Supporting Information

Increase in Solubility of ”Poorly-Ionizable” Pharmaceuticals by Salt Formation. A Case of Agomelatine Sulfonates.

Eliška Skořepová [a,b], *Daniel Bím* [e], *Michal Hušák* [b], *Jiří Klimeš* [d], *Argyro Chatziadi* [a,c], *Luděk Ridvan* [c], *Tereza Boleslavská* [c], *Josef Beránek* [c], *Pavel Šebek* [c], *Lubomír Rulíšek* [e]

[a] Department of Chemical Engineering, University of Chemistry and Technology Prague, Technicka 3, Prague 6, Czech Republic

[b] Department of Solid State Chemistry, University of Chemistry and Technology Prague, Technicka 5, Prague 6, Czech Republic

[c] Zentiva k.s., U Kabelovny 130, Prague 10, Czech Republic

[d] Department of Chemical Physics and Optics, Faculty of Mathematics and Physics, Charles University, Ke Karlovu 3, CZ-12116 Prague 2, Czech Republic

[e] Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo náměstí 2, 166 10 Prague 6, Czech Republic.

eliska.skorepova@vscht.cz

Contents

PXRD stucture solution of AG-MS-II

Comparison of agomelatine crystal structures

DFT optimization

Intrinsic dissolution rate

PXRD stucture solution of AG-MS-II

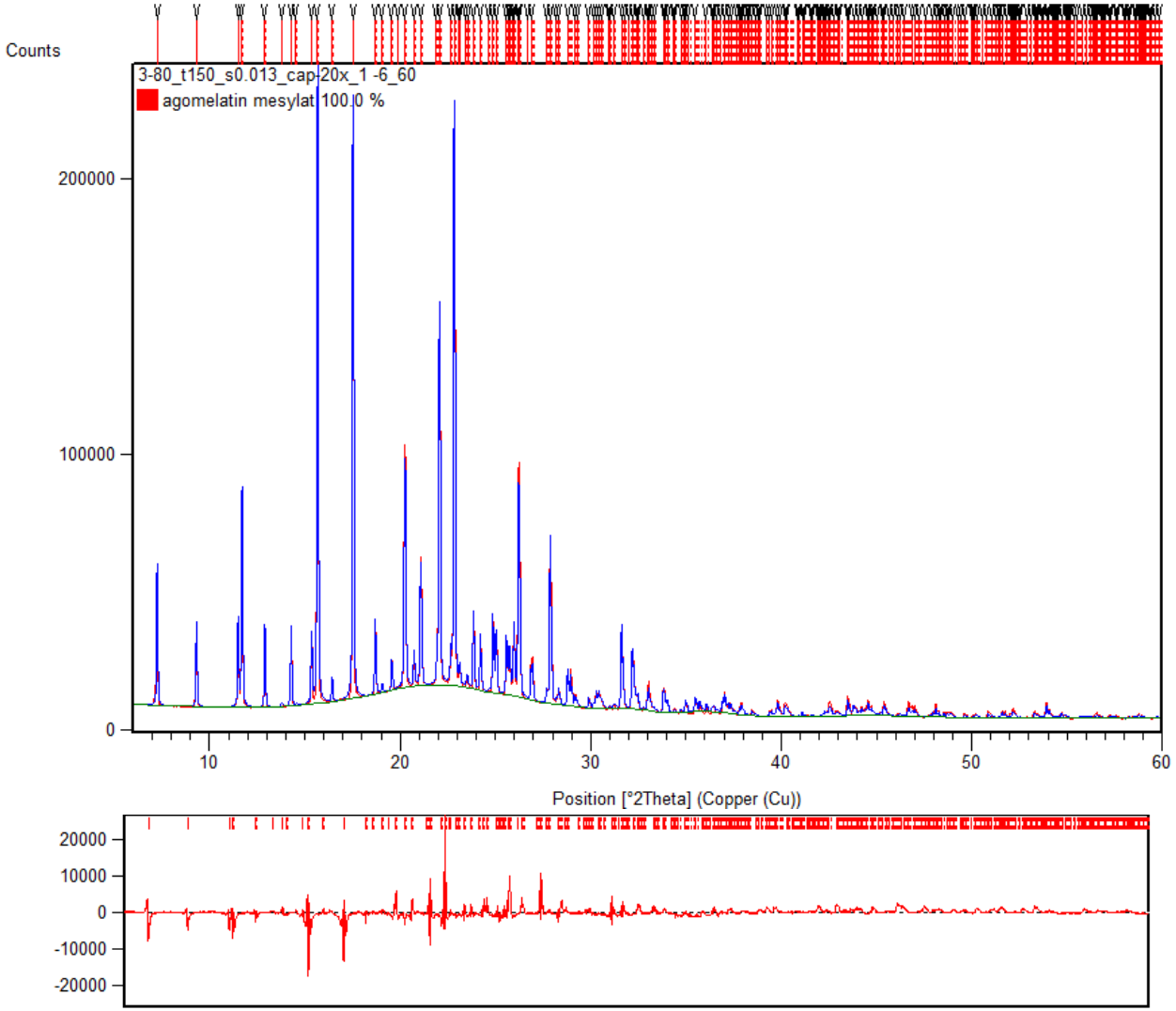

Figure S1 Final Rietveld fit of agomelatine mesylate with a difference curve

Comparison of Agomelatine Crystal Structures

