Evaluating Practical Uses of Molecular Isotopic Engineering

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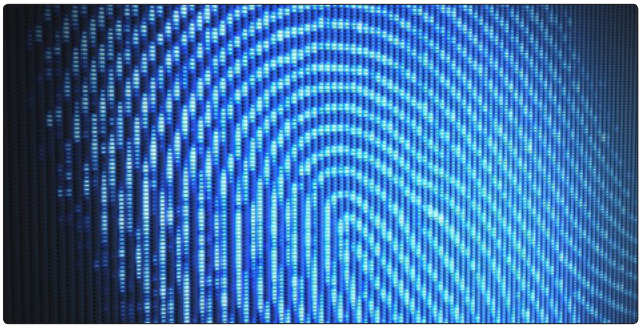

Molecular isotopic engineering (MIE) is the directed stable-isotopic synthesis of chemical products for product authentication and security, as well as intellectual property protection.In tests involving naproxen manufacturing, results showed a generally excellent correspondence between observed and predicted stable-isotopic results ($\delta^{13}C$, $\delta^{18}O$, and δD) for directed synthesis of a racemic mixture from its immediate precursors. The observed carbon-isotopic results can be readily explained by the laws of mass balance and isotope mass balance. The oxygen and hydrogen isotopic results, however, require additional assessment of the effects of oxygen and hydrogen exchange.

A previous study with FDA's Department of Pharmaceutical Analysis showed that individual manufacturers of naproxen could be readily differentiated by their stable-isotopic provenance ($\delta^{13}C$, $\delta^{18}O$, and δD). Results from two out of three of the samples in the latest study corresponded well to previous results, suggesting that MIE can be readily used without altering manufacturing processes other than isotopically selecting and/or monitoring reactants and products.

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Product authentication, product security, and intellectual property (IP) protection remain major concerns in the biopharmaceutical industry (1–6). The directed stable-isotopic synthesis of chemical products allows the stable-isotopic composition of materials to be predetermined to address these challenges (5). Product authentication is typically performed at three levels: overt, covert, and forensic (7). Molecular isotopic engineering (MIE) takes a forensic or analytical approach, analyzing stable isotopes in these products. Naturally abundant stable isotopes are natural tracers that occur in all matter (8).

Early work with FDA on the product characterization of naproxen revealed the manufacturer-level isotopic provenance of this small analgesic molecule (1,9), which was referred to as "the manufacturer's fingerprint." This isotopic provenance represented the convergence of the effects of the stable-isotopic compositions of starting materials and isotopic effects of the synthetic process. Rather than merely accepting the random effects of variable sourcing and synthetic process on the stable-isotopic compositions of products, MIE takes a proactive approach, purposefully directing the stable-isotopic composition of biopharmaceutical products.

The main rationale for MIE is to design the isotopic ranges of products for product identification and security, and also for IP considerations. As an example of MIE, the isotopic products of a later step of naproxen synthesis (**Equation 1)** were analyzed:

2-Bromo-6-Methoxynaphthalene + Bromopropionate → ±Naproxen [Eq. 1]

Pre-selection of three different stable-isotopic compositions of the starting material, 2-Bromo-6-methoxynaphthalene, yielded racemic naproxen products of three discrete stable-isotopic ranges. The resulting MIE naproxen is different from the substitution that would take place in deuterium labeling, in which a different isotope is substituted in a single position (10). The authors' directed isotopic synthesis is just one example of how MIE can be used to predetermine the discrete isotopic ranges of biopharmaceutical products.

In principle, the MIE approach should be readily adapted to existing biopharmaceutical manufacturing operations.

