Electronic Supporting Information (ESI) for:

Growth "Self-Inhibition" of Irbesartan Desmotrope: Surface Intra-annular Tautomer Inter-conversion is the Culprit

Xiang Kang [a], Mingtao Zhang [c], Weiwei Tang [*a], and Junbo Gong [*a, b]

[a.] *State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China.*

[b.] *Collaborative Innovation Center of Chemistry Science and Engineering, Tianjin 300072, China.*

[c.] *State Key Laboratory and Institute of Elemento-Organic Chemistry, Centre of Nanoscale Science and Technology and Key Laboratory of Functional Polymer Materials, Renewable Energy Conversion and Storage Center (RECAST), College of Chemistry, Nankai University, Tianjin 300071, China;*

Table of content

1. Experimental procedures

1.1 Materials

Irbesartan (IBS, 98%), sodium hydroxide (>98%), and 2-propanol (>99.7%) were all purchased from Shanghai Titan Scientific Co., ltd. Hydrochloric acid (AR) was purchased from Tianjin Jiangtian Chemical Technology Co., ltd. All chemicals were used as received, and deionized water was utilized throughout all experiments.

1.2 Preparation of crystal seeds for growth studies

Preparation of IBS 2-propanol solvate crystal seeds. The IBS 2-propanol solution was prepared by dissolving appropriate amounts of IBS powders in a 100 ml beaker with 2-propanol, which was dissolved by rapid agitation at 40 °C until no further dissolution was possible. The obtained supernatant was then filtered through a 0.22 μm filter membrane and transferred into a 50 mL glass bottle which was sealed with sealing film and left at ambient condition for 1-2 days to allow crystallization.

Preparation of IBS Form B crystal seeds. The IBS solution was prepared by dissolving appropriate amounts of IBS powders in a 100 ml beaker with deionized water, which was dissolved by rapid agitation at 60 °C until no further dissolution was possible. The obtained supernatant was then filtered through a 0.22 μm filter membrane and transferred into a 50 mL glass bottle which was sealed with sealing film. The sealing film is perforated with an appropriate number of small holes to accelerate the volatile crystallization The glass bottle was left at ambient conditions for 4-5 days to allow crystallization.

1.3 Structure determination of IBS 2-propanol solvate and Form B

Structure determination of IBS 2-propanol solvate. Acicular IBS 2-propanol solvate crystals was cultured in a supersaturated 2-propanol solution, and the crystal structure was successfully determined by single-crystal XRD for the first time and reported in CSD (2313679). The measurement was performed on a D/MAX 2500 X-ray diffractometer (XRD) with a Cu Kα source (40 kV, 100 mA) and a CCD detector (Table S1).

Phase characterization of IBS Form B. The produced rob-like crystals were characterized by DXRxi Raman microscope (Thermo Fisher Scientific, USA) equipped with an EMCCD detector and a 532 nm laser source. Raman spectra were collected over the spectral range of 0-2000 cm^{-1} at a spectral resolution of 3−5 cm^{-1} under an exposure time of 10 s, confirmed to be IBS Form B (Fig. S2).

1.4 Preparation of supersaturated solution for crystal growth

Growth solutions prepared at different concentrations (6.0-15.0 mM IBS in 2-propanol or 18.0-47.0 mM IBS in aqueous solution) were used in the crystal growth

studies. The IBS aqueous solution was prepared by dissolving appropriate amounts of IBS powders in DI water at 60 ℃ under rapid agitation. The clear solution was cooled to room temperature and adjusted pH 7 by 1M NaOH aqueous solution. The IBS 2-propanol solution was prepared by dissolving appropriate amounts of IBS powders in 2-propanol at 40 ℃ under rapid agitation. All the growth solution is cooled to room temperature and filtered with a filter membrane for immediate use.

