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Supplementary Information

Quantitative Polymorph Contaminant Analysis in Tablets using Raman and Near Infra-Red Spectroscopies.

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Sample Mixing Analysis:

To ensure that the powder mixtures were first homogeneously mixed prior to tablet manufacture, NIR was used to monitor homogeneity at 30 second time points throughout mixing. Spectra were pre-processed using MSC and a 2nd derivative.

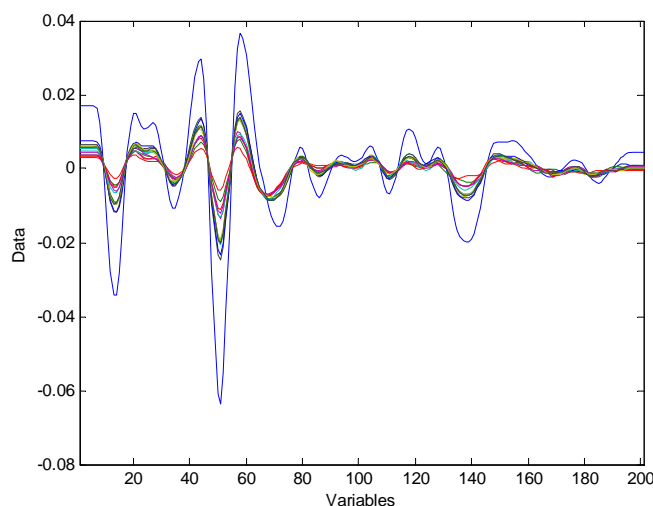


Figure S-1: NIR spectra from mixing experiment, Data pre-processed using SNV and a 2nd derivative. High wavenumber to the left. The blue trace is the first spectrum collected prior to mixing.

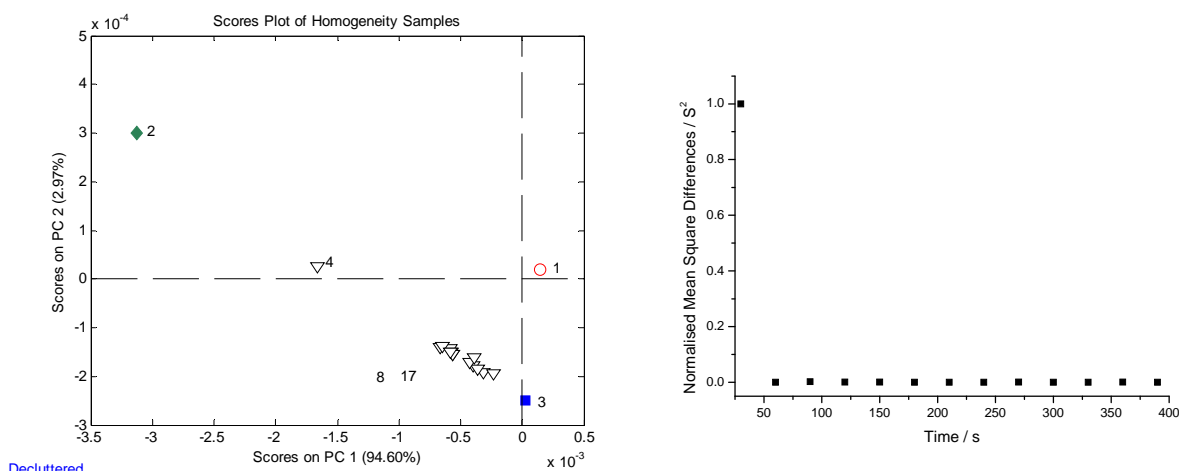


Figure S-2: Right: PCA scores plot of homogeneity samples and left: Mean Squares of Differences plot used to monitor homogeneity.

The resulting spectra were used for Principal Component Analysis (PCA) and the cores plot is shown in Figure S2. Samples 1, 2 and 3 are CaCO_3 , FIII Piracetam and MCC respectively. Sample 4 (large blue spectrum in previous figure) is from time zero with no mixing, with all subsequent measurements collected after 30 seconds of mixing using a Vortex Mixer.

