PARTICLE CHARACTERIZATION UTILIZING PAT (PROCESS ANALYTICAL TECHNOLOGY) TOOLS

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PURPOSE

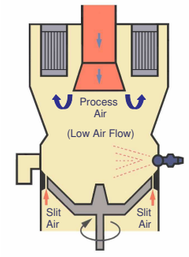
To evaluate the appropriateness of various PAT tools for characterizing particles at the beginning and end of a granulation/ spheronization process.

METHODS

Raw ciprofloxacin was granulated/spheronized with a bowl shaped rotor in a specially designed fluid bed (Vector/Freund Granurex). Dry ciprofloxacin (95%) was mixed with dry PVP (polyvinylprrolidone) powder (5%). A coarser grade of PVP (K30) was made into a 5% solution with water and sprayed on to the rotating dry ciprofloxacin/PVP mixture. Samples of the un-granulated and granulated ciprofloxacin were analyzed with the following PAT tools: Laser Diffraction (Sympatec HELOS); Image Processing (Sympatec QICPIC); Effusivity (Mathis ESP); and Near Infrared (Axsun NIR Analyzer).

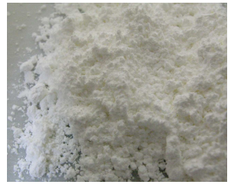
PROCESS EQUIPMENT

Granurex GX-40



PRODUCT PROPERTIES

Un-granulated



0.358 g/cc Bulk Density

2.52 % Moisture/Volatiles

Poor Flowing

100% Ciprofloxacin

Granulated

0.468 g/cc Bulk Density

12.39 % Moisture/Volatiles

Free Flowing

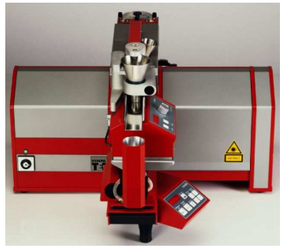
91.94% Ciprofloxacin

4.84% Fine Grade PVP

3.23% Coarse Grade PVP

ANALYTICAL EQUIPMENT

Laser Diffraction



Particle size based on Fraunhofer or Mie theory and the size distribution determined with a parameter free and model independent mathematical algorithm (Phillips-Twomey).

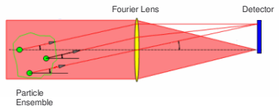
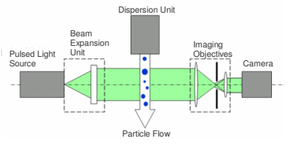


Image Processing

500 images per second

Particle size based on equivalent projected circle area, Feret diameters, etc.

Particle shape evaluation: sphericity and aspect ratio



Effusivity

$$Effusivity = \sqrt{k\rho c_p}$$

Where:
k = thermal conductivity (W/m·K)
ρ = density (kg/m³)
c_p = heat capacity (J/kg·K)

The effusivity sensor works like your fingertip — sensor supplies heat to the material it comes in contact with and measures the heat flow.

Near Infrared (NIR)

NIR Analyzer
Light Source: Semiconductor
Range: 1350-1800 nm
Filter: Tunable Favry-Perot

Sample Sensor
Diffuse Reflectance Integrating Sphere (2mm spot size)

Concentration Prediction: Partial Least Squares
Moisture Level Prediction: SIMCA (Soft Independent Modeling of Class Analogy)

SIMCA is a classification tool that develops principal component models for each set category. In the SIMCA plot the clusters of different components are present and the interclass distance is a measure of the distance from the centroid to the sample clusters.

Interclass distance is a unit less number, and a small number, below 3, indicates that the sample is essentially the same as the calibration set; hence a larger number indicates a shift away from the calibration set.

RESULTS

Laser Diffraction

Un-granulated sample had bi-modal particle size distribution around 8 and 70 micron. Granulated sample had a very narrow distribution centered around 220 micron.