1.5 Crystal growth assays

To determine the crystal growth rate of the IBS 2-propanol solvate and Form B along the lengthwise direction at different concentrations and solvents, a setup for the crystal growth rate measurement as shown in Figure 1 was used. The operation steps were as follows: (a) the IBS solution was prepared with a fixed supersaturation and injected into a quartz cuvette through a filter membrane. (b) Under an inverted microscope (Olympus, CKX53, equipped with a charge-coupled device (CCD) camera), an IBS 2-propanol solvate or Form B crystal with suitable size and morphology was selected at the magnification of 20×. Then, the single crystals were put into the quartz cuvette containing a fixed supersaturation solution. It must be noted that when determining the growth rate of seed crystals in water or 2-propanol, it was necessary to rinse them with a saturated solution of IBS in water or 2-propanol. Otherwise, when the seed crystals were placed in the quartz cuvette, water or 2-propanol would act as an antisolvent and cause the surface of the seed crystals to crystallize. (c) After adjusting the position of the seed crystal in the quartz cuvette, it is fixed in the growth device and the growth unit is sealed. The growth of the seed crystals in a temperature-controlled environment (set at around 22 °C) was monitored using an inverted microscope at a magnification of 20×.

1.6 Density Functional Theory Calculations

All calculations were performed with the software package Gaussian 09(90). To obtain accurate geometries and relative energies of the IBS^- and IBS molecule, we used the complete basis-set, m06-2x/6-311g (d, p), level of theory. Solvation effects were considered by applying the SMD (92) solvation model with the solvent being water or 2-propanol. Boltzmann distribution analysis was applied to calculate the population distribution of each tautomer at 25 °C using the calculated free energies.

1.7 Spectroscopic verification of IBS tautomers in solution

To identify the presence of IBS tautomers in neutral aqueous and 2-propanol solutions, variable-temperature UV-Vis spectroscopy was employed. UV-Vis spectra were recorded on a SINDIN SDC-100 spectrophotometer. UV-Vis spectra of 0.03mM IBS aqueous solution were collected at different temperatures (i.e., 10, 30, 50, and 70℃) in a 4 mL quartz cuvette of a 1 cm optical path length over a spectral range from 190 ~ 350 nm and a scan speed of 120 nm/min ((with a wavelength interval of 0.5 nm). The same method is used for collecting UV-Vis spectra of 0.04mM IBS in 2-propanol. All of the solutions used here were prepared using the same method as described in

Section 1.4.

2 Supplementary text, figures, and table

Table S1. Crystallographic Data of IBS 2-propanol Solvate Reported in This Study (CCDC: 2313679) in Comparison with Form A (solvent-free 1H-IBS) Reported in the Literature (1).

	IBS 2-propanol Solvate In this study	Irbesartan form A Ref.1
Formula	$C_{25}H_{28}N_6O{\cdot}0.562$（$C_3H_8O$）	$C_{25}H_{28}N_6O$
Formula weight	462.29	428.53
Temperature/K	100.0	293
Environment	N_2	/
Crystal colour	colourless	/
Crystal description	needle	/
Wavelength	1.54184	/
Crystal system	trigonal	/
Space group	$R\bar{3}$	/
a/ Å	37.3204(19)	37.269
b/ Å	37.3204(19)	37.269
c/ Å	9.7227(6)	9.793
α/°	90	90
β/°	90	90
γ/°	120	120
V/Å^{-3}	11727.6(14)	11779.91
ρ_{calc}/g cm^{-3}	1.178	/
Z	18	/
R_{int}	0.0374	/
R(ref)	0.0615	/
wR_2(ref)	0.1719	/
CCDC	2313679	/

Table S2. Fractional Atom Coordinates of IBS 2-propanol Solvate at 100 K Obtained from X-ray Diffraction.

Atom Type	X Coordinate	Y Coordinate	Z Coordinate
O	0.75515(10)	0.69582(10)	0.1371(3)
N	0.76816(11)	0.75034(11)	0.2820(3)
N	0.56466(12)	0.77001(12)	0.5561(4)
N	0.58347(12)	0.79866(11)	0.3531(4)
N	0.81636(11)	0.75192(12)	0.4247(4)