As to be expected, the powder blend samples are closely related to MCC due to 80% MCC present in the formulation. Even just after 30 seconds, there is some level of mixing achieved. Mean Square of Differences,¹ was used to determine homogeneity where a spectra from different time points of mixing is subtracted from the spectra preceding it and the difference is squared and normalised and plotted against mixing time. The mean square was initially very high as to be expected but then dropped to ~zero, the values then fluctuated narrowly around the zero value as the mixing time progressed.

Polymorph Characterization:

Differential Scanning Calorimetry (DSC) was performed on a Rheometric Scientific STA625 with a heating rate of 10 °C/min used for all samples. Powder X-Ray Diffraction (PXRD) data was collected using an Inel Equinox 3000 (Artenay, France) powder diffractometer equipped with a CPS180 fixed curved multi-channel detector. Analysis time per sample was 16 minutes with the X-ray generator operating at 35 kV with a 25 mA current. In dedicated sample holders, the samples were spun at 5 rpm during data collection to minimise preferred orientation effects.

¹ Blanco M, Gozález Bañó R, Bertran E *Talanta* **2002**, 56, 203.

The FII and FIII polymorphs were characterised by PXRD and DSC, the data for which is shown below.

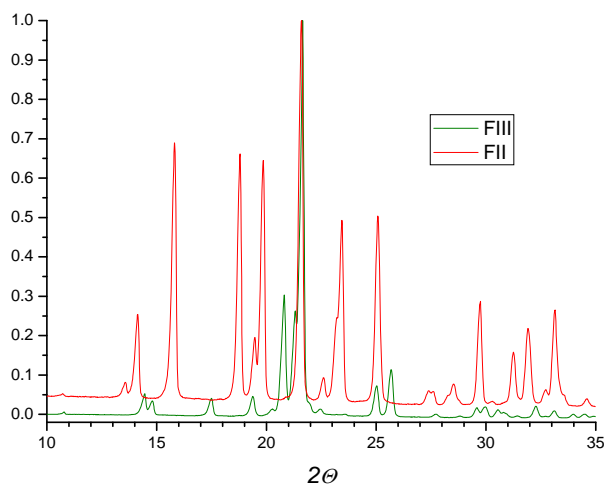


Figure S-3: Normalised (& slightly offset) PXRD patterns of the pure FIII (green) and FII (red) Piracetam polymorphs.

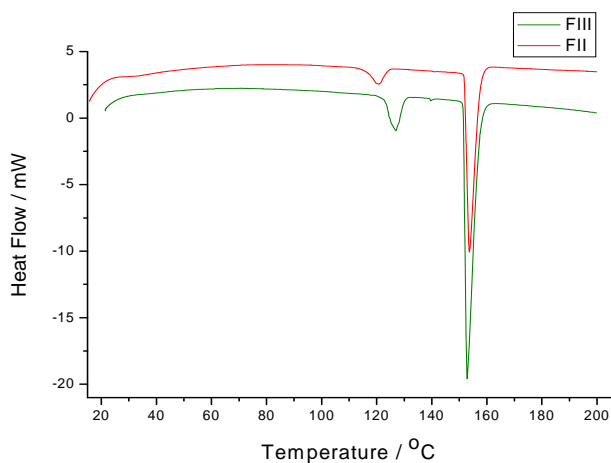


Figure S-4: DSC thermograms of Piracetam Form III (green) and FII (red).

The two polymorphs share an endothermic peak at 152 °C due to the melting of Form I which is formed at 114 and 120 °C as indicated by endothermic peaks for FII and FIII respectively.

Tablet Reproducibility:

Tablet Thickness: After each sample was prepared, 5 measurements of thickness were collected per tablet and the mean and standard deviation of each replicate set containing 15 samples each at 3 different thicknesses totaling 45 samples per thickness was calculated. The % error reported here is the result of dividing the standard deviation by the mean for each tablet thickness and multiplying by 100/1 to put into a percentage.

Replicate	1 mm Tablets		2 mm Tablets		3 mm Tablets	
	Mean	Std	Mean	Std	Mean	Std
A	0.982	0.007	1.969	0.0081	2.938	0.005
B	0.997	0.006	1.977	0.0044	2.987	0.007
C	0.993	0.011	1.968	0.0051	2.987	0.007
AVG Mean	0.991		1.971		2.971	
AVG Std	0.008		0.006		0.006	
% Error	0.813		0.297		0.211	

Table S-1: Thickness data from the tablets used in this study. The error in the thickness of the 1 mm tablets was the greatest at ~0.8%.