The five new crystal structures of agomelatine were compared with all of the 18 various previously published structures, mostly concentrating on its molecular conformations and crystal packing.

Agomelatine has two regions – rigid naphthalene skeleton and a flexible side chain with the amide group. In the agomelatine crystal structures, three basic types of conformation were identified differing by the torsion angles highlighted in Figure S2 and clustering about values of 0° (blue), 90° (dark green) and -90° (light green). These values comply with the statistics from CSD on similar structures (Figure S3).

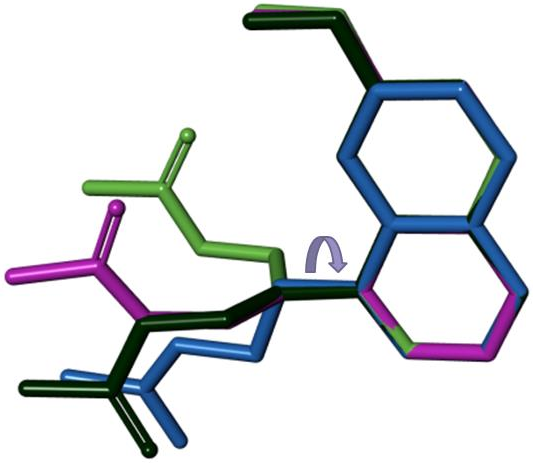

Figure S2 Conformational variability of agomelatine

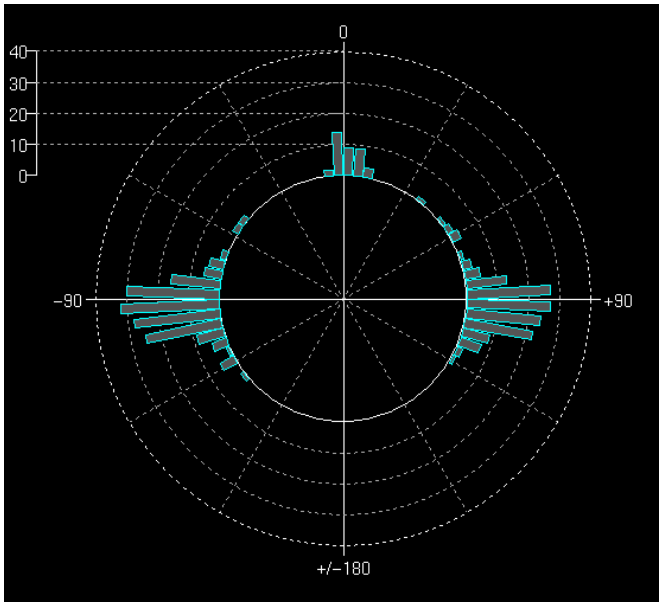

Figure S3 Statistical analysis of the variable torsion angle in similar structures to agomelatine

These three types of conformation of AG molecules appear in the crystal structures in different ways (a) structures with torsion angles around 0°; (b) structures exhibiting the mixture of the 90° and -90° torsion angles in approximately 1:1 ratio (centrosymmetric

structures or some of the structures with multiple AG molecules in the asymmetric unit); (c) structures with either 90° or -90° (enantiomorphic space group).