N	0.57750(12)	0.76014(12)	0.3484(4)
N	0.57575(12)	0.80470(12)	0.4795(4)
C	0.64725(14)	0.73972(13)	0.4543(4)
H	0.641078	0.753666	0.52399
C	0.55316(14)	0.69970(13)	0.5102(4)
C	0.57514(13)	0.67946(13)	0.4769(4)
C	0.61716(13)	0.70034(13)	0.4139(4)
C	0.79467(14)	0.76861(14)	0.3956(4)
C	0.56626(14)	0.74268(14)	0.4726(4)
C	0.55673(14)	0.63719(13)	0.5095(4)
H	0.57075	0.622632	0.486745
C	0.69653(13)	0.73889(13)	0.2933(4)
C	0.73823(13)	0.76043(13)	0.2242(4)
H	0.734506	0.753014	0.12536
H	0.749657	0.790699	0.230807
C	0.68616(14)	0.75899(14)	0.3947(4)
H	0.706115	0.786172	0.422669
C	0.51853(14)	0.61631(14)	0.5741(4)
H	0.506449	0.587621	0.593595
C	0.77378(14)	0.71858(14)	0.2340(5)
C	0.62773(15)	0.68033(14)	0.3134(4)
H	0.607677	0.653286	0.284438
C	0.84546(13)	0.72667(14)	0.2448(4)
H	0.863141	0.756459	0.223674
H	0.83805	0.71076	0.157866
C	0.83297(14)	0.67643(14)	0.4255(4)
H	0.839057	0.680472	0.52521
H	0.830302	0.649667	0.397873
C	0.66656(14)	0.69908(13)	0.2560(4)
H	0.673031	0.684527	0.189474

C	0.80662(13)	0.71864(13)	0.3239(4)
C	0.49806(15)	0.63709(15)	0.6101(5)
H	0.472312	0.622989	0.656988
C	0.79295(14)	0.67687(15)	0.3934(5)
H	0.775061	0.653786	0.331027
H	0.777434	0.674227	0.47893
C	0.86744(14)	0.71188(15)	0.3436(4)
H	0.883758	0.702101	0.291784
H	0.886256	0.734567	0.405713
C	0.51513(15)	0.67847(14)	0.5778(5)
H	0.500833	0.692659	0.601813
C	0.79779(15)	0.80511(14)	0.4661(5)
H	0.806952	0.805867	0.562191
H	0.770177	0.802762	0.468641
H	0.778124	0.79405	0.544059
H	0.786276	0.817169	0.401134
C	0.8277(2)	0.84441(17)	0.3948(6)
H	0.816624	0.845105	0.302967
H	0.854204	0.844849	0.381308
C	0.8358(2)	0.88290(18)	0.4755(7)
H	0.808944	0.880661	0.49966
H	0.85019	0.884088	0.562305
C	0.8616(3)	0.9226(2)	0.3957(9)
H	0.846484	0.92259	0.313325
H	0.8878	0.924507	0.368584
H	0.867247	0.946333	0.453675
C	0.8361(6)	0.8408(6)	0.523(3)
H	0.856425	0.853206	0.446944
H	0.848027	0.830057	0.591311
C	0.8314(7)	0.8751(7)	0.591(3)

H	0.821528	0.887554	0.521029
H	0.810066	0.862822	0.663449
C	0.8712(8)	0.9089(7)	0.653(3)
H	0.878721	0.897775	0.732502
H	0.867264	0.931751	0.683362
H	0.893343	0.91898	0.584564
O	0.9159(5)	0.9476(5)	0.9803(11)
H	0.928406	0.93488	1.001136
C	0.9288(4)	0.9552(4)	0.7379(14)
H	0.938157	0.984892	0.737871
H	0.916542	0.943367	0.648275
H	0.952336	0.951144	0.755164
C	0.8975(4)	0.9346(4)	0.8465(12)
H	0.885063	0.903924	0.838055
C	0.8649(5)	0.9455(4)	0.8286(13)
H	0.844421	0.932852	0.902357
H	0.851356	0.93526	0.739432
H	0.877271	0.975636	0.832139
H	0.5808(13)	0.7509(14)	0.261(5)

Table S3. The Enthalpies and Gibbs Free Energies Difference of Two Tautomers (1H-IBS and 2H-IBS) Calculated by DFT at the level of M06-2X/6-311+G(d, p) in 2-propanol Medium. Note the Values Are Reported Relative to the 1H-IBS. The Population of 1H-tautomer and 2H-tautomer were Calculated based on Boltzmann Distribution Analysis.

