Supporting Information

First crystal structures of the antihypertensive drug Perindopril erbumine: a novel hydrated form and polymorphs α and β

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Experimental details

All starting materials were purchased from Aldrich and used without further purification. Reagent grade solvents were used.

Preparation of single crystals of form α: 500 mg of perindopril erbumine crystalline form α were dissolved by heating in 15 mL of ethyl acetate. The solution was cooled very slowly until the formation of a very small amount of crystals was noticed (about 45ºC) and the temperature maintained for 22 hours. The resulting suspension was slowly cooled to 30ºC in 3 hours and allowed to stand for 4 hours. The remaining solvent was decanted. Crystalline form α of Perindopril erbumine was obtained.

Preparation of single crystals of form β: 1 g of perindopril erbumine crystalline form α was dissolved by heating in 30 mL of dichloromethane. The solution was cooled to room temperature and allowed to stand for 8 days in a closed system. Very slow evaporation at room temperature was allowed until the formation of a very small amount of crystals was noticed after 9 days. By heating slightly, the crystals were dissolved. The solution was cooled and seeded with form β (obtained as described in EP 1 294 689{Pfeiffer, 2002, Industrial prodn. of perindopril tert. butylamine salt}). Crystallization was allowed by very slow evaporation at room temperature, during 14 days. Perindopril erbumine β crystalline form was quantitatively obtained.

Preparation of the new hydrated form of perindopril:

1. 0.0634 g (0.1436 mmol) of perindopril form α were dissolved in 3 mL of ethanol with agitation. Solution was left to dry at room temperature by slow evaporation. Colourless plate-like crystals were formed after one day.

2. 0.1341 g (0.3036 mmol) of perindopril form α were dissolved in 6 mL of ethanol with agitation. Solution was left to dry at room temperature by slow evaporation. Colourless plate-like crystals were formed after one day.

3. 0.3319 g (0.7516 mmol) of perindopril form α were dissolved in 6 mL of ethanol with agitation. Solution was left to dry at room temperature by slow evaporation in a vessel with a narrow crystallization area and stirring was maintained during the crystallization process. Colourless plate-like crystals were formed after one day.

4. 0.1163 g (0.2633 mmol) of perindopril form α were dissolved in 2 mL of methanol with agitation. Solution was left to dry at room temperature by slow evaporation. Colourless plate-like crystals were formed after one day.

5. 2.578 g (5.838 mmol) of perindopril form α were manually ground using an agate mortar and a pestle with a few drops of ethanol (used to keep the powder slightly wet) for 30 minutes and the conversion into the new hydrated form described herein was achieved.

6. 0.0773g (0.1750 mmol) of perindopril form β were dissolved in 7 mL of ethanol with agitation. Solution was left to dry at room temperature by slow evaporation. Colourless plate-like crystals were formed after one day.

7. 0.3653g (0.8298 mmol) of perindopril form β were manually ground using an agate mortar and a pestle with a few drops of ethanol (used to keep the powder slightly wet) for 30 minutes and the conversion into the new hydrated form described herein was achieved.

8. 0.0484g (0.1096 mmol) of perindopril form γ were dissolved in 4 mL of ethanol with agitation. Solution was left to dry at room temperature by slow evaporation. Colourless plate-like crystals were formed after one day.

9. 0.3832 g (0.8704 mmol) of perindopril form γ were manually ground using an agate mortar and a pestle with a few drops of ethanol (used to keep the powder slightly wet) for 30 minutes and the conversion into the new hydrated form described herein was achieved.

10. 0.50 g of perindopril form α were suspended in water and left stirring for 24 hours. Full conversion into the new hydrated form was confirmed by XRPD.

11. 0.53 g of the novel hydrated form were suspended in water for 24 hours. No changes were detected in the crystal form were detected by XRPD.

Single crystal X-Ray diffraction (SCXRD): Crystalline structures of the three forms of perindopril erbumine were determined at 150K on a Bruker AXS-KAPPA APEX II diffractometer with graphite-monochromated radiation (Mo Kα, λ=0.71069 Å). The X-ray generator was operated at 50 kV and 30 mA and the X-ray data collection was monitored by the APEX2[1] program. All the data were corrected for Lorentzian, polarization and absorption effects using SAINT+[2] and SADABS[3] programs. SIR97[4] was used for structure solution and SHELXL-97[5] was used for full matrix least-squares refinement on F^2. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were added in calculated positions and refined riding on their host atoms.

Due to the low quality of α and β single crystals, the distances and some torsion angles had to be restrained for the typical values in order to stabilize the refinement.

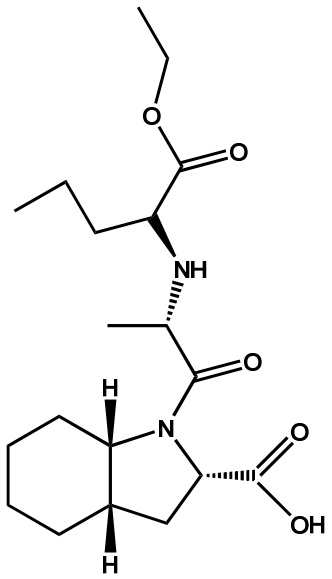
Powder X-Ray diffraction (PXRD): X-Ray powder data were collected in the reflection mode using a D8 Advance Bruker AXS θ-2θ diffractometer, with a copper radiation (Cu Kα, λ=1.5406 Å) and a secondary monochromator, operated at 40kV and 30mA. The program PowderCell 2.4 was used for calculation of the X-ray powder patterns from SCXRD data. The comparisons between the bulk materials obtained by the solid-state processes and the single respective crystal structure were verified by comparing calculated and observed powder diffraction patterns.

Vibrational Spectroscopy (ATR-FT-IR and FT-Raman): Fourier Transform Infrared (FT-IR) spectra (range 3600-250 cm^{-1}) were measured on a Matson 7000 FT-IR spectrometer. Fourier Transform Raman (FT-Raman) spectra (range 4000-300 cm^{-1}) were recorded on a Bruker RFS 100 spectrometer with a Nd:YAG coherent laser (λ = 1064 nm).

