, Hanna and his coworkers investigated 22 lots of trimethoprim from five manufacturers in China, Israel, and the United States using the compendial TLC method as well as the compendial gradient HPLC method. While the TLC method revealed the impurity 3-anilino-2-(3,4,5-trimethoxybenzyl)acrylonitrile, the HPLC methods detected two more unidentified recurring impurities in 17 of the 22 lots with an AUC (Area Under The Curve) of more than 1%. Isolation of the impurities by preparative TLC and subsequent identification by mass spectrometry and NMR led to the two synthetic side products, 2,4-diamino-5-(3-bromo-4,5-dimethoxybenzyl)pyrimidine and 2,4-diamino-5-(3-bromo-4,5-dimethoxybenzyl)pyrimidine. These compounds undetectable by the compendial method were present at significant levels in 17 of the 22 lots, with the total impurity concentrations ranging between 0.1% and 2.1%. For an unknown reason, potentially sensitivity limitations, Hanna did not report the use of NMR for the quantification of these impurities.

In 2000, Hanna published a study about an assessment of the prilocain enantiomers by NMR, as a means of monitoring the stereospecific biotoxication process of prilocaine, and in order to distinguish between the two enantiomers. The $R(-)$-enantiomer is known to rapidly hydrolyze to ortho-toluidine, a metabolite that has been recognized to cause methemoglobinemia in humans.

Between 1999 and 2006, George Hanna continued to publish studies on the enantiomeric purity of APIs: He worked on bupivacaine, propranolol, (R)$(-)$-desoxyephedrine, and its antipode methamphetamine, simultaneously identified and quantified aristolochic acid in mixtures, and evaluated the stability and purity of timolol, iopamidol, and iothalamate. He measured propantheline and moved into the field of dietary supplements by analyzing S-adenosyl-L-methionine and performed isolation and purity evaluation of trimethoprim.

### 3 CONCLUSIONS

From a technique and instrumentation point of view, it should be highlighted that George Hanna pioneered the use of qNMR between 1984 and 1998 using magnets with a field strength of only 90 MHz. While even at the time this was considered low-end instrumentation, today such magnetic fields drive benchtop NMR instruments that make modern pulse sequences available and are increasingly affordable for education, research, and analytical laboratories. Hanna’s work not only pioneered the use of a structural technique for quantitation, but also was an early demonstration of the quantitative potential of NMR at low-field strengths. Relating Hanna’s work over some two decades to contemporary work, the impressive general progress in NMR instrumentation, including the fairly routine use of field strengths equivalent to 800–1000+ MHz yet remains to be fully leveraged for qNMR applications. The early work of Hanna also demonstrated that determination of impurities is well within reach of the modern 60-MHz data, in particular where gradient-based, NUS 2D experiments can be leveraged.

Hanna’s success in developing qNMR methods on 90-MHz instruments might be explained by the fact that he focused on compounds with similar structural motifs, in particular N-alkyl moieties that give rise to readily identified and disperse signals, justifying their designation as “qNMR hooks.” It is also noteworthy that Hanna carefully selected the internal calibrants for each sample to minimize signal overlap.

It is noticeable that George Hanna’s early publications on qNMR were distributed among multiple peer-reviewed journals, rather than in a few select outlets. Considering the pioneering nature of his work, this might potentially indicate that his qNMR work was perceived as unconventional and/or that he might have faced a certain degree of editorial and/or peer review bias. However, Hanna’s substantial body of work documents the rationale behind his obvious enthusiasm for qNMR. This speaks volumes about the untapped potential of qNMR for unbiased quantitation, enantiomeric purity determination, and a host of common pharmacopeial analyses.
Notably, qNMR has great untapped pharmacopeial potential for identification, assay, impurity analysis, degradation, and stability studies currently relegated to the diverse analytical instrumentation.

In recognition of George Hanna’s pioneering qNMR achievements, it is now planned to inaugurate a George Hanna Award as part of future qNMR Summit (qnmrsummit.com) conferences.

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