In 2-propanol	**ΔH(kcal/mol)**	**ΔG(kcal/mol)**	**Population**
1H-IBS	0	0	86 %
2H-IBS	1.93	1.08	14%

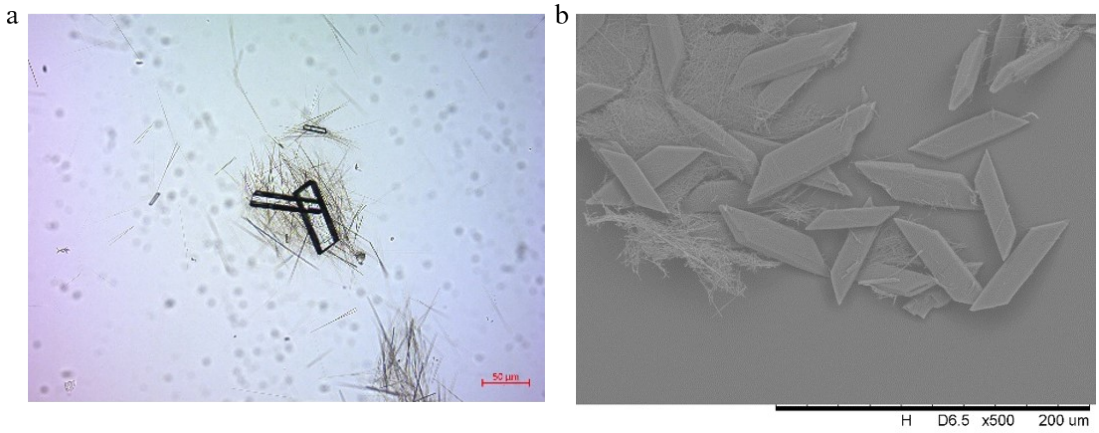

Figure S1. The optical micrograph (a) and SEM (b) showing the co-existence of IBS desmotropes, form A and form B, during the phase transition process from form A to form B as reported.[1]

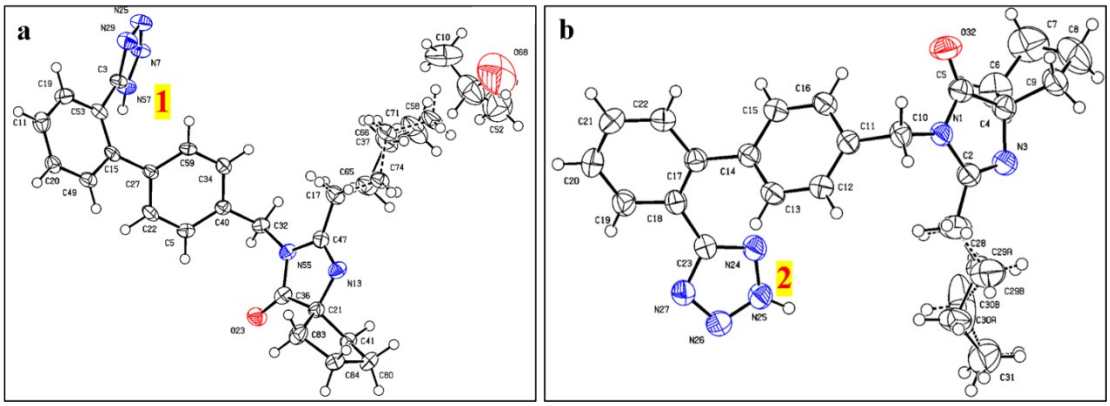

Figure S2. The crystal structure of the IBS 2-propanol solvate (a) and form B (b).