Thermal Analysis (TGA, DSC and HSM): Thermogravimetric analyse (TGA) were carried out using a Shimadzu TGA 50 apparatus, from room temperature to *ca.* 300ºC, with a heating rate of 2ºC/min, under a continuous nitrogen stream with a flow rate of 20 cm^3/min. Differential Scanning Calorimetry (DSC) study was performed in a Shimadzu DSC 50 equipment between the room temperature and *ca.* 160 ºC, and using a heating rate of 10ºC/min. Hot-Stage microscopy (HSM) experiments were carried out using a Linkam TP94 device connected to a Linkam LTS350 platinum plate. Images were collected with the imaging software Cell, from an Olympus SZX10 stereomicroscope.

Karl-Fischer: Karl-Fischer tests were carried out on a 831 KF Coulometer Metrohm device.

Elemental analysis: Elemental analyses were performed in a Fisons Instrument Mod EA-1108, at *Laboratório de Análises* of *Instituto Superior Técnico*.



Scheme S1. Chemical diagram of perindopril

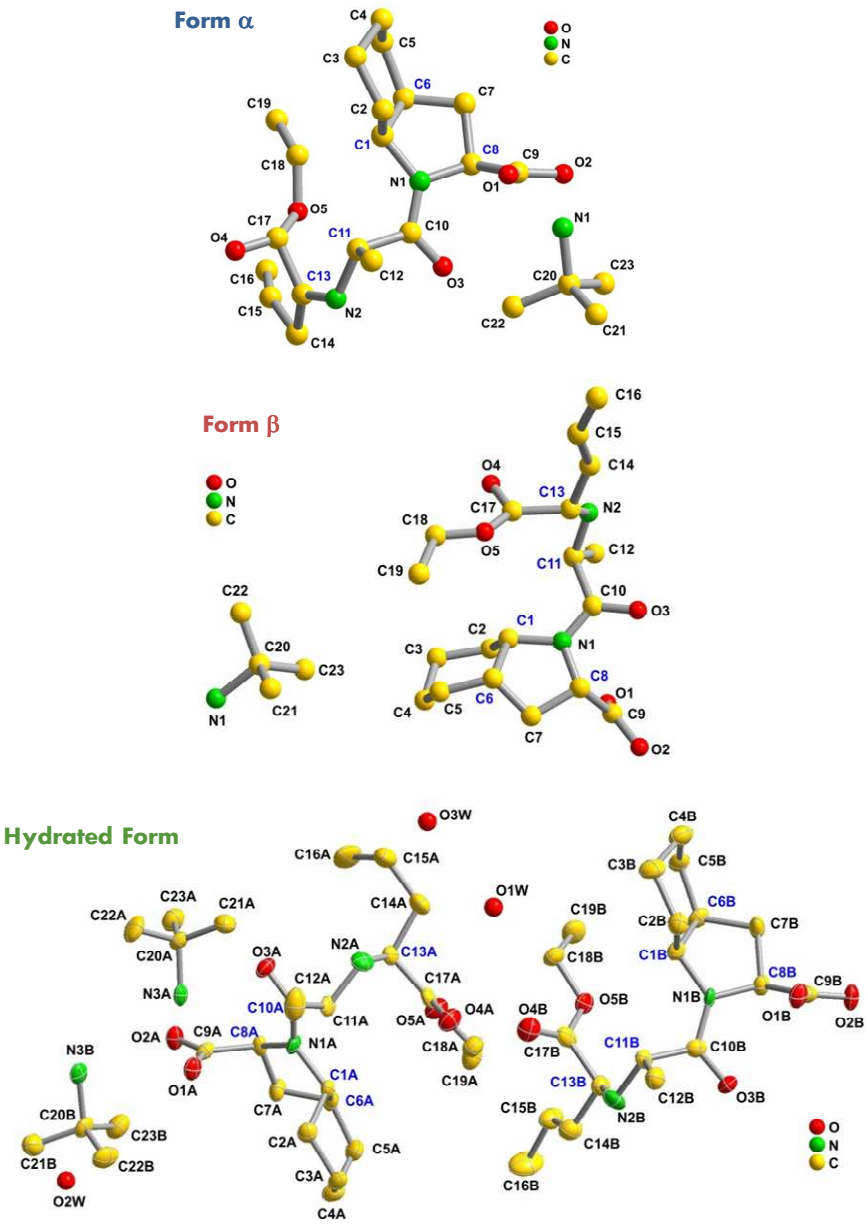


Figure S1. Asymmetric Unit content for α (top), β (middle) and the hydrated forms of perindopril erbumine. Chiral centres are labelled in blue, ellipsoids are set at 50% probability level and H-atoms were omitted for clarity purposes. The oxygen atom of O3W water molecule refined with 0.5 occupancy factor.

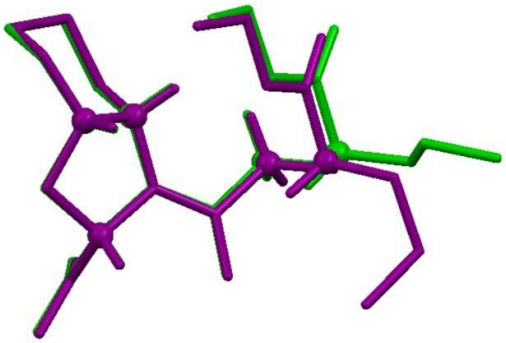


Figure S2. Overlap of the two crystallographic independent perindopril anions in the hydrated form, highlighting the chiral centres with ball models. For clarity proposes only the H-atoms bonded to chiral centres are drawn.