Spectral Comparison of TRS and BR

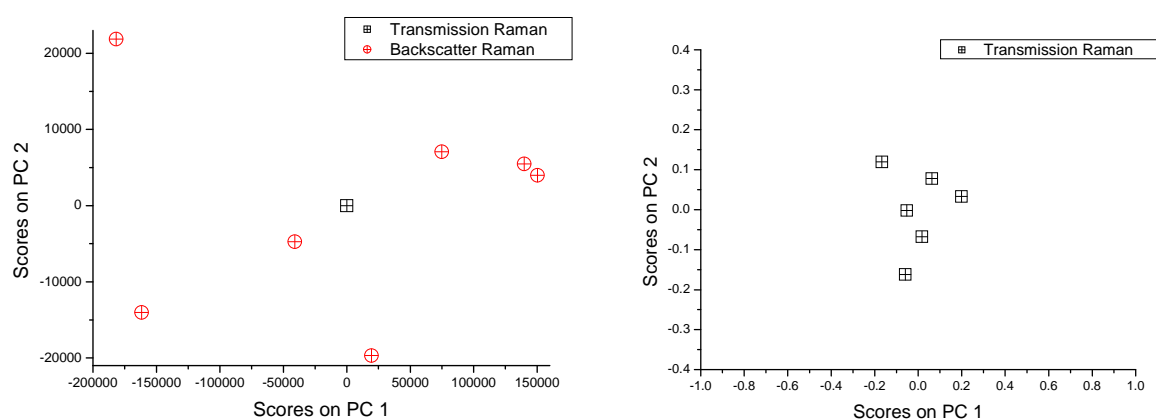


Figure S-5: PCA scores plots of raw spectra taken from six replicates of the 3 mm thick tablets at one concentration (10:90% FII:FIII) and analysed by TRS and BR. Right: Zoomed in view of points corresponding to TRS spectra.

PCA scores plots (Figure S-5) of raw Raman spectra (TRS and BR) taken from the 3 mm samples of one concentration (seven replicates) show that the BR data is much more variable than the TRS. The TRS spectra form a small cluster near the middle of the scores plot and when this area is zoomed in on it shows much less variation between samples. This is due to the different volumes being sampled by both techniques and because this BR method is more sensitive to surface inhomogeneities.

Spectral pre-processing:

Pre-processed spectral data collected by Raman and NIR methods

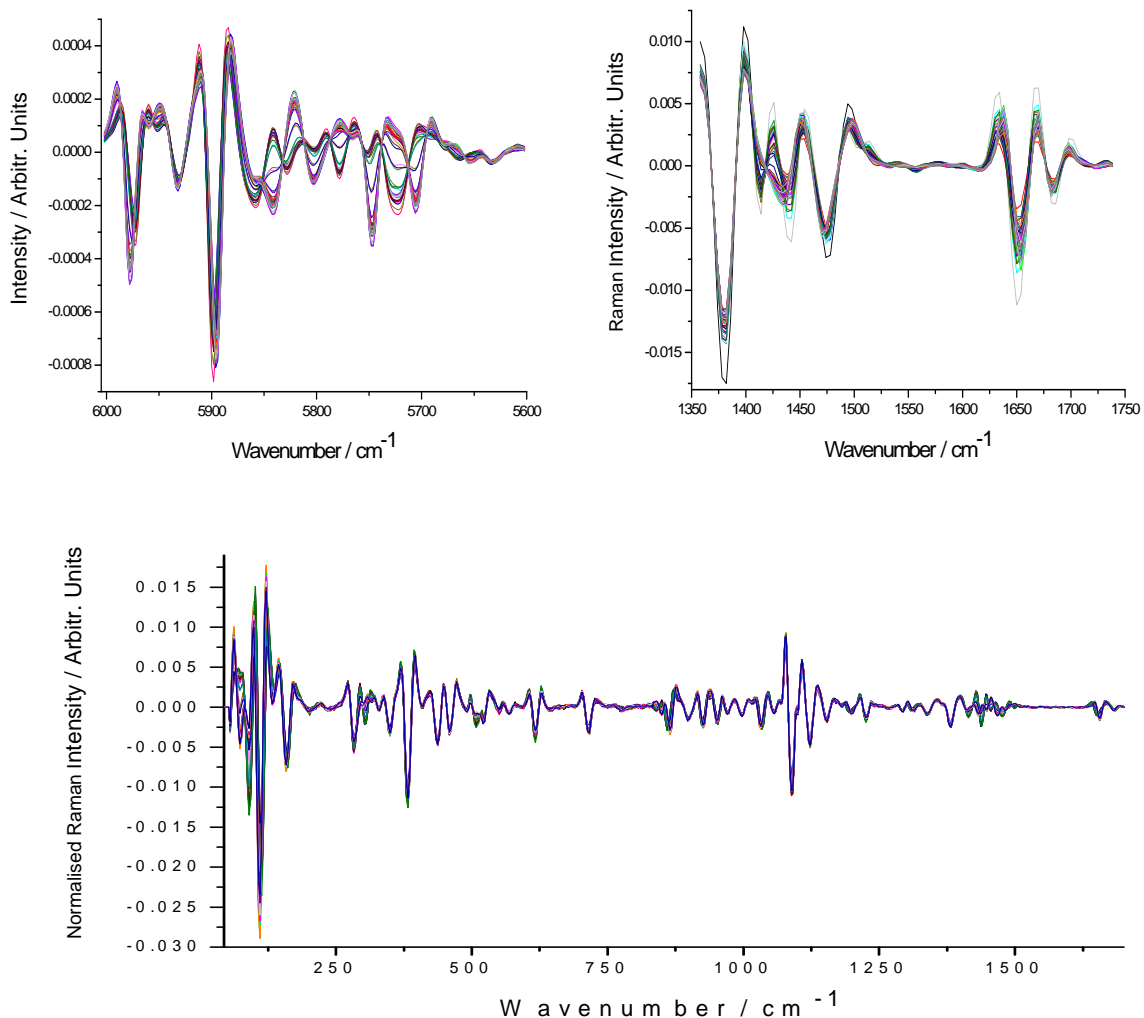


Figure S-6: Top left: MSC and 2nd derivative pre-processed NIR spectra, Top right: BR pre-processed spectra, Bottom: TRS pre-processed spectra.

Performance of Regression Models for Quantification of FII Piracetam

Pre-processing	Region	LV	RMSEC	r ²	RMSECV	RMSEP
Raw data	Full	6	0.47	0.994	0.59	0.47
	Half	5	0.48	0.994	0.57	0.23
	A and B	4	0.48	0.994	0.55	0.86
	A	3	0.47	0.994	0.54	0.40
	B	3	0.63	0.989	0.72	0.20
MSC	Full	4	0.57	0.991	0.66	0.31
	Half	4	0.51	0.993	0.59	0.45
	A and B	3	0.45	0.994	0.51	0.45
	A	3	0.44	0.995	0.50	0.27
	B	2	0.59	0.990	0.64	1.19
MSC & 2 nd deriv.	Full	1	0.51	0.993	0.54	0.26
	Half	1	0.51	0.993	0.54	0.26
	A and B	1	0.52	0.992	0.55	0.11
	A	1	0.48	0.994	0.50	0.20
	B	1	0.59	0.990	0.68	0.93

Table S-2: Performance of the regression models for quantifying FII in the 2 mm thick tablets using different pre-processing methods on the NIR spectra. RMSE values in % w/w.

Pre-processing	Region	LV	RMSEC	r ²	RMSECV	RMSEP
Raw data	Full	6	0.48	0.994	0.62	0.43
	Half	5	0.50	0.993	0.59	.99
	A and B	4	0.61	0.990	0.70	1.13
	A	3	0.5	0.992	0.60	0.43
	B	4	0.58	0.991	0.69	0.61
MSC	Full	4	0.54	0.992	0.63	0.88
	Half	4	0.49	0.993	0.57	0.97
	A and B	3	0.49	0.993	0.55	0.73
	A	2	0.57	0.991	0.64	0.87
	B	3	0.70	0.987	0.78	1.00
	Full	1	0.52	0.993	0.55	0.19

MSC & 2 nd deriv.	Half	1	0.52	0.993	0.55	0.19
	A and B	1	0.53	0.992	0.56	0.16
	A	1	0.50	0.993	0.52	0.18
	B	1	0.87	0.979	0.92	0.10

Table S-3: Performance of the regression models for quantifying FII in the 3 mm thick tablets using different pre-processing methods on the NIR spectra. RMSE values in % w/w.