The similarities and differences in the molecular crystal packing were analyzed employing a *packing similarity tree diagram*. The tree diagram is used for a clear analysis of similarity in the crystal packing of structures of one compound. It can compare the crystal packing of only the largest molecule in the structure (in our case either the neutral or protonated molecule of agomelatine). Therefore, it can be easily used to analyze a family of polymorphs, hydrates, solvates, salts and co-crystals. Figure S4 shows the diagram for the AG structures calculated by the CrystalCMP software[48]. As we can directly see from Figure S4, the structures are very dissimilar and mostly, do not form structural types. All but five structures are totally unlike any of the others. The similarity score (top in Figure 7) between most of the structures is well over 15, which corresponds to significant differences in the crystal packing[48]. These parts of the diagram are filled in brown. This lack of similarity is quite unusual, because, when a larger number of crystal structures of the same compound is studied, typically, they are comprised of several 'isostructural' families[3,48–50] .

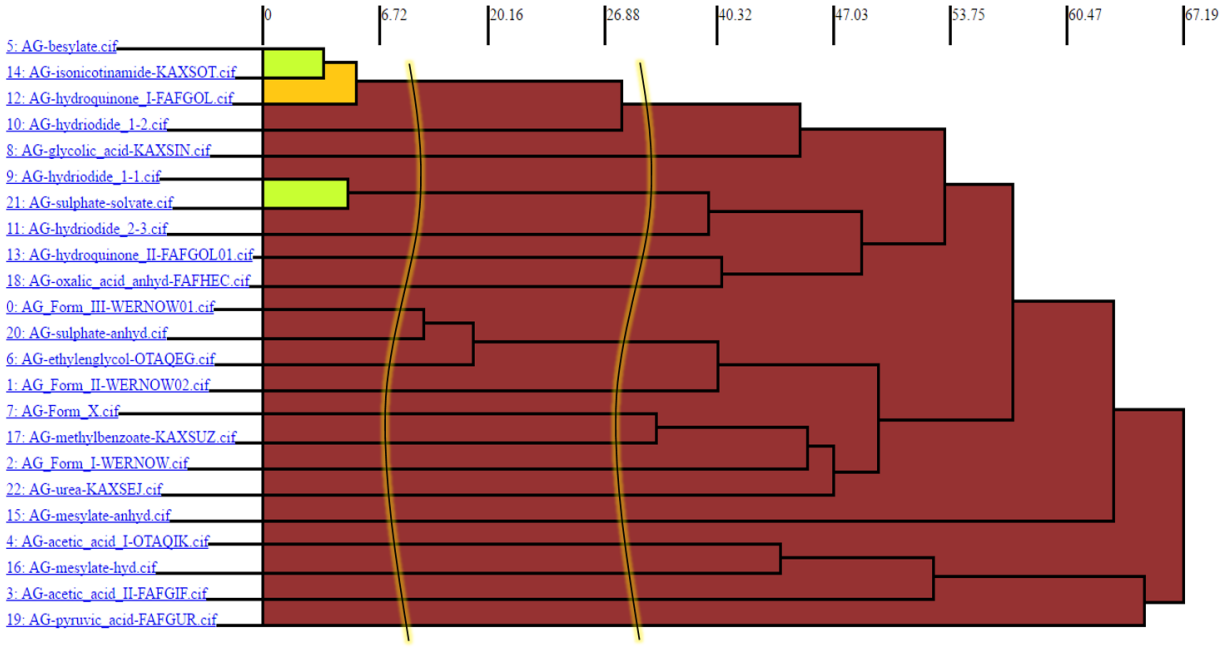

Figure S4 Packing similarity tree diagram for all known AG crystal structures calculated by CrystalCMP. Parts of the tree diagram between 6 and 20 and between 26 and 40 were removed to make the figure shorter and more readable; the vertical curved lines indicate these deletions.