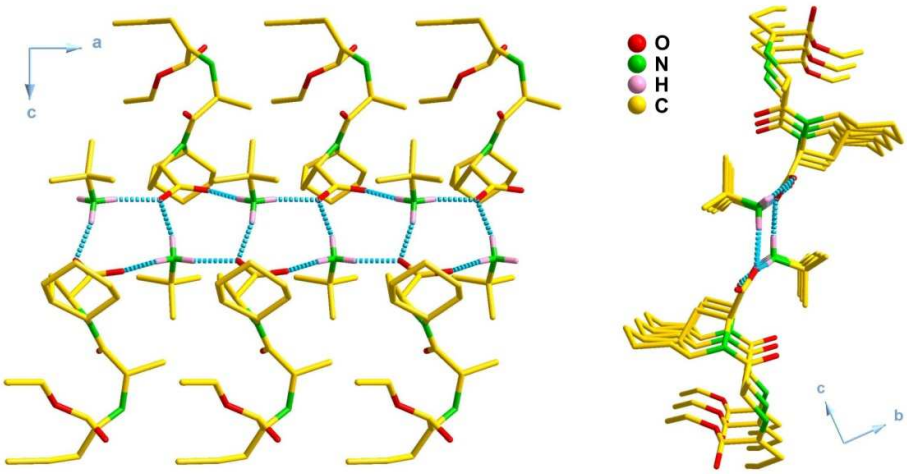


Figure S3. Two distinct views of the supramolecular arrangement with the perindopril anions and erbumine cations organized in double-chains, in form α; hydrogen bonds represented as blue dashed lines

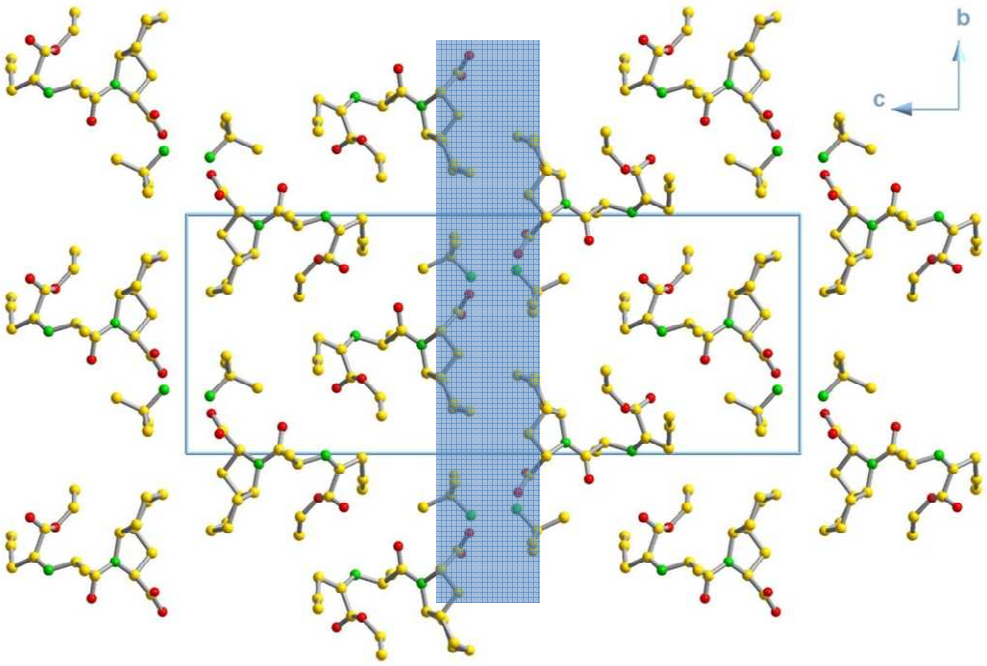


Figure S4. Crystalline packing of perindopril erbumine form α. Double-chain array formed by $C_2^2(6)$ and $D_1^1(2)$ motifs is highlighted in blue.

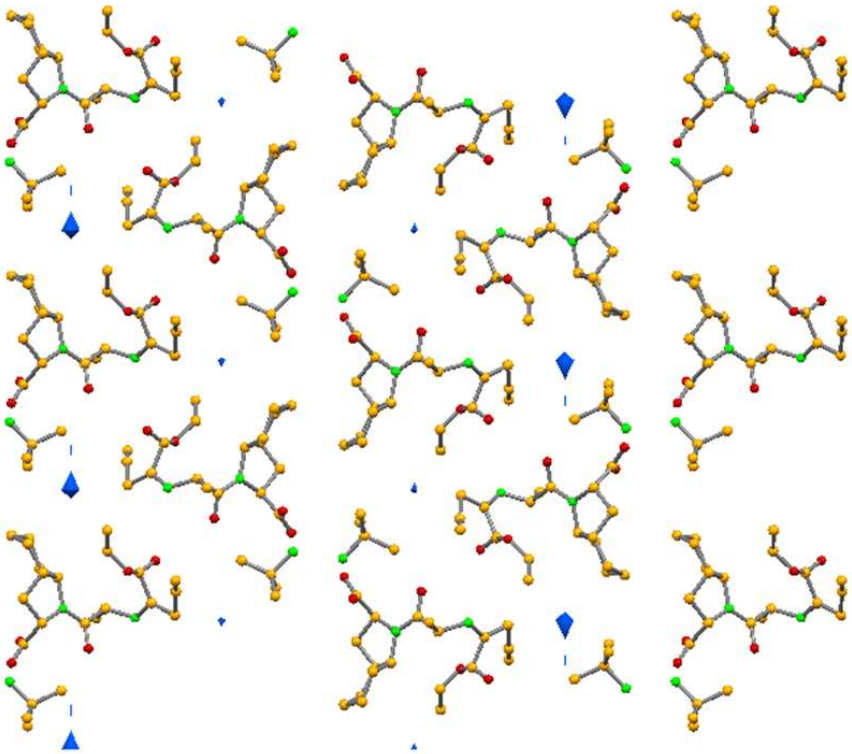


Figure S5. Crystalline α form supramolecular arrangement depicting the VOIDS represented in blue. The space corresponding to these VOIDS is occupied with water in the hydrated form.

