Supplementary Materials

There are two legitimate labeled content of chlorpheniramine maleate (CPM) in commercial CPM tablets: 1mg and 4mg (the Chinese pharmacopoeia, 2010 Edition, Volume II). Commercial CPM tablets containing 4mg CPM were purchased from local pharmacy (due to the protection of intellectual property, the pharmaceutical producer and production batch number were not demonstrated). The main excipients of this brand CPM tablets were starch and dextrin. Both starch and dextrin were purchased from Beijing FengliJingqiu Commerce and Trade Corporation (Beijing, P.R. China). Pure compound reference tablets of starch and dextrin were produced under the same compaction parameters as described in the manuscript.

Each pure NIR image (starch and dextrin) was obtained using Spotlight 400N FT-NIR Imaging Systems (PerkinElmer, UK). Three absorbance spectra of the major compounds (CPM, starch and dextrin) were obtained from the pure images, respectively, as Figure 1 (a) showed. Different pretreatment methods were used to raw spectra of three major ingredients. The spectra preprocessed by the combination of Savitzky–Golay (SG) smoothing with a 9-point window and first derivative showed a distinct, sharp absorption feature for CPM at 6032cm^{-1} (see Figure.1 (c)). Therefore, the characteristic wavenumber method could also be used to extract the distribution of CPM on the tablet surface.

The commercial CPM tablet was fixed onto the microscope slide and measured directly on the surface of tablet. The images of different regions on the tablet surface were obtained to compare the differentiation of CPM distributions. The CPM distribution on the tablet surface was obtained by characteristic wavenumber method (Figure 2). The red area (high first derivative of absorbance) represented the CPM distribution. Furthermore, by setting a threshold limit for the first derivative of absorbance at 6032cm^{-1}, the binary images of CPM tablets were obtained (Figure 3). Statistical measurement was performed to derive numerical information from Figure 3 and the results were displayed in Table 1. Through calculating the proportion of white region in the binary image, the CPM contents of different regions on the tablet surface

were obtained. The relative standard deviation (RSD) value of CPM contents was 12.01%>3.00%, indicating the inhomogeneous distribution of CPM on the tablet surface (Tablet 1).

The same HPLC method, recommended by the Chinese Pharmacopoeia (Ch.P. 2010 Edition, Volume II), was used to determine the volume content of CPM in the sample and assess its volume content uniformity (VCU) in whole region and part region of the tablets. Firstly, ten CPM tablets were selected and each of them was dissolved by mobile phase for VCU analysis. The evaluation index of volume content uniformity was 12.69 less than 15.00 (Table 2), indicating the content uniformity satisfied the Ch.P. (2010 Edition) standard. Secondly, another ten commercial CPM tablets were selected and averaged into four pieces. One piece of each tablet was dissolved for HPLC determination. The evaluation index of volume content uniformity was 27.39 >15.00 (Table 3), meaning the VCU did not satisfy the requirement. This consequence also demonstrated that API might not distribute homogeneously in the sample, even though the volume content uniformity determined by HPLC method conformed to the regulations, i.e. Ch.P. (2010 Edition).

Therefore, the related methods described in the manuscript were feasible for application in commercial CPM tablets. NIR-CI technique is suitable for surface content uniformity measurements, and is suitable for the use in the quality control of pharmaceutical products.

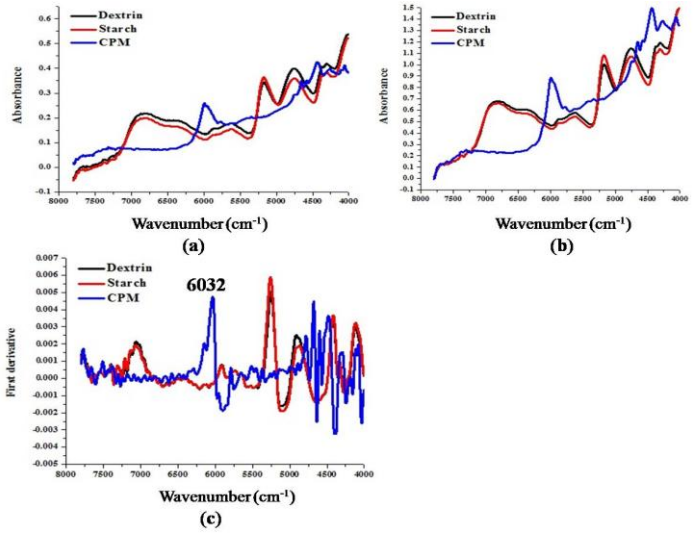

Figure 1: Raw and preprocessed spectra, (a) raw spectra, (b) spectra preprocessed by SG smoothing and normalize, (c) spectra preprocessed by SG smoothing and first derivative of three major ingredients (CPM, starch and dextrin)