Despite the general lack of similarity, two 'isostructural' groups can be found. The first group of similar structures are the first three structures in Figure S4 (5: AG besylate, 14: AG - isonicotinamide, 12: AG - hydroquinone Form I). All three structures contain an aromatic/cyclic coformer or counterion. There is only a single other structure of multicomponent AG form containing such molecular partner (13: AG - hydroquinone Form II) and it has a different packing from the three discussed structures. The second similar group is the pair 9, which is agomelatine hydriodide trihydrate, and 21, which is agomelatine

hydrogensulphate MeOH solvate hemihydrate. We find it quite surprising that two structures with such a different composition can have a so similar packing. The sterical end electronic properties of the guest molecules are probably just right to promote the same packing of the agomelatine molecules. The last interesting observation from the AG packing tree diagram is the apparent lack of similarity between solvated and desolvated AG sulfates (20, 21), for which a SCSC transformation has been observed. Therefore, one would expect that the packing of the AG molecules would be conserved upon the desolvation. This seems to be the case at the first look (Figure 3c, g), but a detailed analysis reveals that every other column of AG molecules is rotated by 90° resulting in the low similarity score calculated by CrystalCMP.

DFT optimization

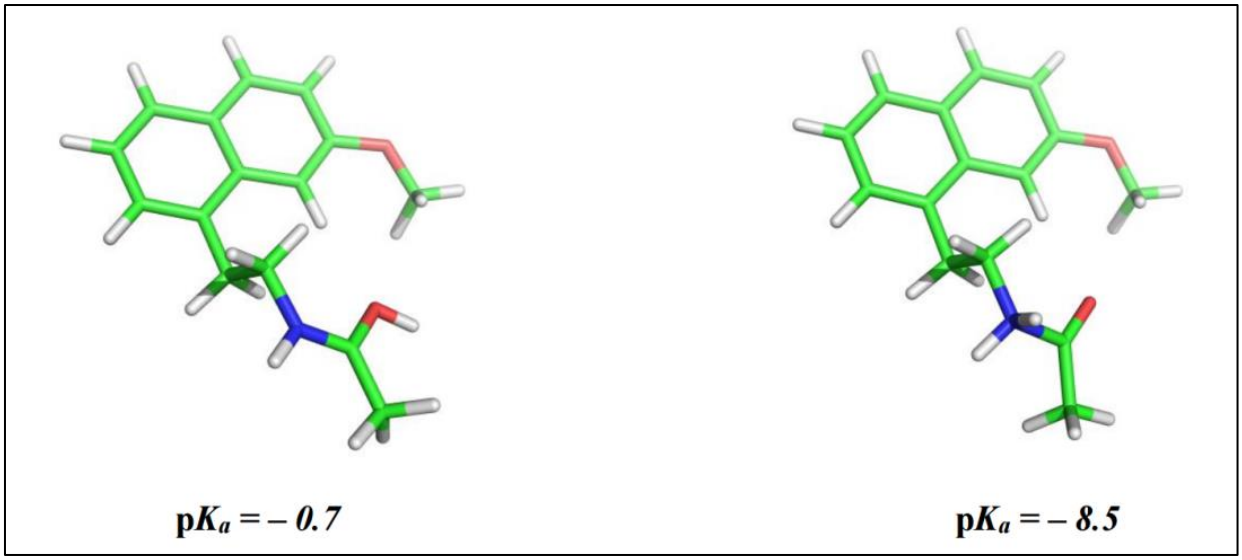

Figure S5 Calculated values for p*K*a of *O*- (left) and *N*- protonated (right) agomelatine molecule

The atomic coordinates of the optimized structures (for the calculation of pKa and for the calculation of the bond lengths in COSMO):