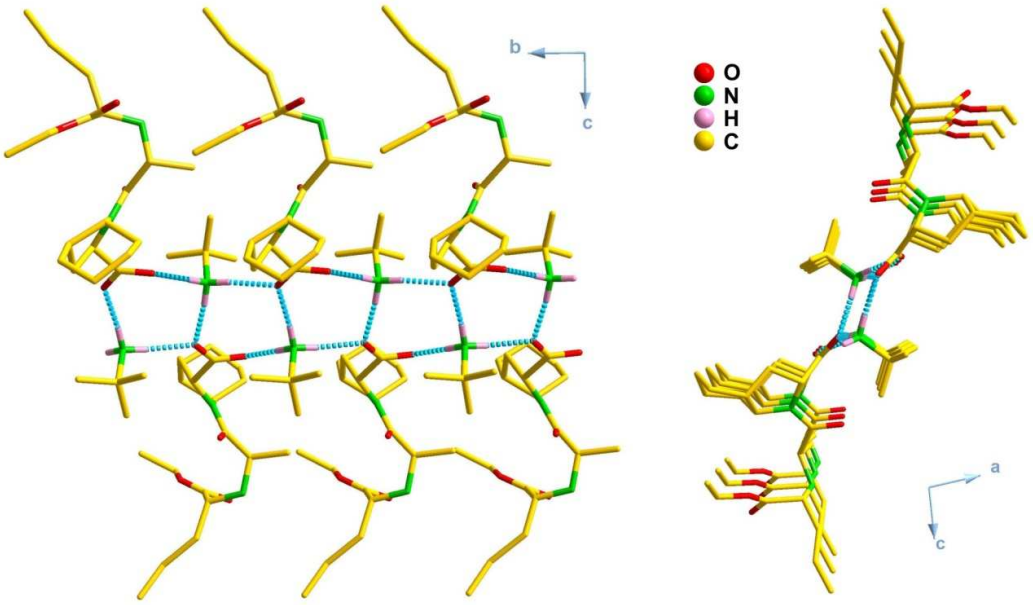


Figure S6. Two distinct views of the supramolecular arrangement with the perindopril anions and erbumine cations organized in double-chains, in the form β; hydrogen bounds represented as blue dashed lines

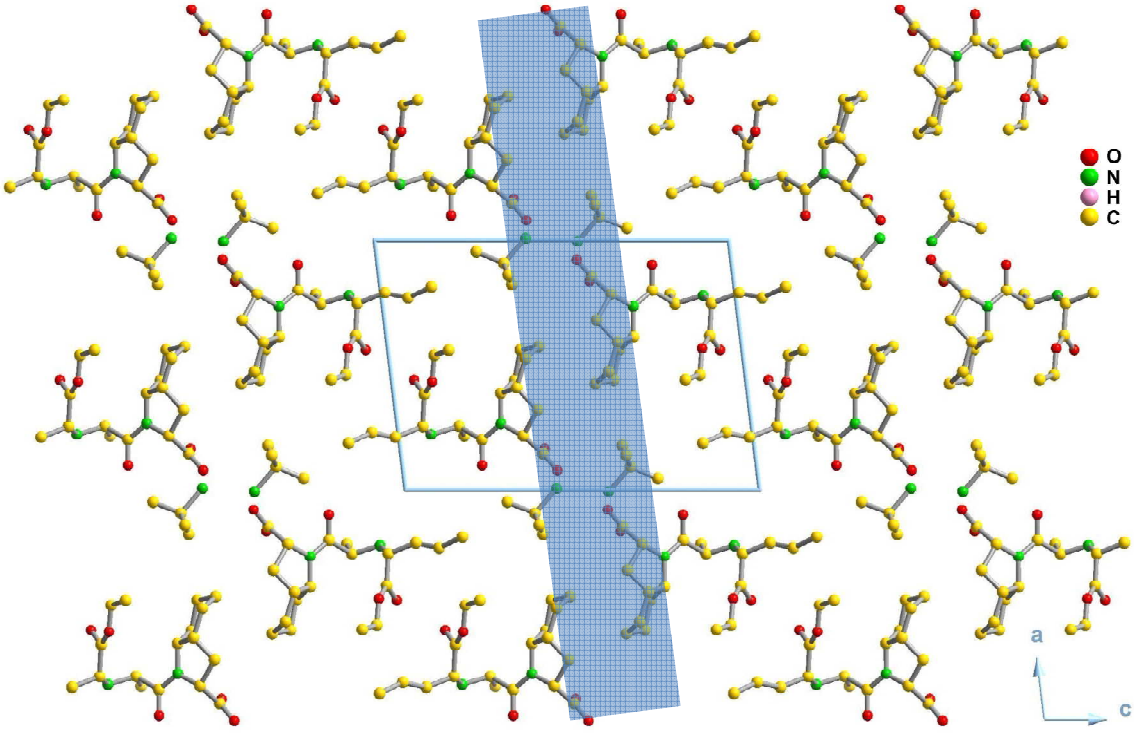


Figure S7. Crystalline packing of perindopril erbumine form β. Double-chain array formed by $C_2^2(6)$ and $D_1^1(2)$ motifs is highlighted in blue.