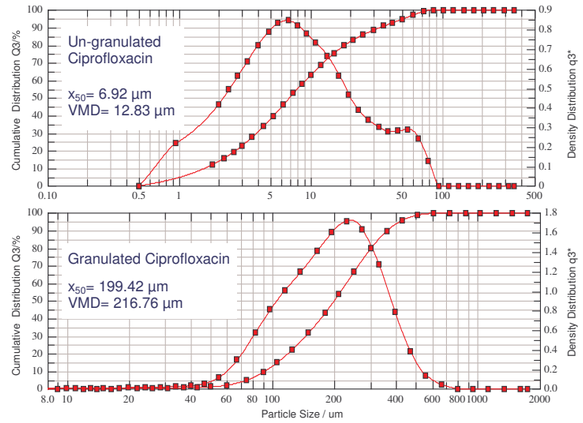
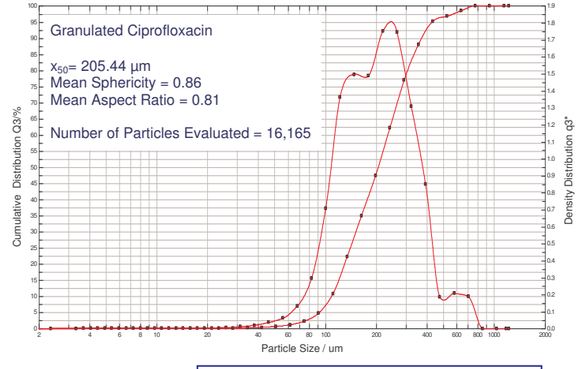
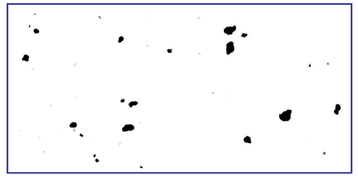


Image Processing

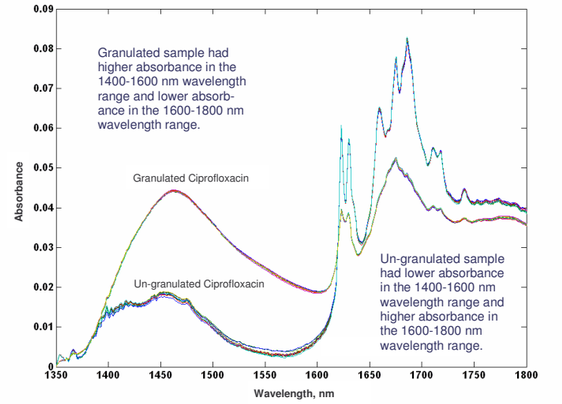
Un-granulated sample would clump together and would mask the particle size analysis, but silhouetted pictorials showed small needle shaped particles and more spherical particles approximately 100 micron in size. Granulated sample showed a shift in the particle size distribution as well as a significant number of silhouetted pictorials in the 250 micron range.



Sample of Silhouetted Pictorials - Granulated Ciprofloxacin

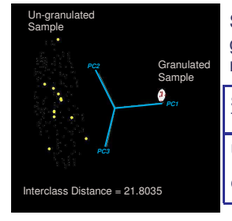


Near Infrared (NIR)



Partial Least Squares prediction method provided an excellent correlation (r=0.997) for component concentration.

Component Type	Predicted Concentration	Measured Concentration	Difference
Ciprofloxacin	91.940 %	91.940 %	0.000 %
Fine PVP	4.839 %	4.840 %	0.021 %
Coarse PVP	3.220 %	3.230 %	0.310 %



SIMCA showed a shift between un-granulated and granulated samples with regards to moisture.

Sample Type	Predicted Moisture	Measured Moisture	Difference
Un-granulated	2.519 %	2.515 %	0.159 %
Granulated	12.379 %	12.385 %	0.048 %

Effusivity

Un-granulated sample had an effusivity value of 175.0 and the granulated sample effusivity value was 178.2. The slight increase in effusivity was attributed to the change in density, moisture, and particle size.

CONCLUSIONS

All the PAT tools analyzed showed a change between un-granulated and granulated samples with the greatest changes seen with laser diffraction, image processing, and near infrared. However, no single PAT tool provided a complete picture of what occurred during the granulation of the ciprofloxacin. Therefore, controlling a granulation process and characterizing the particles will require two or more PAT methods.

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