Pre-processing	Region	LV	RMSEC	r ²	RMSECV	RMSEP
Raw	Full	4	0.91	0.977	1.10	1.07
	Half	2	0.93	0.976	1.03	1.09
	A	2	0.87	0.979	0.98	1.3
	B	2	0.88	0.978	0.99	1.14
MSC	Full	4	0.92	0.977	1.11	1.08
	Half	2	0.97	0.974	1.08	1.15
	A	2	0.92	0.977	1.03	1.10
	B	2	0.91	0.977	1.01	1.13
MSC & 2 nd deriv.	Full	2	0.87	0.979	0.98	1.10
	Half	2	0.86	0.979	0.98	1.06
	A	2	0.86	0.979	0.95	1.14
	B	1	0.89	0.978	0.95	1.08

Table S-4: Performance of the regression models for quantifying FII in the 2 mm thick tablets using different pre-processing methods on the BR spectra. RMSE values in % w/w.

Pre-processing	Region	LV	RMSEC	r ²	RMSECV	RMSEP
Raw	Full	4	1.12	0.965	1.35	0.91
	Half	3	1.07	0.968	1.32	0.81
	A	1	1.13	0.964	1.19	0.79
	B	2	1.10	0.966	1.28	0.70
MSC	Full	4	1.06	0.969	1.30	0.77
	Half	3	1.08	0.967	1.29	0.73
	A	1	1.22	0.957	1.28	0.80
	B	2	1.15	0.963	1.31	0.66
MSC & 2 nd deriv.	Full	2	1.11	0.966	1.26	0.69
	Half	1	1.28	0.954	1.34	0.60
	A	1	1.12	0.965	1.16	0.64
	B	2	1.10	0.966	1.28	0.67

Table S-5: Performance of the regression models for quantifying FII in the 3 mm thick tablets using different pre-processing methods on the BR spectra. RMSE values in % w/w.

Pre-processing	Region	LV	RMSEC	r ²	RMSECV	RMSEP
Raw data	Full	6	0.45	0.995	0.58	0.59
	Half	4	0.56	0.991	0.72	0.47
	A	4	0.53	0.992	0.61	0.88
	B	3	0.46	0.994	0.52	0.37
	C	2	0.87	0.979	0.93	1.17
MSC	Full	4	0.54	0.992	0.65	0.16
	Half	4	0.48	0.994	0.56	0.37
	A	3	0.47	0.994	0.54	0.74
	B	2	0.60	0.990	0.64	0.46
	C	3	0.59	0.990	0.67	1.29
MSC & 2 nd deriv.	Full	1	0.29	0.998	0.30	0.42
	Half	1	0.29	0.997	0.30	0.42
	A	1	0.34	0.997	0.36	0.45
	B	1	0.29	0.998	0.30	0.35
	C	1	0.30	0.998	0.31	0.44

Table S-6: Performance of the regression models for quantifying FII in the 2 mm thick tablets using different pre-processing methods on the TRS spectra. RMSE values in % w/w.

Pre-processing	Region	LV	RMSEC	r ²	RMSECV	RMSEP
Raw data	Full	3	0.42	0.995	0.53	0.27
	Half	3	0.42	0.995	0.52	0.27
	A	3	0.31	0.997	0.38	0.22
	B	4	0.33	0.997	0.41	0.19
	C	2	0.44	0.995	0.53	0.34
MSC	Full	2	0.31	0.997	0.35	0.31
	Half	2	0.31	0.997	0.34	0.30
	A	2	0.43	0.995	0.49	0.38
	B	3	0.36	0.997	0.42	0.28
	C	1	0.36	0.996	0.41	0.46
MSC & 2 nd deriv.	Full	1	0.33	0.997	0.35	0.30
	Half	1	0.33	0.997	0.35	0.30
	A	1	0.42	0.995	0.46	0.41
	B	1	0.42	0.995	0.45	0.34
	C	1	0.33	0.997	0.35	0.31

Table S-7: Performance of the regression models for quantifying FII in the 3 mm thick tablets using different pre-processing methods on the TRS spectra. RMSE values in % w/w.