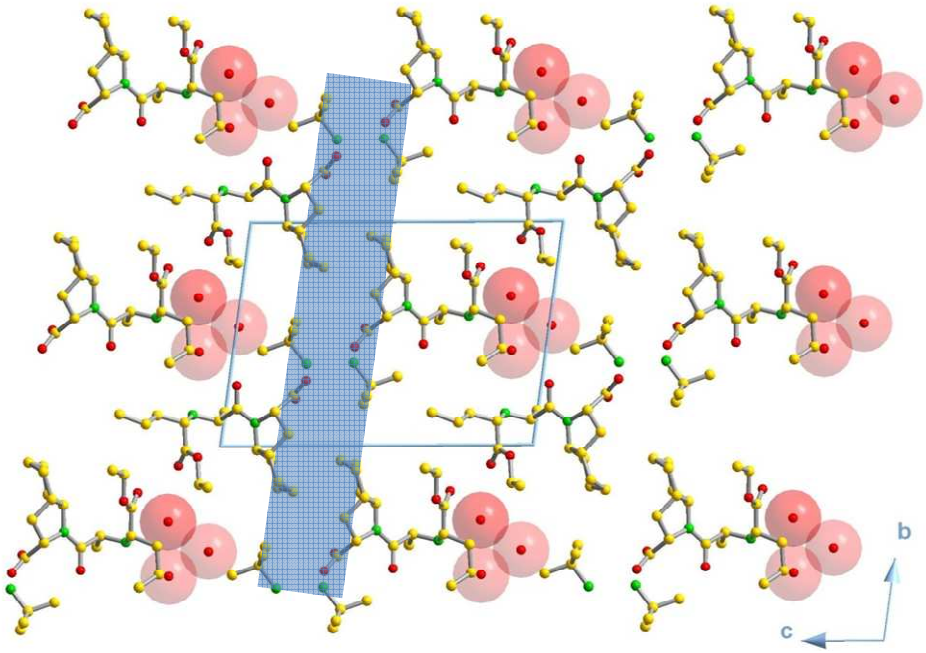


Figure S8. Crystalline packing of perindopril erbumine hydrated form. Double-chain array formed by $C_2^2(6)$ and $D_1^1(2)$ motifs is highlighted in blue.

POWDER DIFFRACTION ANALYSIS:

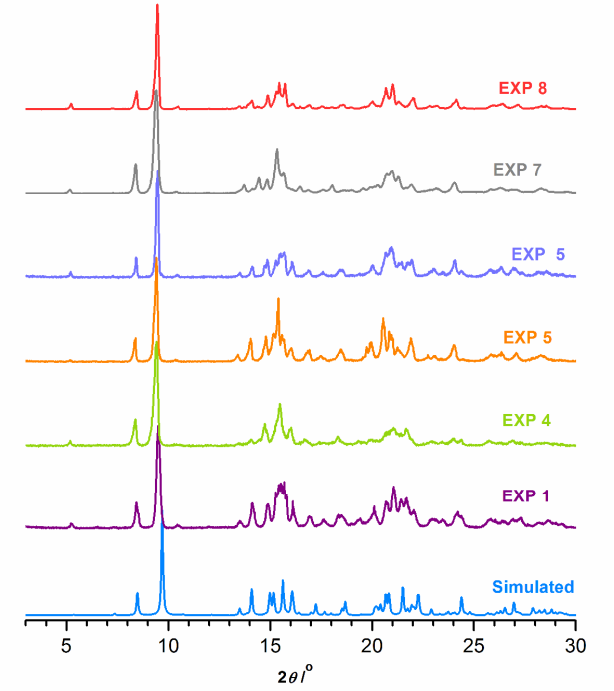


Figure S9. Room temperature diffractograms for various experiments described in the experimental details section used to prepare the novel hydrated form.

VIBRATIONAL SPECTRSOCOPY:

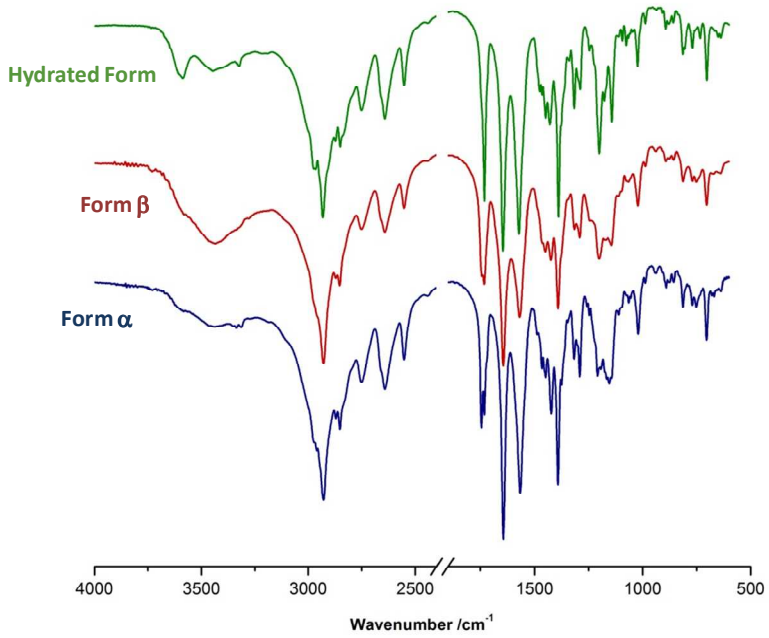


Figure S10. FTIR spectra for all the forms of perindopril erbumine reported.

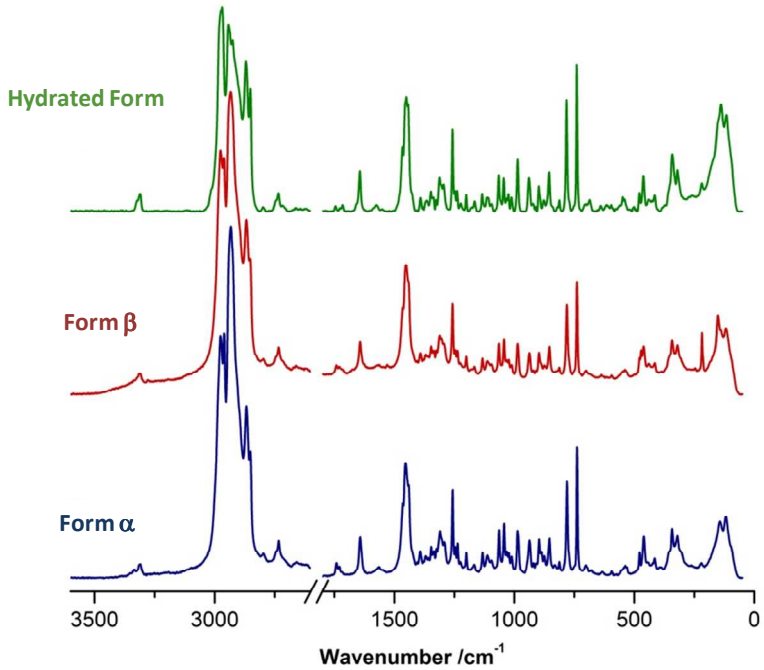


Figure S11. FT-Raman spectra for all the forms of perindopril erbumine reported.