AG 'N protonated' BP86/def-TZVP(COSMO=80.0)

C	-0.1063838	0.0417145	0.0033405
C	-0.0814573	0.0156464	1.4284660
C	1.1043683	-0.0149473	2.1235743
C	2.3403968	-0.0164461	1.4184620
C	2.3616327	0.0143554	0.0319475
C	1.1446237	0.0391459	-0.7095706
H	-1.0294868	0.0184255	1.9707586
H	1.1236303	-0.0383553	3.2141413
H	3.3128502	0.0136156	-0.4955443

C	1.1176467	0.0625528	-2.1435726
C	-1.3294792	0.0713940	-0.7168902
C	-0.1032618	0.0907416	-2.8027222
C	-1.3296733	0.0969803	-2.0983711
O	3.4539253	-0.0503264	2.2136239
C	4.7392648	-0.0809794	1.5611467
H	5.4780503	-0.1191962	2.3680672
H	4.8378383	-0.9723762	0.9224923
H	4.8983520	0.8246926	0.9549669
H	-2.2693845	0.0739091	-0.1601610
H	-2.2699387	0.1225153	-2.6513785
H	-0.1161356	0.1102195	-3.8949572
C	2.4011390	0.0232493	-2.9453466
C	2.9745394	-1.3961246	-2.9681720
H	2.2001717	0.3463285	-3.9770681
H	3.1398903	0.7228208	-2.5262834
N	4.2844974	-1.4472089	-3.7131276
H	3.1715883	-1.7840829	-1.9629080
H	2.3016501	-2.0875697	-3.4879641
C	5.4866946	-0.7639090	-2.9829764
H	4.1843797	-1.0365592	-4.6542806
O	5.3606348	-0.5311386	-1.8164191
C	6.6322025	-0.5191752	-3.8893204
H	6.8876013	-1.4372099	-4.4389625
H	6.3434820	0.2364939	-4.6371654
H	7.4894470	-0.1623457	-3.3111558
H	4.5563475	-2.4303675	-3.8731926

AG 'O protonated' BP86/def-TZVP(COSMO=80.0)

C	-0.1512281	-0.0104189	0.0236933
C	-0.1115738	-0.0470555	1.4481222
C	1.0814277	-0.0426743	2.1317001
C	2.3094997	0.0027794	1.4148688
C	2.3162847	0.0488502	0.0289265
C	1.0918564	0.0385505	-0.7010484
H	-1.0536366	-0.0810908	1.9994420
H	1.1123072	-0.0742459	3.2217998
H	3.2608037	0.0911128	-0.5086957
C	1.0524912	0.0784292	-2.1348585
C	-1.3814577	-0.0195466	-0.6852144
C	-0.1756238	0.0666382	-2.7816235
C	-1.3948665	0.0186357	-2.0663267
O	3.4316394	-0.0019383	2.2002212
C	4.7106649	-0.0031533	1.5368467

H	5.4581793	-0.0213016	2.3364263
H	4.8237530	-0.8972801	0.9033991
H	4.8436190	0.9054867	0.9282322
H	-2.3156593	-0.0569938	-0.1201266
H	-2.3406206	0.0135421	-2.6106332
H	-0.1997337	0.0977410	-3.8735122
C	2.3280804	0.0994753	-2.9456705
C	2.9672842	-1.3040765	-3.0073580
H	2.1167963	0.4369154	-3.9694049
H	3.0539694	0.8068643	-2.5164195
N	4.2709788	-1.2744956	-3.6923420
H	3.1195466	-1.7154605	-2.0018176
H	2.3308546	-1.9960504	-3.5689695
C	5.3949537	-0.9052705	-3.1388473
H	4.2998217	-1.5159758	-4.6821213
O	5.3343743	-0.5713805	-1.8611465
C	6.6785268	-0.8575382	-3.8788244
H	6.5575542	-1.1764728	-4.9187677
H	7.0690598	0.1703378	-3.8536245
H	7.4072622	-1.5107109	-3.3770911
H	6.2194321	-0.3221019	-1.5257003