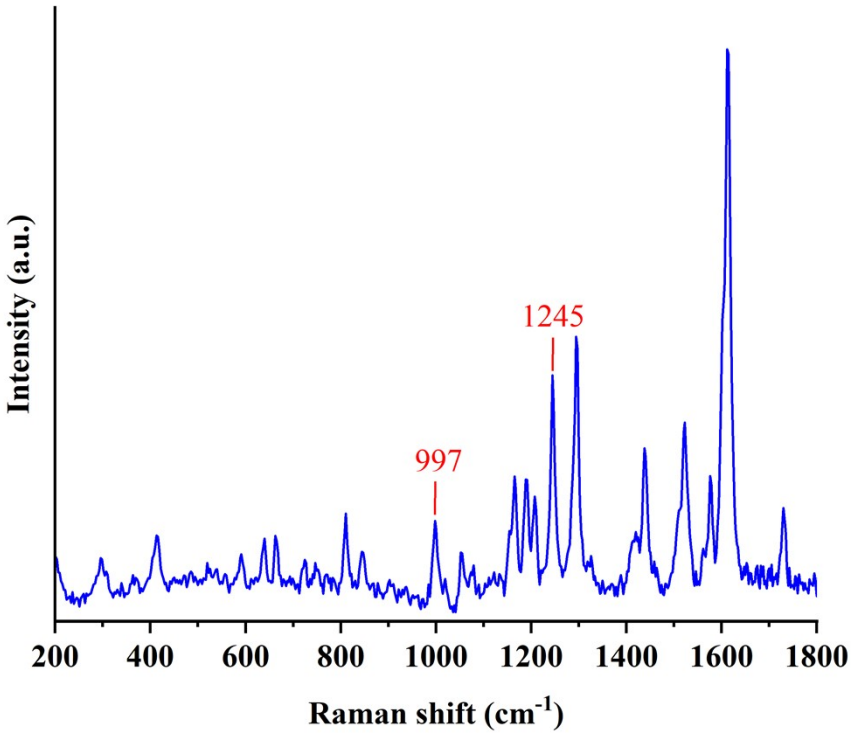

Figure S3. The micro-Raman spectrum of IBS crystals prepared in the IBS aqueous solution confirming the form B crystal with two characteristic peaks appeared at 997 and 1245 cm^{-1}.[2]

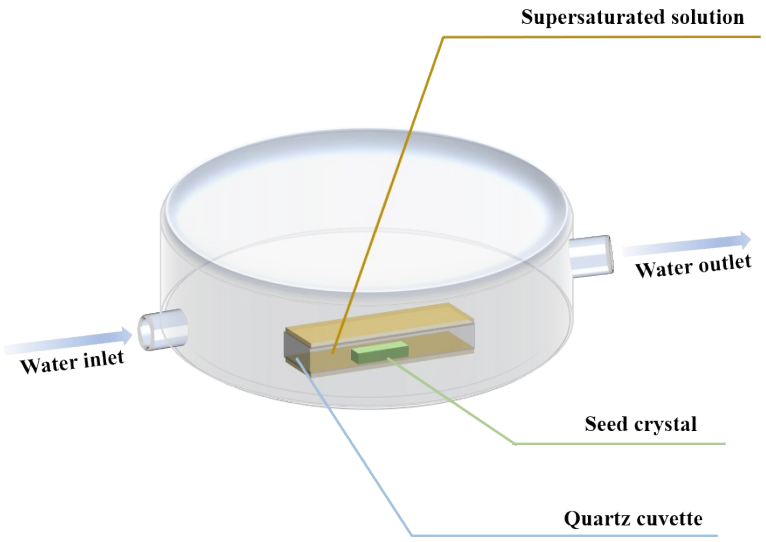

Figure S4. Experimental setup for the measurement of crystal growth rates.

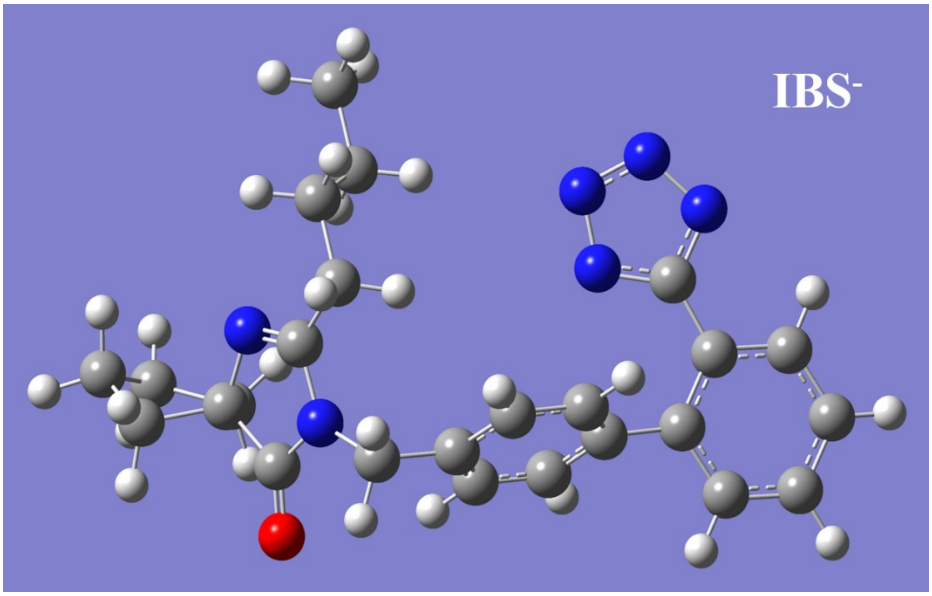

Figure S5. The optimal geometry of IBS anion species (IBS^-) calculated by DFT at the level of M06-2X/6-311+G(d, p) level in the implicit aqueous medium.