THERMAL ANALYSIS:

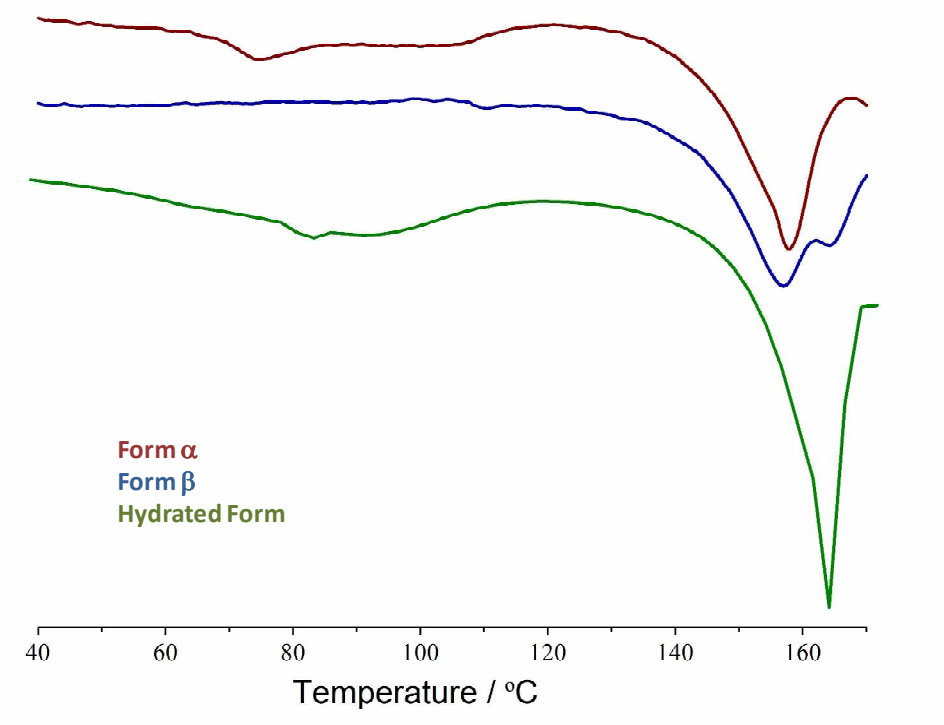


Figure S12. DSC pattern for all the forms of perindopril erbumine reported.

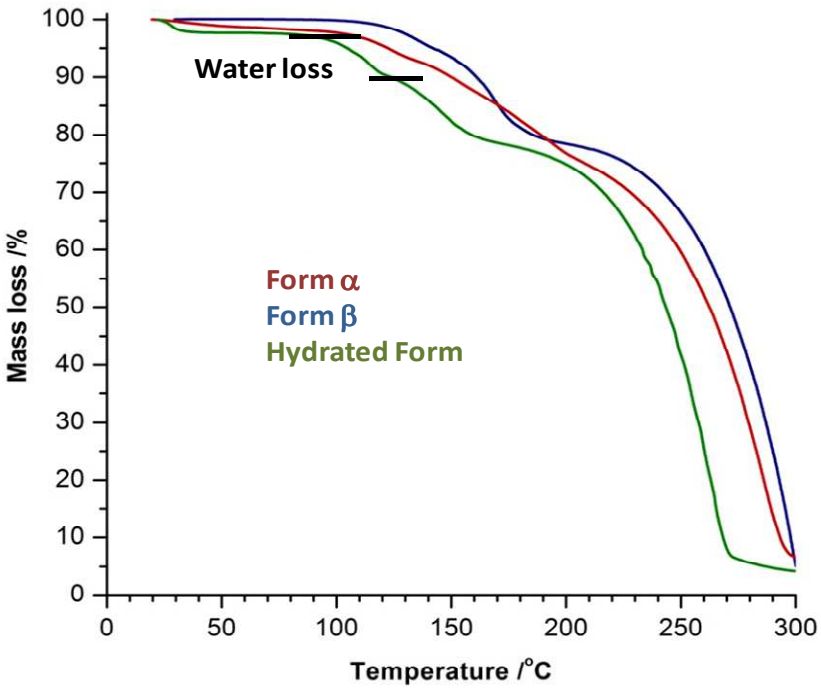


Figure S13. TGA pattern for all the forms of perindopril erbumine reported.

