Quantitative Component Analysis of Solid Mixtures by Analyzing Time-Domain ^{1}H and ^{19}F T_1 Saturation Recovery Curves (QSRC)

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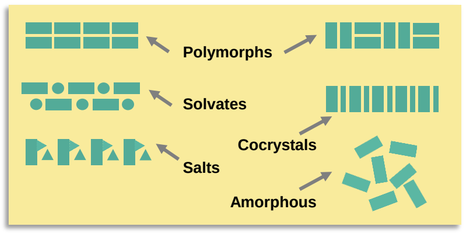
Background

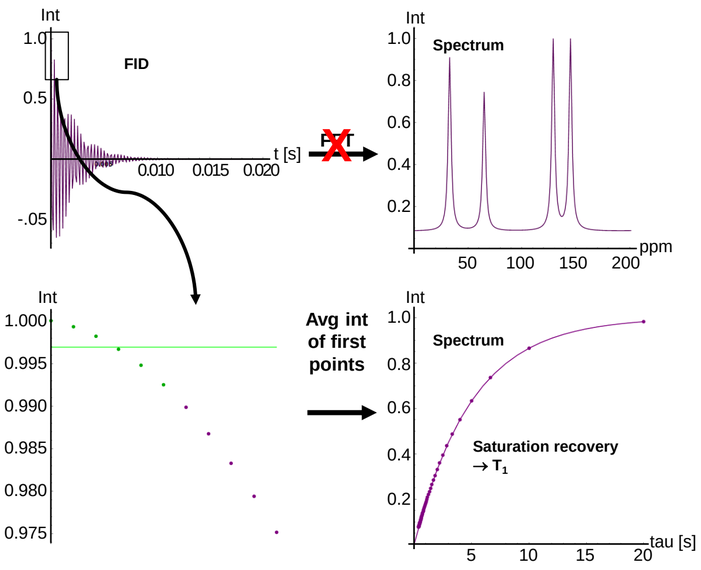
Active pharmaceutical ingredients (APIs) often exhibit extensive polymorphism and the tendency to form solvates and hydrates. In addition, the interaction of the desired API lead form with excipients in formulations during processing or during long-term storage may lead to form change and/or amorphization. Consequently, API and formulated materials studied in early drug development often contain complex mixtures composed of the desired API lead form in the presence of other polymorphs, solvates, amorphous material, and excipients. The ability to characterize and quantify relevant API forms in these complex mixtures in the presence of each other and excipients is crucial in the early development process because polymorphs often exhibit distinct physical properties that may alter the dissolution and bioperformance, processability, and/or chemical stability of formulated drug product.[1]

Typical analytical tools to analyze API and formulated pharmaceutical materials include X-ray powder diffraction, optical and vibrational spectroscopy, and thermometric methods like differential scanning calorimetry (DSC) and thermogravimetry (TG).[2] In recent years, high-field and high-resolution solid-state NMR (ssNMR) has emerged as an invaluable tool for analyzing API and formulated pharmaceutical materials in the solid state.[3] Several ssNMR-based methods to quantify components in mixtures have been proposed and successfully applied. These methodologies include a number of chemometrics approaches, signal deconvolution, corrected signal integration, and relaxation-based methods. Among the chemometrics NMR tools, the direct exponential curve resolution algorithm (DECRA) has been applied most frequently on a variety of materials, including pharmaceuticals, polymers, and human brain MRI.[4]

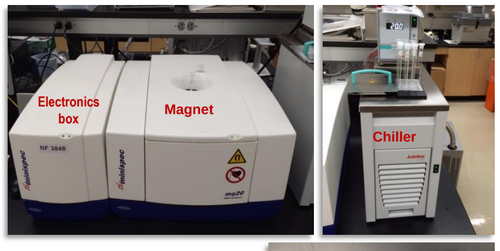
The method proposed here, QSRC, represents a new and very efficient approach for quantifying the components in solid mixtures. It utilizes ^{1}H and ^{19}F T_1 saturation recovery curves (SRCs) measured on a Bruker Minispec mq20 benchtop TD-NMR instrument.[5] For the analysis of a given mixture, the SRCs for the relevant pure components, as well as for the mixture itself, are measured. The relative amounts of the mixture components are obtained from a fit of the mixture SRC with a linear combination of weighted pure component SRCs.