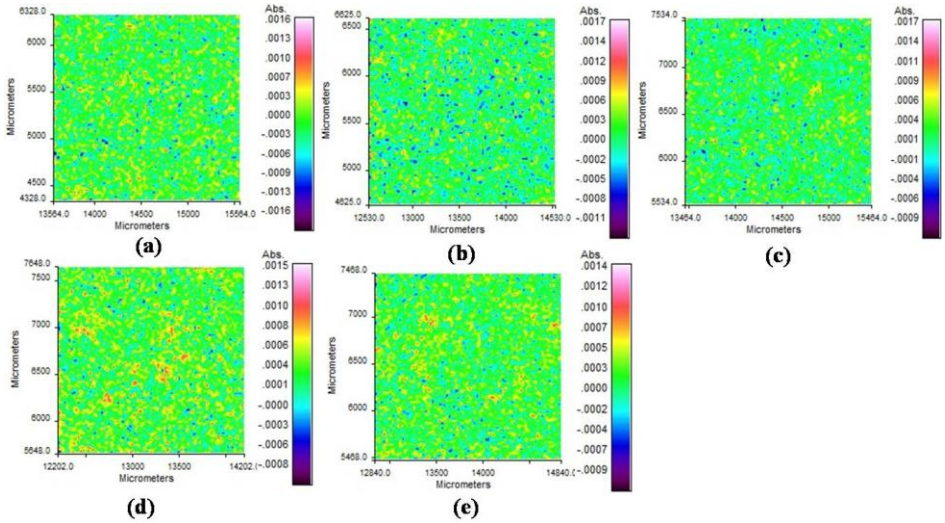

Figure 2: The characteristic images for CPM at 6032cm^{-1}, (a) upper-left region, (b) upper-right region, (c) lower-left region, (d) lower-right region and (e) middle region on the tablet surface.

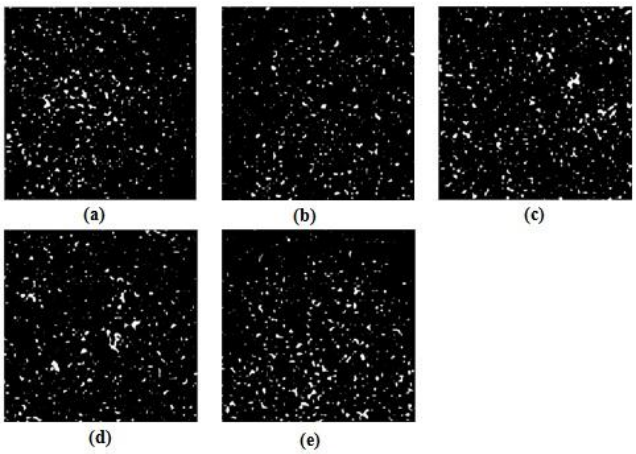

Figure 3: Binary images of CPM tablet. (a) upper-left region, (b) upper-right region, (c) lower-left region, (d) lower-right region and (e) middle region on the tablet surface. White region represented the cluster of CPM and black region represented the cluster of other components.

Table 1: The consequence of statistical measurement by NIR-CI

Number	Range of diameter (μm)	Average diameter (μm)	Proportion of white region
1	16.32-29.38	22.82	4.57%
2	16.75-35.48	24.49	5.80%
3	14.24-31.74	21.21	5.18%
4	8.70-30.46	18.70	4.49%
5	17.21-39.20	26.19	5.73%

* Number1-5 represented upper-left region, upper-right region, lower-left region, lower-right region and middle region on the tablet surface, respectively.

Table 2: Volume content uniformity assessment (Whole tablets) using HPLC

Number	1	2	3	4	5	6	7	8	9	10
Peak area (mAU•s)	624.9	691.9	711.7	703.3	684.1	641.4	649.1	686.3	646.0	633.4
Content(mg)	3.57	3.95	4.06	4.01	3.90	3.67	3.71	3.92	3.69	3.62
A+1.8S	12.69<15.00									

Table 3: Volume content uniformity assessment (Quartered tablets) using HPLC

Number	1	2	3	4	5	6	7	8	9	10
Peak area (mAU•s)	671.5	748.3	673.6	635.7	712.8	693.4	715.9	727.2	757.6	751.2
Content(mg)	0.765	0.855	0.766	0.723	0.810	0.788	0.813	0.826	0.861	0.853
A+1.8S	27.39>15.00									