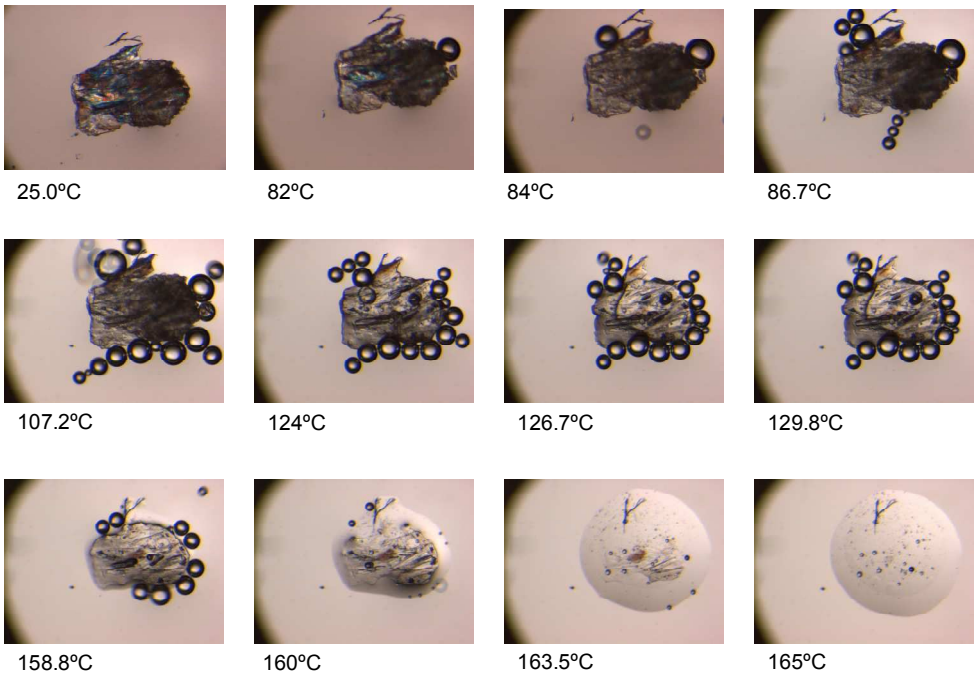


Figure S14. Images obtained from HSM at different temperatures (from room temperature up to 145ºC) using a crystal of the novel hydrated form.

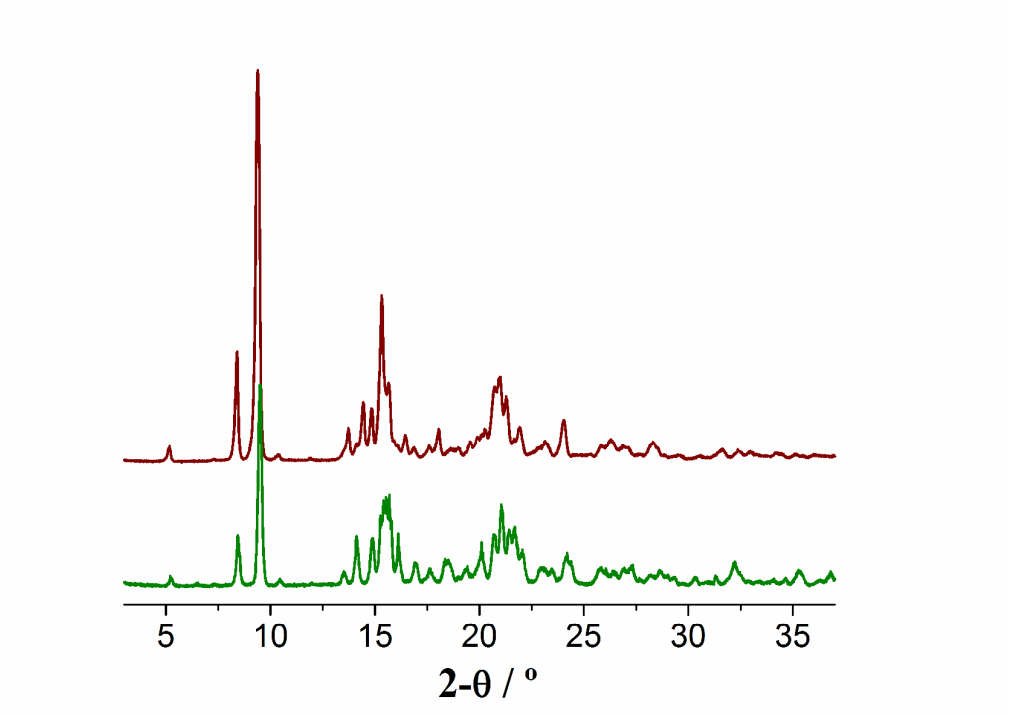


Figure S15. Diffractograms of the novel hydrated form (top) and the product obtained after slurrying the novel hydrated form in water for 24 yielding the same novel hydrated form (bottom).

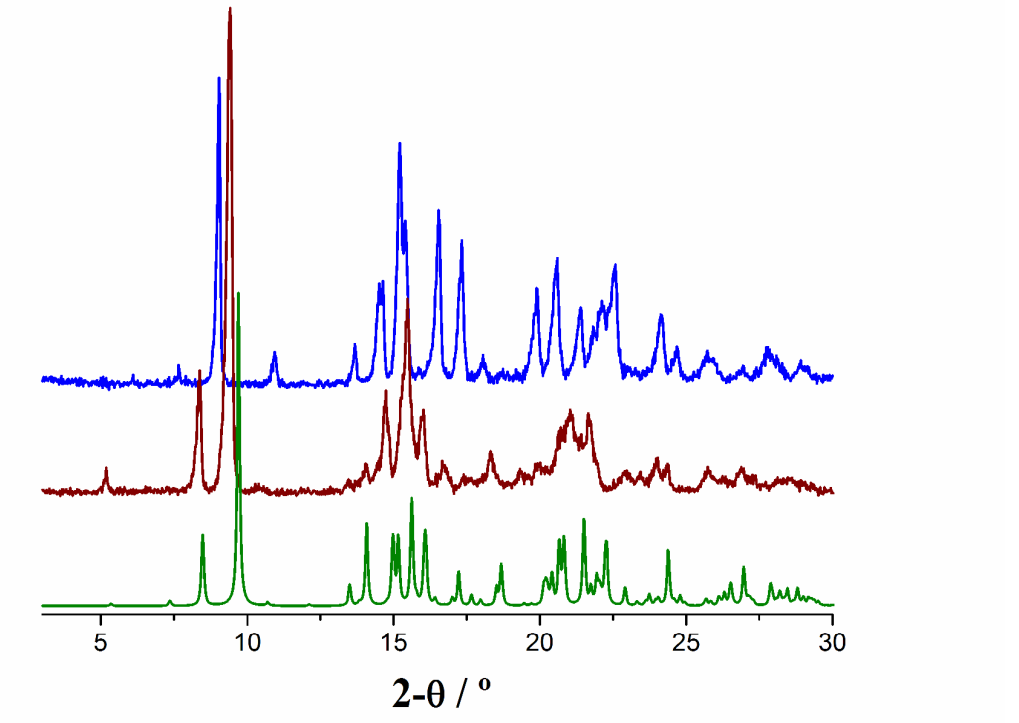


Figure S16. Diffractograms of the alpha form (top), the product obtained after slurrying perindopril form α for 24 hours in water (middle) and the novel hydrated form (bottom).