AG neutral BP86/def-TZVP(COSMO=80.0)

C	-0.1223263	-0.0129549	0.0222232
C	-0.0549736	-0.0429486	1.4457374
C	1.1519909	-0.0334365	2.1049704
C	2.3658291	0.0045730	1.3632967
C	2.3482160	0.0381720	-0.0233903
C	1.1071094	0.0286528	-0.7267353
H	-0.9859513	-0.0728021	2.0161144
H	1.2042685	-0.0567601	3.1946606
H	3.2842438	0.0448386	-0.5828884
C	1.0421967	0.0670273	-2.1612005
C	-1.3667755	-0.0245836	-0.6624286
C	-0.1996850	0.0528680	-2.7819398
C	-1.4057397	0.0068117	-2.0432049
O	3.5033047	0.0028340	2.1278666
C	4.7680967	0.0618999	1.4354021
H	5.5328043	0.0346360	2.2187857
H	4.8927133	-0.7913920	0.7526981
H	4.8574817	0.9954405	0.8578573
H	-2.2901102	-0.0575731	-0.0792315
H	-2.3619364	-0.0005862	-2.5695424
H	-0.2452412	0.0829198	-3.8734697

C	2.3040571	0.0867299	-2.9900768
C	2.9727156	-1.3056470	-3.0626702
H	2.0770408	0.4249694	-4.0114059
H	3.0339084	0.7949504	-2.5687479
N	4.2965498	-1.2528124	-3.6745352
H	3.0806144	-1.7220559	-2.0516253
H	2.3518369	-1.9948418	-3.6490830
C	5.3864768	-0.8192812	-2.9910014
H	4.3817958	-1.4436872	-4.6688836
O	5.3256600	-0.5023273	-1.7856557
C	6.6864500	-0.7476420	-3.7668223
H	6.5992057	-1.1000711	-4.8025031
H	7.0352727	0.2947408	-3.7714821
H	7.4429104	-1.3489469	-3.2439575

AG 'N protonated' BP86/def-TZVP(COSMO=6.0)

C	-0.0865171	0.0711345	-0.0173987
C	-0.0732950	0.0610728	1.4078493
C	1.1051409	0.0156588	2.1126065
C	2.3467478	-0.0163814	1.4186063
C	2.3798090	-0.0043431	0.0314495
C	1.1693892	0.0363367	-0.7202426
H	-1.0252600	0.0892299	1.9418319
H	1.1171650	0.0060517	3.2031675
H	3.3370994	-0.0243573	-0.4849701
C	1.1485434	0.0449223	-2.1538341
C	-1.3029315	0.1196946	-0.7464162
C	-0.0662633	0.0933704	-2.8230499
C	-1.2959287	0.1326082	-2.1278594
O	3.4496404	-0.0579031	2.2246690
C	4.7408647	-0.1132233	1.5917724
H	5.4680912	-0.1491309	2.4093295
H	4.8387570	-1.0149607	0.9671055
H	4.9210350	0.7824746	0.9758610
H	-2.2458000	0.1481487	-0.1957975
H	-2.2320348	0.1746912	-2.6862692
H	-0.0722733	0.1050138	-3.9156560
C	2.4350635	-0.0343043	-2.9485130
C	2.9722282	-1.4675638	-2.9475082
H	2.2469480	0.2829599	-3.9850665
H	3.1891373	0.6515360	-2.5308352
N	4.2886004	-1.5538902	-3.6879357
H	3.1603246	-1.8400415	-1.9345529
H	2.2852308	-2.1538000	-3.4564171

C	5.4836509	-0.8239829	-2.9638667
H	4.1901138	-1.1889759	-4.6471606
O	5.4210943	-0.7389485	-1.7749956
C	6.5217491	-0.3567546	-3.9119981
H	6.8110316	-1.1653666	-4.5994843
H	6.1050362	0.4591845	-4.5257468
H	7.3903510	0.0086174	-3.3559768
H	4.5691055	-2.5422947	-3.7892206