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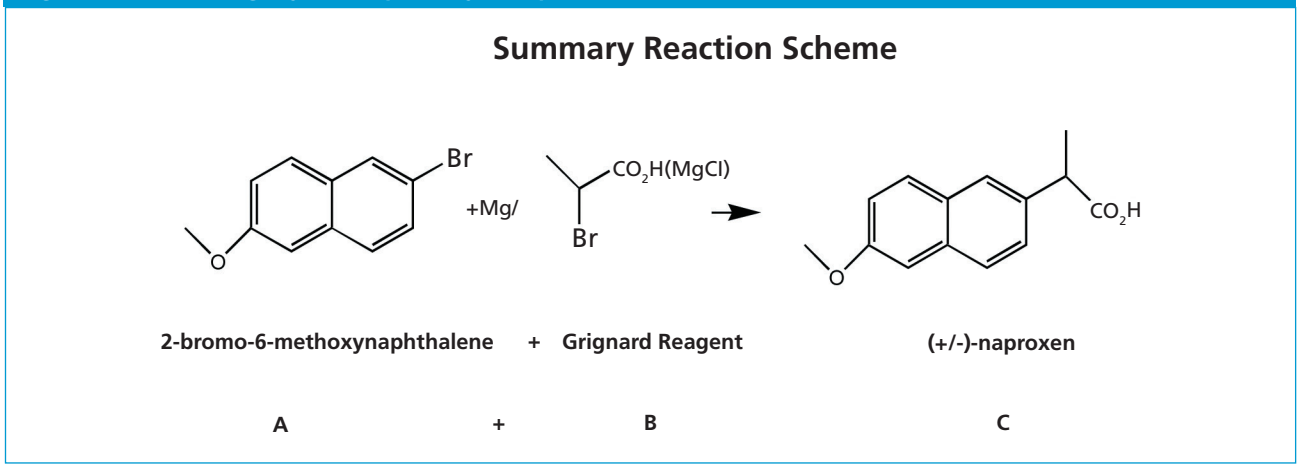
Figure 1: The late-stage synthetic pathway of naproxen.



The only adjustment to an existing manufacturing process would be the use of starting materials or synthetic intermediates of premeasured stable-isotopic compositions. The manufacturing apparatus would remain unchanged. This approach could have broad application in securing drug identity and provenance from manufacturing plant to consumer. Molecular Isotope Technologies has developed four patented or patent-pending generations of stable-isotopic methods and technologies (5):

- Product characterization (for both small molecules and biologics) (6, 9, 10)
- Process characterization (notably, process patent protection) (12)
- In-process (continuous) analysis (5)
- Molecular isotopic engineering or MIE (5).

Experimental design

Three groups of samples were analyzed to examine the natural-abundance stable-isotopic compositions for naproxen synthesis, including the two reactants (2-bromo-6-methoxynaphalene and bromopropionic acid) and the end product (racemic naproxen).

Naproxen synthesis. A late-stage synthesis of naproxen was performed by IsoSciences, LLC (King of Prussia, PA) as shown in **Figure 1.**

Reactants. Eight samples of 2-bromo-6-methoxynaphthalene were collected from a worldwide selection of suppliers (**Table I**). A Grignard reagent (bromopropionic acid) was acquired from Sigma-Aldrich (St. Louis, MO). Three of the 2-bromo-6-methoxynaphthalene samples, from CombiBlocks, Matrix, and Aesar, were selected for this study based on their differing ^{13}C compositions: one high, one low, and one intermediate. Samples of racemic naproxen were synthesized from the three different starting materials.

Grignard formation. 2-Bromo-6-methoxynaphthalene was dissolved in a round bottom flask of anhydrous toluene and anhydrous tetrahydrofuran (THF), with heating and degassing. The bromonaphthalene solution was added dropwise to the magnesium via an addition funnel. The reaction was allowed to cool to room temperature under nitrogen.

Magnesium salt formation on bromopropionic acid. Alpha-bromopropionic acid was dissolved in anhydrous THF. The solution was cooled to -15 °C in a dry ice/acetone bath and methyl magnesium chloride was added via syringe while maintaining the temperature below 0 °C. The temperature was kept below 0 °C until the solution was used.

Coupling reaction. The Grignard solution was transferred into a two-neck round bottom flask with a thermometer and a septum via cannula and was then degassed. The solution was cooled in an ice bath, and the mixed magnesium halide complex was added via cannula, maintaining the temperature at 15–20 °C. The reaction was stopped after two hours. The resulting solution was then cooled in an ice bath, and a solution of 10 mL of 12N HCl in 75 mL of water was added. After stirring for five minutes, the biphasic mixture was filtered, and the filter was washed with 25 mL of toluene and 25 mL of water.