TD-NMR on a Bruker Minispec mq20



Bruker Minispec mq20



Sample:
10-mm glass tube
100–200 mg

- No FFT, no spectrum
- Record only first points of FID and average → build relaxation curves
- No resolution necessary → obs. ^{1}H
- Well-characterized relaxation curves
- Very simple and fast sample prep
- Automation and T-control available

QSRC: Form Quantification Using TD-NMR SRC Data

QSRC approach:

- SRC_{mix} is a linear combination of component SRCs (SRC_i)
- Linear coefficients, c_i, are relative concentrations

N mixture components

$$SRC_{mix} = \sum_{i=1}^{N} c_i \, SRC_i + b$$

Intensities I_i at n recovery time points

$$SRC_i = \{I_{i,1}, I_{i,2}, I_{i,3}, \ldots, I_{i,n}\}$$

- Component SRCs are normalized

$$SRC_i^{norm} = \frac{SRC_i \; x_{nuclei/molecule}}{I_{i,\tau>5T1} \; M_i}$$

$x_{nuclei/molecule}$ = moles of observed nuclei per moles of molecules.

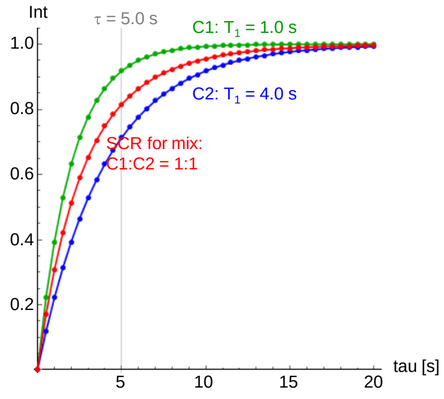
M = molecular mass.

- Optimal coefficients are determined in minimization

$$\text{Minimize}\left[SRC_{mix} - \left(\sum_{i=1}^{N} c_i^{norm} \, SRC_i^{norm} + b^{norm} \right) \right]$$

- Optimization routine implemented in mathematica code

Illustration of method: Hypothetical two-component system



$$I_{mix,\tau=5.0s} = {}^{1}/_{2} \, I_{1,\tau=5.0s} + {}^{1}/_{2} \, I_{2,\tau=5.0s}$$

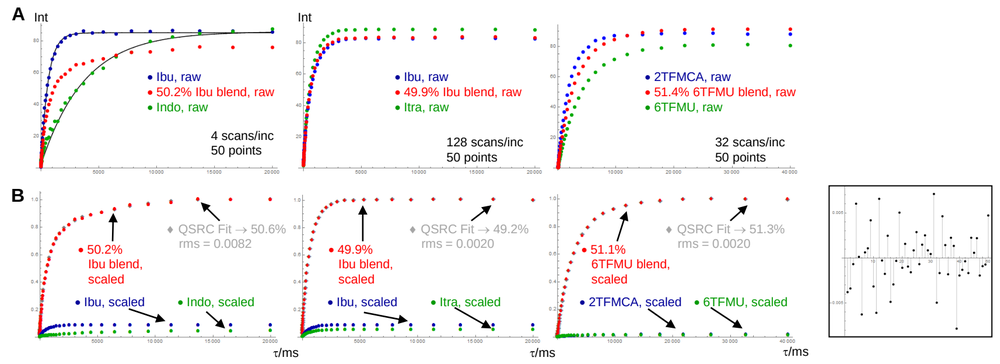
- Binary blends of model compounds with known compositions were analyzed with QSRC
- Model compounds have different and similar ^{1}H/^{19}F T_1s
- Model compounds are small pharmaceutical molecules