AG 'O protonated' BP86/def-TZVP(COSMO=6.0)

C	-0.1531069	-0.0181972	0.0221444
C	-0.1216635	-0.0607123	1.4463968
C	1.0662861	-0.0547593	2.1370730
C	2.2980071	-0.0002748	1.4281364
C	2.3135694	0.0489420	0.0422065
C	1.0934550	0.0377572	-0.6953034
H	-1.0668521	-0.0996992	1.9915954
H	1.0923498	-0.0889713	3.2269036
H	3.2618013	0.0998297	-0.4884378
C	1.0585259	0.0834624	-2.1282330
C	-1.3790483	-0.0258974	-0.6928282
C	-0.1658341	0.0735566	-2.7820378
C	-1.3876371	0.0203489	-2.0734358
O	3.4133963	0.0002436	2.2221694
C	4.6953050	0.0252450	1.5742292
H	5.4350489	0.0133404	2.3813297
H	4.8315544	-0.8623659	0.9346462
H	4.8207390	0.9409910	0.9733414
H	-2.3155981	-0.0679128	-0.1323769
H	-2.3309761	0.0183565	-2.6213469
H	-0.1853917	0.1119881	-3.8738881
C	2.3370178	0.1068652	-2.9345573
C	2.9709596	-1.2989452	-2.9959332
H	2.1288439	0.4479437	-3.9580959
H	3.0637423	0.8110407	-2.5008608
N	4.2688486	-1.2789741	-3.6983191
H	3.1341287	-1.7038992	-1.9896345
H	2.3253765	-1.9928539	-3.5451734
C	5.4044625	-0.9198817	-3.1619480
H	4.2799747	-1.5100133	-4.6910561
O	5.3667943	-0.5967364	-1.8798929
C	6.6774118	-0.8720286	-3.9236472
H	6.5405106	-1.1822444	-4.9645416
H	7.0743429	0.1537692	-3.9000722

H 7.4131330 -1.5328944 -3.4419134
H 6.2571434 -0.3562928 -1.5531045

AG neutral BP86/def-TZVP(COSMO=6.0)
C -0.1219473 -0.0136504 0.0220072
C -0.0541366 -0.0429376 1.4451950
C 1.1525603 -0.0337927 2.1039387
C 2.3663587 0.0044152 1.3626144
C 2.3480882 0.0379715 -0.0240481
C 1.1072506 0.0284425 -0.7267503
H -0.9851950 -0.0721574 2.0154470
H 1.2070730 -0.0566776 3.1933081
H 3.2842022 0.0467866 -0.5829991
C 1.0413343 0.0666010 -2.1608289
C -1.3658110 -0.0249186 -0.6626389
C -0.2001646 0.0527237 -2.7816009
C -1.4058603 0.0065544 -2.0430660
O 3.5025944 0.0029458 2.1268631
C 4.7661127 0.0613001 1.4349278
H 5.5305918 0.0348577 2.2186710
H 4.8924768 -0.7920588 0.7524428
H 4.8567852 0.9939966 0.8559463
H -2.2889029 -0.0576626 -0.0791529
H -2.3623047 -0.0002718 -2.5688043
H -0.2457927 0.0842048 -3.8731584
C 2.3034341 0.0862840 -2.9895251
C 2.9717731 -1.3058700 -3.0623805
H 2.0765252 0.4266456 -4.0104966
H 3.0338042 0.7934651 -2.5675658
N 4.2959022 -1.2561738 -3.6751652
H 3.0805369 -1.7206887 -2.0509932
H 2.3490666 -1.9967224 -3.6455093
C 5.3867071 -0.8186625 -2.9897863
H 4.3807684 -1.4415797 -4.6700867
O 5.3250604 -0.5002631 -1.7883976
C 6.6876740 -0.7474855 -3.7664614
H 6.6031398 -1.1000058 -4.8026617
H 7.0370284 0.2945351 -3.7698061
H 7.4432762 -1.3484367 -3.2423473