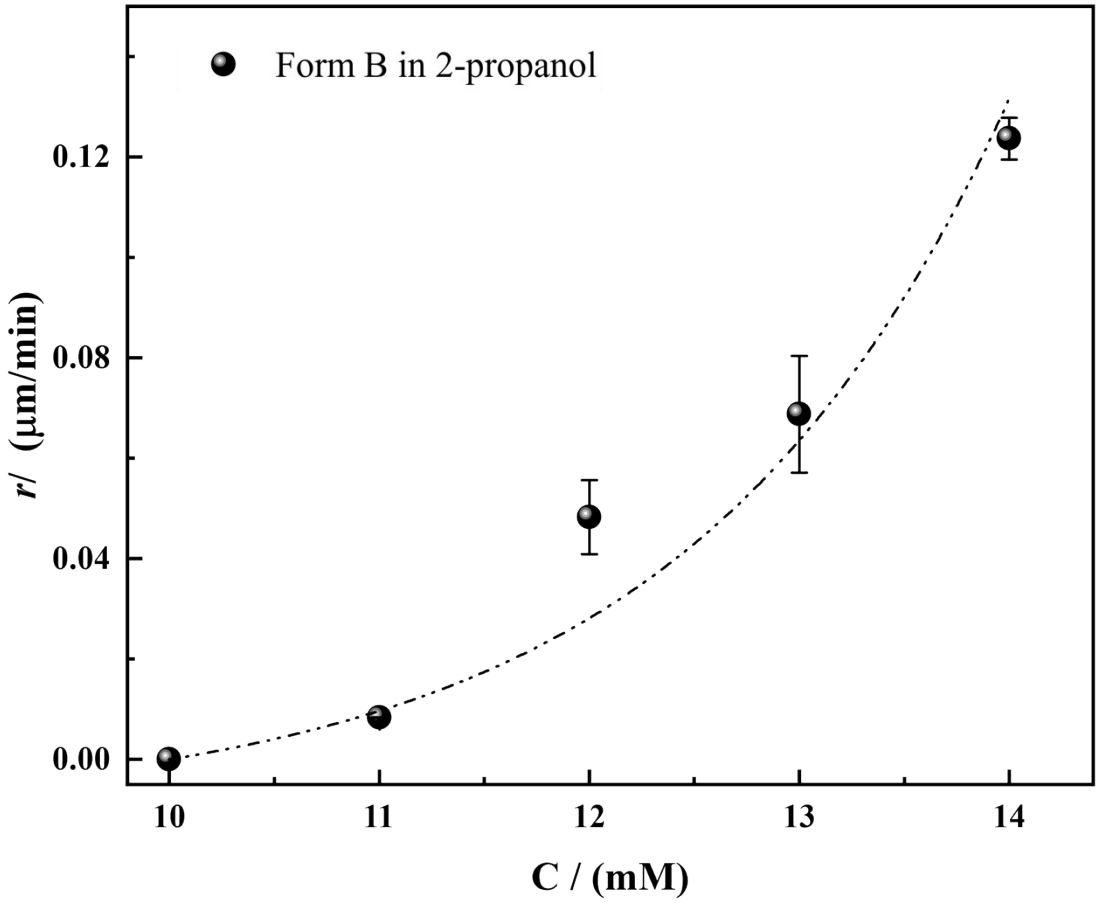

Figure S6. The growth rates of form B along the length direction as a function of IBS concentration in 2-propanol solutions.

Reference

1. E. Garcia, C. Hoff and S. Veesler, *J. Cryst. Growth*, 2003, **237-239**, 2233–2239.
2. A. M. Araya-Sibaja, C. E. Maduro de Campos, C. Fandaruff, J. R. Vega-Baudrit, T. Guillen-Giron, M. Navarro-Hoyos and S. L. Cuffini, *J. Pharm. Anal.*, 2019, **9**, 339-346.