The layers were separated, and the organic phase was extracted with 2 x 75 mL of 10% NaOH solution. The basic extracts were combined, washed with toluene (~25 mL) and filtered. To the filtrate was added 7.5 mL of methanol and 6 mL of toluene. This mixture was then acidified with concentrated HCl to a pH of 5. The resulting slurry was heated to reflux for one hour and allowed to cool overnight with stirring. The product was washed with 10 mL of water, 2 x 2 mL of toluene, and 2 x 2 mL of hexane, and dried to give an off-white solid. After drying under high vacuum for 48 hours, there was 5.8828 g (53% yield).

Stable-isotopic analyses. Three stable isotopic measurements ($\delta^{13}C$, $\delta^{18}O$, and δD) were made of each of the components of this study. In the starting material survey study, three stable-isotope ratios were measured on each of the eight samples of 2-bromo-6-methoxynaphthalene in triplicate analysis (i.e., 8 batches × 3 isotope ratios × 3 replications = 72 measurements) to assess analytical precision (13).

Table I. Stable isotopic compositions of 2-Bromo-6-Methyoxynaphthalene. Std. dev = standard deviation.

Sample	$\delta^{13}C$	$\delta^{18}O$	$\delta^{2}H$	$\delta^{13}C$	±1σ Std dev.	$\delta^{18}O$	±1σ Std dev.	δD	±1σ Std dev.
Name	‰ vs VPDB	‰ vs VSMOW	‰ vs VSMOW	‰ vs VPDB	‰	‰ vs VSMOW	‰	‰ vs VSMOW	‰
Matrix Scientific/W12M - 1	-23.97	24.24	-116.6						
Matrix Scientific/W12M - 2	-24.02	24.31	-114.3	-24.01	0.04	24.24	0.07	-115.1	1.3
Matrix Scientific/W12M - 3	-24.04	24.17	-114.3						
AK Scientific/LC33871 - 1	-23.97	24.17	-115.7						
AK Scientific/LC33871 - 2	-23.99	24.27	-116.4	-24.01	0.05	24.25	0.07	-116.2	0.5
AK Scientific/LC33871 - 3	-24.06	24.30	-116.6						
Oakwood Chemical/D13F - 1	-24.48	13.77	-64.2						
Oakwood Chemical/D13F - 2	-24.53	13.76	-68.0	-24.49	0.04	13.77	0.02	-65.9	1.9
Oakwood Chemical/D13F - 3	-24.46	13.80	-65.6						
Sigma Aldrich/MKBR4254V - 1	-24.51	13.86	-70.6						
Sigma Aldrich/MKBR4254V - 2	-24.49	13.95	-68.6	-24.50	0.01	13.96	0.10	-69.2	1.2
Sigma Aldrich/MKBR4254V - 3	-24.49	14.07	-68.6						
Combi-Blocks/L74583 - 1	-28.76	0.36	-65.4						
Combi-Blocks/L74583 - 2	-28.70	0.54	-65.0	-28.73	0.03	0.45	0.09	-64.6	1.0
Combi-Blocks/L74583 - 3	-28.75	0.45	-63.5						
Tokyo Chemical Industry Co., Ltd. (TCI)/GJ01-CSBE - 1	-29.67	-2.45	-144.9						
Tokyo Chemical Industry Co., Ltd. (TCI)/GJ01-CSBE - 2	-29.65	-2.38	-146.4	-29.67	0.03	-2.42	0.04	-145.9	0.8
Tokyo Chemical Industry Co., Ltd. (TCI)/GJ01-CSBE - 3	-29.71	-2.44	-146.3						
Apollo Scientific Limited/ AS447149 - 1	-29.82	3.84	-116.5						
Apollo Scientific Limited/ AS447149 - 2	-29.85	3.89	-116.5	-29.85	0.02	3.80	0.11	-116.7	0.4
Apollo Scientific Limited/ AS447149 - 3	-29.87	3.68	-117.1						
Alfa Aesar/10137505 - 1	-29.90	13.79	-109.0						
Alfa Aesar/10137505 - 2	-29.84	14.13	-111.0	-29.88	0.04	14.07	0.25	-110.2	1.1
Alfa Aesar/10137505 - 3	-29.91	14.28	-110.5						

Table II. Stable isotopic composition of bromopropionic acid.