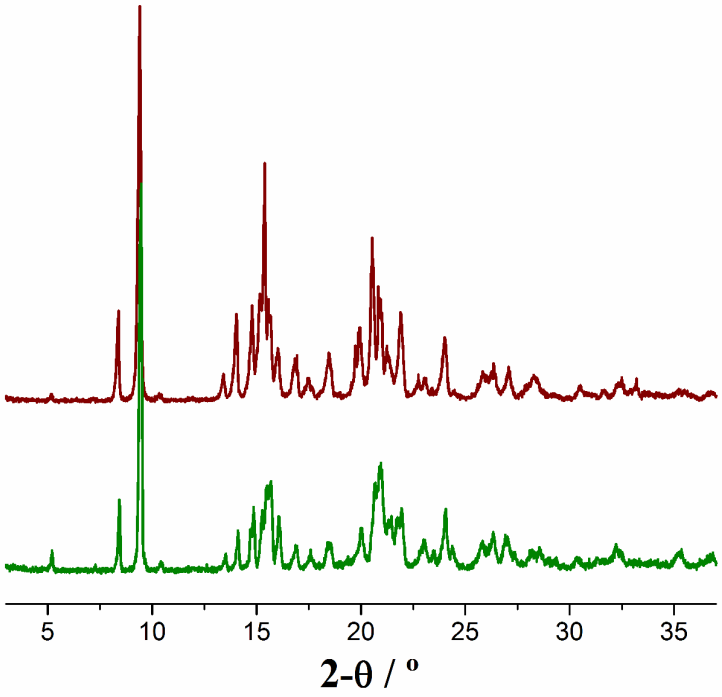


Figure S17. Perindopril novel hydrated form after synthesis (top) and after 3 months on the shelf (bottom).

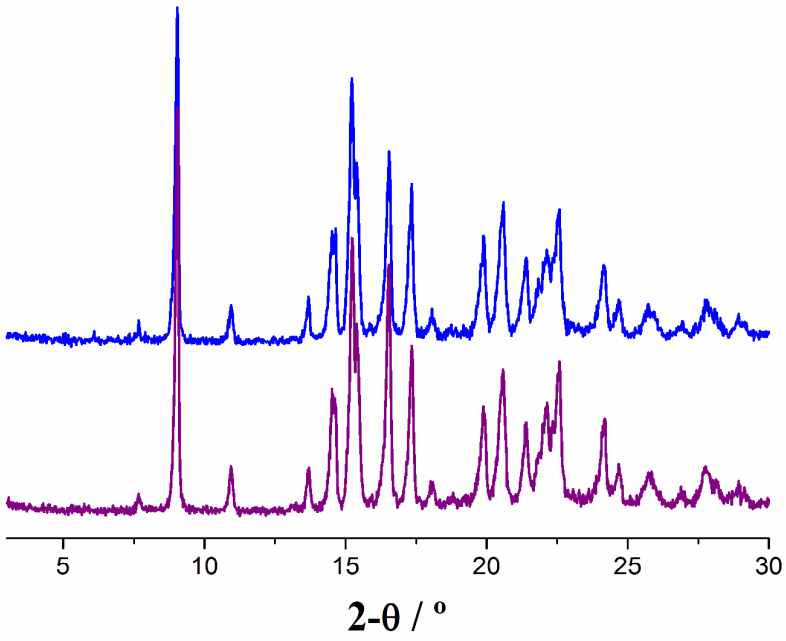


Figure S18. Perindopril form α after synthesis (top) and after 3 months on the shelf (bottom).

Table S1- Hydrogen bonding geometry details

Structure	*Sym. Op.*	*D-H···A*	*d(H···A) (Å)*	*d(D···A) (Å)*	*(DĤA) (deg)*
α	1+x, y, z	N3-H3C...O1	1.91	2.803(7)	167
	x, y, z	N3-H3D...O2	1.87	2.778(7)	175
	1/2+x, 1/2-y, -z	N3-H3E...O1	1.88	2.770(8)	166
β	-1+x, 1+y, z	N3-H3C...O1	1.88	2.765(9)	179
	-1+x, y, z	N3-H3D...O2	1.91	2.788(10)	169
	1-x, 1/2+y, 1-z	N3-H3E...O2	1.85	2.738(9)	175
hydrate	-1+x, y, z	N2A-H02A...O1W	2.46	2.97(1)	119
	-1+x, y, z	N2A-H02A...O3W	2.43	3.26(1)	163
	1+x, y, z	N1C-H01C...O1A	1.86	2.75(1)	178
	1+x, -1+y, 1+z	N1C-H02C...O2B	1.92	2.79(1)	165
	x, y, z	N1C-H03C...O2A	1.94	2.81(2)	165
	x, y, z	N1D-H01D...O2A	1.91	2.79(1)	170
	x, -1+y, 1+z	N1D-H02D...O2B	1.92	2.80(1)	167
	1+x, -1+y, 1+z	N1D-H03D...O1B	1.91	2.80(1)	178
	x, y, z	O1W...O2W	---	2.86(2)	---
	x, y, z	O1W...O3W	---	2.93(2)	---
	x, y, z	O2W...O3W	---	2.64(2)	---
	x, y, z	O3W...O3B	---	2.72(2)	---

Table S2- Elemental analyses results

		N / %	C / %	H / %
α form	Theoretical	10.31	67.78	10.14
	Experimental average	10.18	67.15	10.15
Novel hydrate	Theoretical	10.19	64.23	9.77
	Experimental average	9.98	64.06	9.57

Table S3- Karl-Fischer results

		Results / %
Alpha	Theoretical	0.0
	Experimental	0.4
Novel hydrate (1:1:1.25)	Theoretical	4.85
	Experimental	4.83
Monohydrate	Theoretical	3.9
Sesquihydrate	Theoretical	5.76

References

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