PCA of NIR spectra of All Tablet Thicknesses

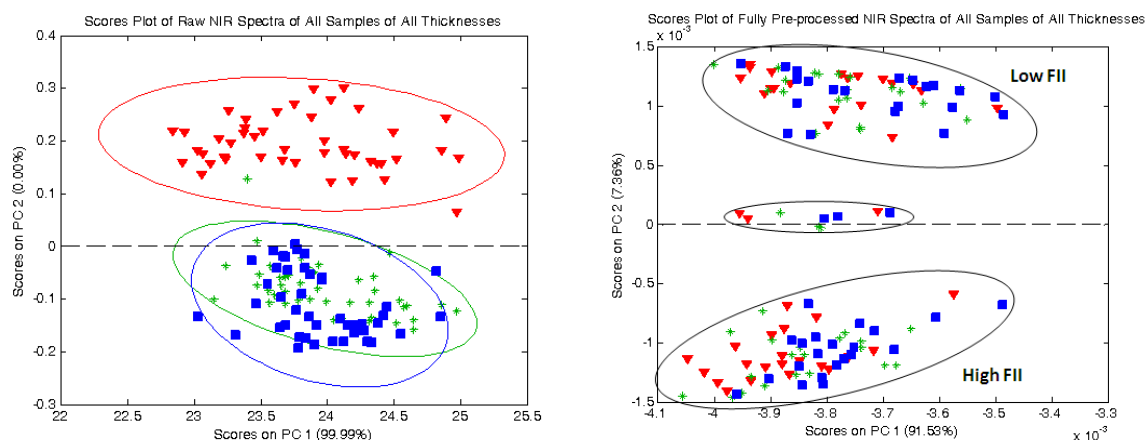


Figure S-5: (left) PCA analysis of the raw, unprocessed NIR data collected from the 1 (red triangles), 2 (blue blocks) and 3 mm (green asterisks) thick samples. The 1mm tablets are denoted by the red ellipses. (right) PCA analysis of MSC, 2nd derivative NIR data collected from the 1 (red triangles), 2 (blue blocks) and 3 mm (green asterisks) thick samples.

PCA was performed on all NIR spectra of all thicknesses and using the raw data we see a clear separation between 1 mm samples and all other thicknesses. Combination of MSC with a second derivative shows no segregation of the 1 mm samples from the remaining samples and we see all the samples of different thicknesses separating into three distinct clusters representing those samples with a high concentration of FII, a low concentration of FII and then the 50:50 samples containing 50:50 FII:FIII. This is the same for all techniques as pre-processing maximises chemical information which in this case is the concentration differences of the polymorph contaminant.

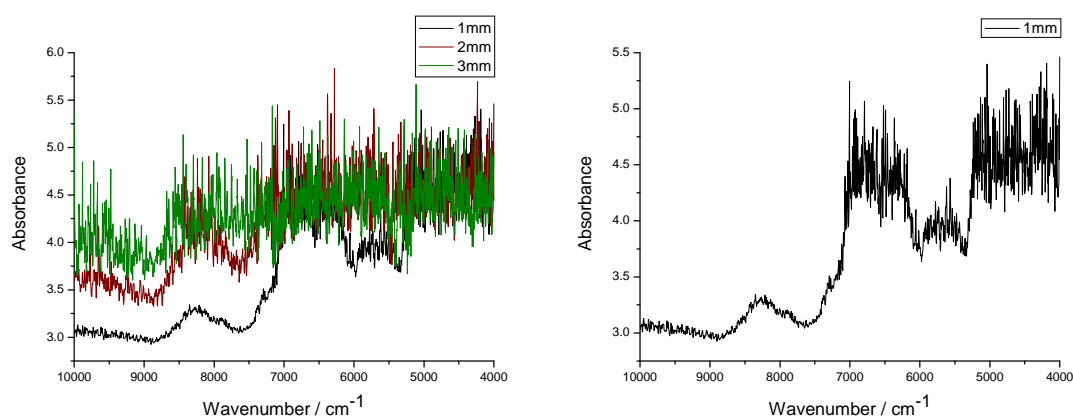


Figure S-6: Left: Transmission NIR spectra of tablets of 3 thicknesses, right: transmission NIR spectrum of a 1 mm thick tablet.