Sample	$\delta^{13}C$	$\delta^{18}O$	δD
Name	‰ vs VPDB	‰ vs VSMOW	‰ vs VSMOW
2-bromopropionic acid / 1	-30.05	11.01	-19.0
2-bromopropionic acid / 2	-30.13	10.84	-20.8
2-bromopropionic acid / 3	-30.21	11.35	-21.1
Average	-30.13	11.07	-20.3
Standard Dev.	0.08	0.26	1.1

Nine analogous isotopic measurements were made on the bromopropionic acid reagent (3 isotope ratios × 3 replications). Triplicate analyses were also performed for each of the three isotope ratios of the five batches of naproxen synthesized here, yielding 45 isotope measurements. Thus, a total of 126 stable-isotopic measurements of the samples were performed in this study.

Carbon and oxygen isotope analyses. As detailed elsewhere (10), carbon ($\delta^{13}C$) and oxygen ($\delta^{18}O$) isotopic analyses were performed respectively on:

- A Carlo Erba 1108 Elemental Analyzer, interfaced using a Conflo III interface to a Thermo Scientific Delta V isotope ratio mass spectrometer (EA/IRMS)

38 Pharmaceutical Technology Europe JULY 2016 PharmTech.com

Figure 2: Carbon-isotopic composition ($\delta^{13}C$) as a function of either reactant or product. Predicted values of mass balance/isotopic mass balance for racemic naproxen are shown adjacent to the observed values for comparison.

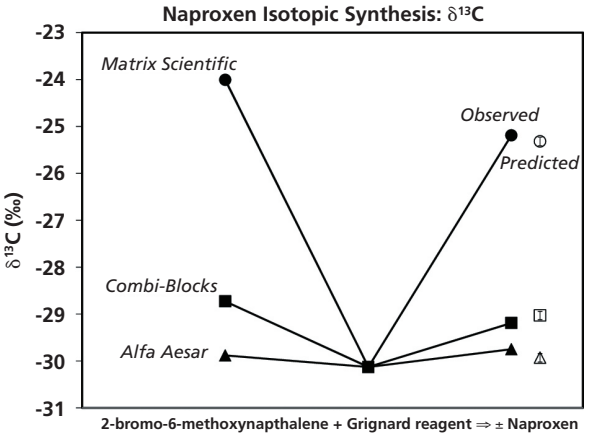
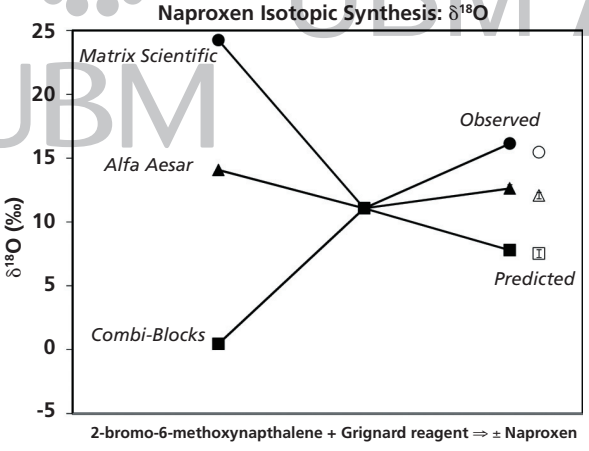


Figure 3: Oxygen-isotopic composition ($\delta^{18}O$) as a function of either reactant or product. Predicted values for mass balance/isotopic mass balance for racemic naproxen are shown adjacent to the observed values for comparison.



- A Finnigan Thermal Conversion/Elemental Analyzer (TCEA) interfaced to Finnigan Delta V Plus isotope-ratio mass spectrometer (thus, a TCEA/IRMS).