Model System	Blends	Nucleus	T_1 [s]	M [g/mol]	x
Ibuprofen/indomethacin	5%-50%m Ibu	^{1}H	0.64 3.40	206.29 357.79	18 16
Ibuprofen/itraconazole	5%-50%m Ibu	^{1}H	0.64 0.69	206.29 705.64	18 38
2-trifluoromethyl cinnamic acid/ 6-trifluoromethyl uracil	5%-90%m 2TFMCA	^{19}F	2.08 4.22	216.16 180.09	3 3
2-trifluoromethyl cinnamic acid/ fluoxetine HCl	10%-70%m 2TFMCA	^{19}F	2.08 1.85	216.16 345.79	3 3

^{1}H and ^{19}F QSRC analysis for model systems (binary blends)

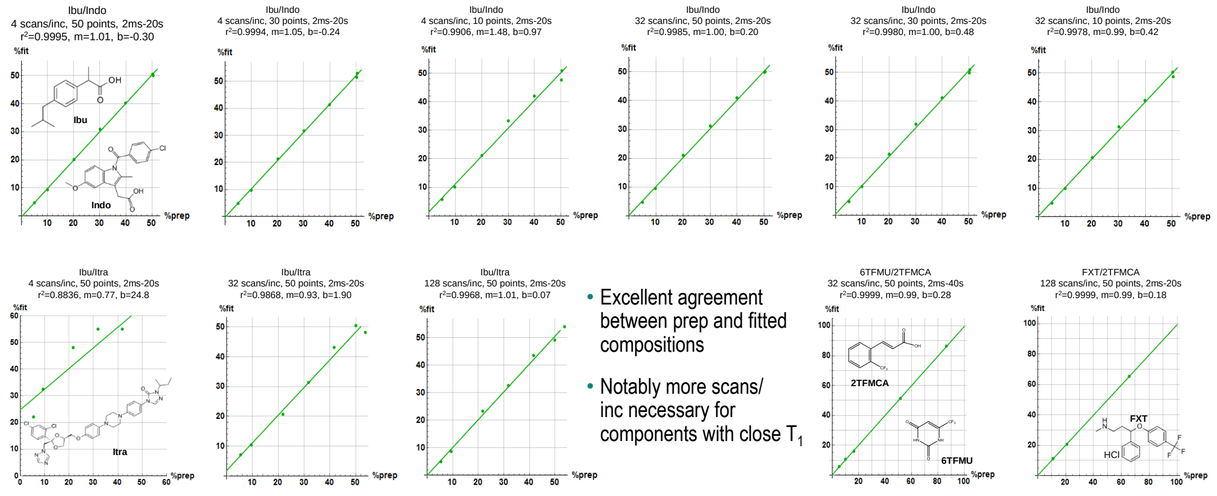
A. Selected experimental pure component and blend SRCs, and corresponding QSRC fits

B. Point-by-point deviations for QSRC fit for 50.2% Ibu/ Indo blend



Ibu=ibuprofen; Indo=indomethecin; Itra=itraconazole; 2TFMCA=2-trifluoromethyl cinnamic acid; 6TFMCA=6-trifluoromethyl cinnamic acid; FXT=fluoxetine

Correlation plots for QSRC ^{1}H and ^{19}F fitting on model systems



- Excellent agreement between prep and fitted compositions
- Notably more scans/ inc necessary for components with close T_1

Summary/Conclusions

- Proposed QSRC method uses ^{1}H and ^{19}F T_1 SRCs as fingerprints for expected components in solid mixtures
  - *SRC_{mix} = weighted linear comb $SRCs_{comp}$*
- SRCs are efficiently collected on a Bruker Minispec mq20 benchtop NMR instrument
- POC for using QSRC method for ^{1}H and ^{19}F SRCs has been shown for several model systems
- Separation of components with close T_1s requires more scans/inc
- Significant total time savings with respect to conventional ssNMR techniques
- Advantages of QSRC – Bruker Minispec mq20:
  - Robust, accurate, and fast
  - Trivial sample preparation (glass tube sample holder), T-control, and automation possible
  - No requirements on sample texture or homogeneity (tablets, gels, polymers, …)
  - Amenable to industrial high-throughput settings, production sits (Pharma Industry, …)
- Patent for QSRC – Bruker Minispec mq20 filed (QSRC module in Dynamics Center)

References

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