Intrinsic dissolution rate

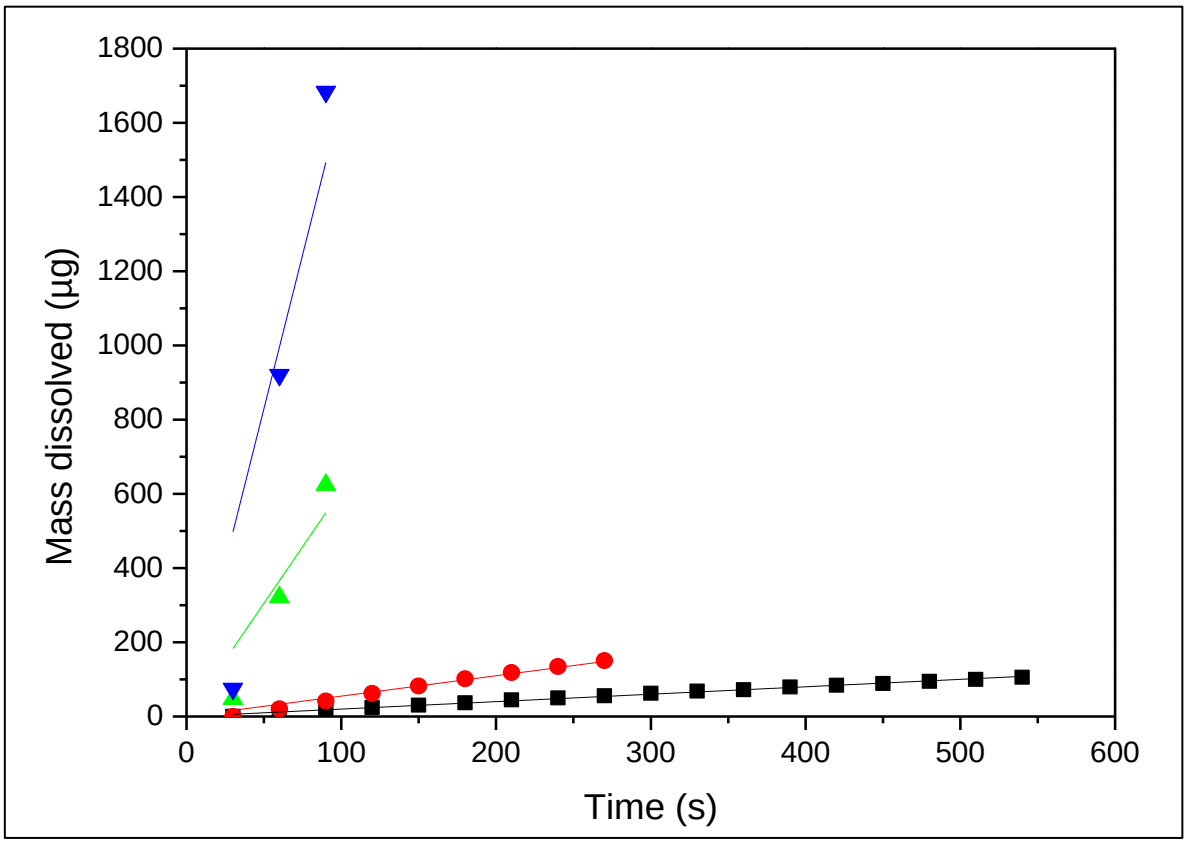

Figure S6 Intrinsic dissolution of agomelatine sulfates

Table S1 Intrinsic dissolution of agomelatine sulfates

AG solid form	Intrinsic dissolution rate			
	measurement 1 µg min^{-1} cm^{-2}	measurement 2 µg min^{-1} cm^{-2}	average µg min^{-1} cm^{-2}	The increase in the dissolution rate
AG - pure polymorph II (AGII)	36	34	35	-
AG hydrogensulfate (AG-HS-II)	117	107	112	3.2
AG mesylate (AG-MS-II)	9000*	5000*	7000	200.0
AG besylate (AG-BS)	1800*	1800*	1800	51.4

* More accurate values not available due to the extremely fast dissolution of the material.