Hydrogen (δD) isotopic analyses. Hydrogen that is not bound to carbon in a molecule may readily exchange with other hydrogen atoms present in ambient moisture (i.e., H_2O). This exchange happens even at room temperature and is difficult to control. To generate precise δD values for a given compound, the exchangeable hydrogen portions must be accounted for or controlled.

Samples were weighed into individual 3.5 mm x 5 mm silver "boats" and equilibrated with reference waters of known δD values to calculate the amount of exchangeable hydrogen in the sample (14). The samples were allowed to equilibrate for two hours at 50° C inside a container with an aliquot of calibrated reference water.

The equilibration process was repeated twice on separate aliquots of sample using reference water samples that have a difference of -233‰ in δD value. After equilibration, the samples were dried overnight in a vacuum oven at 50° C, then immediately transferred to the Costech Zero Blank autosampler of a Finnigan MAT Thermal Conversion Elemental Analyzer (TC/EA) and evacuated to remove ambient moisture.

Several reference standards accompanied each batch of samples, including a polyethylene standard that has no exchangeable hydrogen and is therefore unaffected by ambient moisture. In the TC/EA, the samples were reduced at 1400 °C in the presence of glassy carbon. The resulting hydrogen was then separated from other gases via a gas chromatograph and transmitted into an isotope ratio mass spectrometer (IRMS) for isotopic analysis to obtain the δD values. Using post-analysis calculations (15), the δD value of the non-exchangeable hydrogen could be quantified from the equilibrated sample data sets.

Units of stable isotopic measurement. Carbon (and all other) isotopic results are expressed in δ values (‰ = parts per thousand differences from international standards), as expressed in **Equation 2**:

$$\delta\ (‰) = ([(R_{smpl})/(R_{std})] - 1) \times (1000) \quad \text{[Eq. 2]}$$

where R_{smpl} = the $^{13}C/^{12}C$ ratio of the sample material and R_{std} = the $^{13}C/^{12}C$ ratio of an International Atomic Energy Authority standard (IAEA, known as "VPDB" [Vienna Pee Dee Belemnite], whose $^{13}C/^{12}C$ ratio has been defined as the official zero point of the carbon-isotopic scale).

$^{18}O/^{16}O$ and D/H values are given relative to IAEA Vienna Standard Mean Ocean Water (VSMOW) standard, which gives the zero points of the oxygen and hydrogen-isotopic scales.

Estimates of uncertainty. Because all measurements in this study were made in triplicate, the averages and 1σ-standard deviations are reported here for the observed isotopic data in **Tables I and II**. Two sigma standard deviations are shown for the deviations from mass balance and isotope mass balance.

Characteristic one sigma (1σ) standard deviations for the isotope measurements reported in this study were: $\delta^{13}C$ (±0.03‰), $\delta^{18}O$ (±0.09‰), and δD (±1.0‰) as shown in **Table I**.

Results and discussion

Stable isotopic composition of reactants. The $\delta^{13}C$, $\delta^{18}O$, and δD compositions of eight samples of the reactant 2-bromo-6-methoxy-naphthalene measured in triplicate are shown in **Table I,** and those of bromopropionic acid are shown in **Table II**.

The stable isotopic records of naproxen synthesis. The directed stable-isotopic synthesis of naproxen is discussed in two parts: the mass-balance/isotope-mass balance (MB/IMB) component, and then the deviations (if any significant) from MB/IMB. Because these results are compared to the MB/IMB frame of reference, that topic is briefly described.

Comparing observed versus predicted isotopic values. The laws of mass balance and isotope mass balance (14) provide a primary frame of reference for assessing the results of the naproxen isotopic synthesis. The basic mathematics of MB/IMB (15) is summarized in **Equations 3–7**.

Mass Balance: $n_A + n_B = n_C$ [Eq. 3]

Isotope Mass Balance: $n_A\delta_A + n_B\delta_B = n_C\delta_C$ [Eq. 4]

Isotopic Fractionation (one component in excess):

$n_A(\delta_A + \Delta_A) + n_B\delta_B = n_C\delta_C$ [Eq. 5]

$\delta_A + \Delta_A = (n_C\delta_C - n_B\delta_B)/n_A$ [Eq. 6]

$\Delta_A = [(n_C\delta_C - n_B\delta_B)/n_A] - \delta_A$ [Eq. 7],

where

n_A, n_B, n_C = number of moles of compounds A, B, and C;

δ_A, δ_B, and δ_C = isotopic compositions of compounds A, B, and C; and

Δ_A = isotopic fractionation of compound A.

Carbon. The observed carbon isotopic results and the predicted MB/IMB results for the naproxen synthesis are shown in **Figure 2**. Observed and predicted values align well and will be further examined below.

Oxygen. The observed oxygen isotopic results and the predicted MB/IMB results for the naproxen synthesis are shown in **Figure 3.** Observed and predicted values deviate slightly from each other and will be further examined below.

Hydrogen. Observed isotopic results and predicted MB/IMB results for the naproxen synthesis are shown in **Figure 4**. In one case, observed and predicted values deviate notably from each other and will be further examined below.

Mass balance and isotope mass balance: correspondence and deviations. The correspondence to and deviations from MB/IMB (**Figures 2–5**) are examined here to account for the three isotope ratios examined.

Carbon: no significant deviation. A plot of the observed $\delta^{13}C$ values versus the predicted values on the basis of MB/IMB is shown in **Figure 6**. The excellent correspondence indicates that the carbon-isotopic synthesis is consistent with the MB/IMB model.

Figure 4: Hydrogen-isotopic composition (δD) as a function of either reactant or product. The mass balance/isotopic mass balance-predicted values of racemic naproxen are shown adjacent to the observed values for comparison.

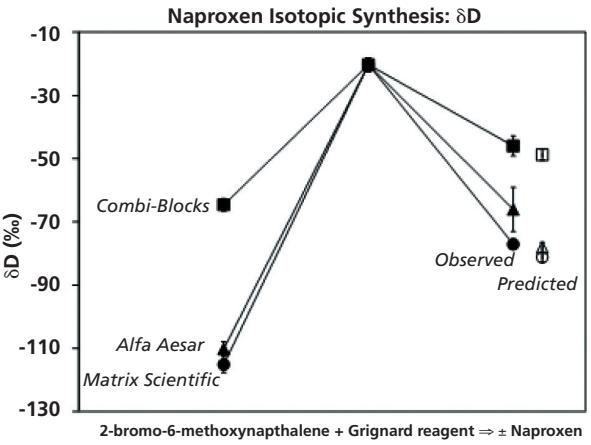
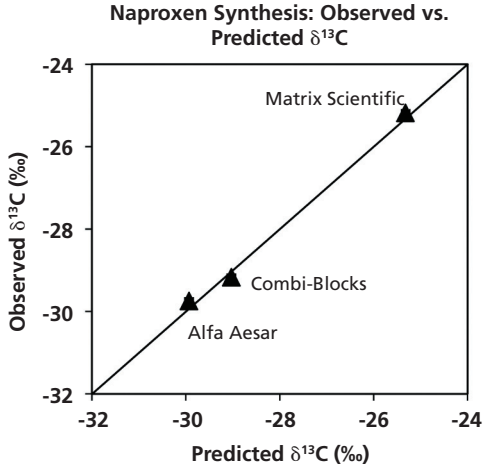


Figure 5: Observed versus predicted carbon-isotopic compositions of racemic (±) naproxen values demonstrating excellent (±1 s.d.) correspondence between mass-balance/isotope-mass balance estimation and observed values.



Oxygen and hydrogen: fractionation due to equilibration with water. The O and H data, however, both show significant differences between observed and predicted values. In both cases, the observed values are isotopically enriched relative to the predictions. The oxygen data argue against direct incorporation of water into the samples, because local water should have a $\delta^{18}O$ value of -5‰ (16).

Contin. on page 44

Contin. from page 41

Figure 6: Observed versus predicted values for oxygen-isotopic compositions of racemic (±) naproxen showed excellent (±2 standard deviation) correspondence between mass-balance/isotope-mass balance estimation plus H_2O/RCOOH equilibration and observed values

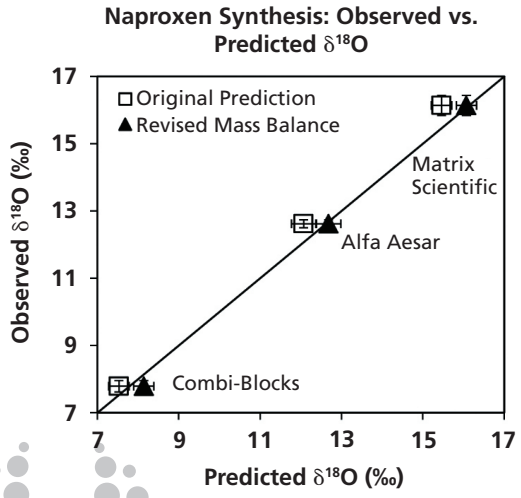
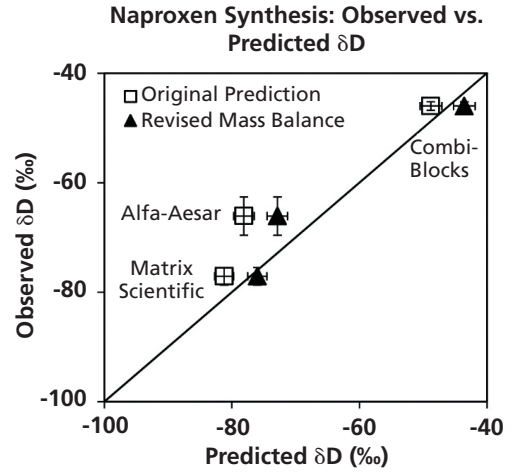


Figure 7: Observed versus predicted hydrogen-isotopic compositions of racemic naproxen values demonstrated generally good correspondence between mass-balance/isotope-mass balance estimation plus H_2O/RCOOH equilibration and observed values. The reason for the Alfa Aesar excursion from the 1:1 line is not explicitly known.



However, if the water is incorporated through an equilibrium isotope effect, then one might suggest that ^{18}O would favor being bound to the carboxyl position (the more stable bonding environment), whereas ^{16}O would favor remaining in the water phase.

With that, the following equilibrium is plausible, and the forward direction is favored, as shown in **Equation 8**.

$$RC^{16}O^{16}OH + H_2{}^{18}O \Leftrightarrow RC^{18}O^{16}OH + H_2{}^{16}O^{18/16}\alpha_{RCOOH/H2O} > 1.00 \quad \text{[Eq. 8]}$$

Thus, the isotope mass balance equation is solved by considering the O from the original methoxynapthalene, plus the Grignard reagent contribution of one unaltered O and one carboxylic acid O that has been equilibrated with water. For accounting purposes, the three oxygens are A, B, and C – the methoxynapthalene (A), the carbonyl (B), and the exchangeable OH (C), as shown in **Equation 9.**

$$\delta_{tot} = f_A\delta^{18}O_A + f_B\delta^{18}O_B + f_C(\alpha(\delta H_2O + 1000) - 1000) \quad \text{[Eq. 9]}$$

where $\alpha = (\delta^{18}O_{RCOOH} + 1000)/(\delta^{18}O_{H2O} + 1000)$ specifically for the carboxyl-OH group. The best fit solution indicates that $\alpha = 1.018$.

Comparison of results with literature data

From the outset, the authors are comparing stable-isotopic data for racemic naproxen with the only other naproxen-isotope data (*viz.*, *S*-naproxen) (10) that, to the authors' knowledge, exists. Assuming that the isotopic fractionation of naproxen is small between the racemic mixture and the purified enantiomer (S), the authors make the present comparison but acknowledge that this assumption must be tested in ongoing research.

The carbon- and oxygen-isotopic results of the present syntheses of naproxen are superimposed on pre-existing data (6) in **Figure 8**. Although there was no intent to reproduce the pre-existing naproxen-isotope data, the present naproxen data fall within the range of the pre-existing data.

In addition, two of the present naproxen values (Matrix Scientific and Alfa Aesar) lie within approximately 2σ of pre-existing results (namely, "India Manufacturer B" and "India Manufacturer A," respectively). By contrast, the Combi-Blocks-sourced naproxen does not lie near any of the pre-existing clusters of naproxen data, plausibly because no such naproxen was obtained for the earlier study.

Product identification, security, and IP protection

MIE allows unprecedented stable-isotopic definition of chemical products from isotopically-known starting materials. In fact, its use in naproxen synthesis permits the precision of compound production to within a few tenths of a permil for carbon and oxygen and approximately one permil for hydrogen when the ranges of starting materials may span tens of a permil. Such narrow delimitation of products' isotopic fingerprint decreases their vulnerability to various IP infringements. MIE thus allows for the design and synthesis

of drug molecules with discrete stable isotopic composition for a wide range of stable isotopes.

Starting with a small survey suite of readily-available reactants, various chemical products can be produced via existing chemical processes. The only difference from pre-existing processes is that the stable-isotopic compositions of the reactants and products are now measured either offline or online.

The major result of MIE is to generate chemical products of narrowly-delimited isotopic ranges as compared to the seemingly random distribution of typically-produced products in which no explicit effort is made to delimit their compositions. In other words, MIE allows for the design of a unique and characteristic isotopic array or internal "bar code" or "fingerprint" for a drug molecule. The potential implications for product authentication, supply chain custody, security, and anticounterfeiting are enormous.

Furthermore, because MIE-designed drug molecules are essentially new chemical entities, MIE has some potentially interesting IP implications. Consider for example, a conventionally-synthesized, but isotopically-labeled drug molecule, where the resulting product is a new entity that was not previously found in nature. By using MIE, one can go beyond merely positionally-labeling a drug molecule with an isotope to design new molecules (9), rationally and selectively, with far more complex (i.e., multipositional), and, thus, highly specific isotopic fingerprints.

Conclusion

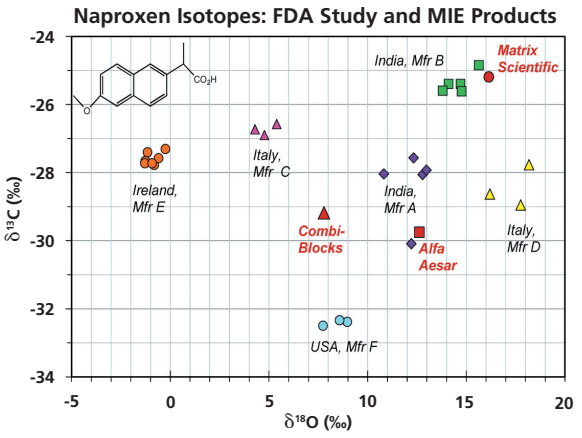
Consistent with principles of mass balance and isotope mass balance, directed stable-isotopic synthesis (or, Molecular Isotopic Engineering) permitted the production of racemic naproxen of pre-determined isotopic compositions (C,O,H) for reasons of product authentication, security, and, perhaps, IP protection. A small, worldwide survey of a key naproxen intermediate (2-bromo-6-methoxynaphthalene) gave a wide range of C, O, and H isotopic values for the present starting material.

Mass balance and isotope mass balance (MB/IMB) account for the carbon-isotopic relationship between the reactants and product naproxen very well. In addition to MB/IMB considerations, the equilibration between O and H and naproxen is readily accounted for by equilibrium isotopic exchange with reaction water.

In general, the use of existing synthetic manufacturing methods indicate that MIE should generate products in predetermined isotopic ranges for product authentication and security, and may present a new mode of pharmaceutical patenting: "isotopic composition of matter."

AUTHORS' NOTE: Pending patent applications are on file with respect to the technology, which has already been granted US Patents No. 7.323,341 and 8,367,414 B2.

Figure 8: Naproxen samples produced for this study superimposed over the naproxen-isotope values previously observed in a cooperative study with the US FDA's Department of Pharmaceutical Analysis (17).



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