

Characterization of Technically Unavoidable Particles in Bulk Excipients

Dr. Viraj Kulthe^a *, Divya Rajvadi^a, Amit Raj Sinha^b

^a SIGACHI® Industries Limited, Dahej SEZ - I, Bharuch, Gujarat, India.

^b SIGACHI® Industries Limited, 2nd Floor, Kalayan's Tulsiram Chambers, Madinaguda, Hyderabad, Telangana, India.

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ABSTRACT

In the bulk of excipients, a few particles having different size, shape, color, etc., than the rest of the particles are permissible, if they are arising out of normal processing conditions and if they are investigated sufficiently. Regulatory guidance is limited in this area and as a result, materials may be rejected unnecessarily by the excipient users. For example, consider the situation for cellulosic excipients, like microcrystalline cellulose MCC which chars at temperature greater than 230°C. When this material is manufactured by processes such as spray drying, a few discolored or charred particles may be generated because of overheating of particles at certain locations in the processing equipment. In fact, such particles are inherent to the bulk of excipients in many of these materials being used for pharmaceutical product development and production. In pharmaceutical excipient manufacturing, some level of physical change of particles is often technically unavoidable due to the nature of the manufacturing process itself. The resulting particles are referred to as “Technically Unavoidable Particles” (TUPs). Excipient manufacturers are generally aware of the origin, type, and quantity of such unusual visible particles in their products; however, their identity is often not investigated to demonstrate that they present no risk to the product's purity. This article aims to provide a brief outline for ways to demonstrate the purity of pharmaceutical excipients containing visibly different particles. Digital and scanning electron microscope images of white and discolored particles of MCC were used to establish morphological similarity. Differential scanning calorimetry and powder X-ray diffraction tools demonstrated polymorphic nature of batches. In addition, analytical tools such as: FT-IR, SEM-energy dispersive spectroscopy, and solid-state ¹³C NMR were employed to confirm chemical similarity. The combination of these techniques represents a possible testing framework for the identification and characterization of TUPs in excipient batches that could lead to more appropriate disposition of an affected excipient lot.

*Corresponding author

SIGACHI® Industries Limited Unit - 2: Plot No. Z-16, Dahej SEZ, Part - 1
Dahej, District - Bharuch, Gujarat-392130, India. Mobile: +91 - 63570 65502,
E-mail - viraj.kulthe@sigachi.com

INTRODUCTION

Guidance available from the EMA states that traces of prohibited substances shall be permitted in the product provided that such presence is in conformity with safety requirements (to the patients)¹. Despite this, there are numerous examples of the USFDA issuing Form 483 notices to pharmaceutical product manufacturers for adverse findings from an FDA inspection based on trace amounts of TUPs in excipients. It is important to note that such warning letters are issued for inadequate or insufficient documentation of unusual, visible particles in the ingoing excipients, and not because of the presence of such particles in the products^{2,3}. Compendia and regulatory authorities have not dealt with this issue in sufficient detail, and as a result, raw materials can be rejected unnecessarily due to concerns regarding the nature of the TUPs and implications for the quality and safety of any batch they are present in. Early in 2024 the International Pharmaceutical Excipients Council's (IPEC) guidelines on Technically Unavoidable Particle Profiles (TUPP), Version 2, emphasized the importance of understanding and managing visual changes in bulk excipient particles during their manufacturing. The goal is to ensure that excipient quality and safety are unchanged with the presence of trace amounts of such 'visibly' different particles^{3,4}.

Understanding and effectively managing TUPs is crucial for setting realistic quality control standards, ensuring safety, and meeting regulatory expectations. Particle analysis techniques employed for assessing size, shape, and distribution of such TUPs help to understand their 'profile' (the TUPP). It is essential to document these tolerance levels as part of the quality control standards and ensure that they are communicated effectively to all relevant stakeholders such as excipient users and regulatory authorities, when required.

In this study, Microcrystalline cellulose (MCC) has been used as a model excipient to help understand this situation. Discolored particles can be present in the ingoing pulp and may also occur during manufacture of MCC by spray drying because of excessive localized overheating and continued friction against metal surfaces of the spray dryer equipment. A previous article⁵ presented an automated system based on the specimen color, contrast, and size thresholds, proposed to

eliminate the disadvantages of manual counting during detection of non-white particles (TUPs). However, that study did not consider the fact that this guide is focused on visible particles, and not microscopic (sub-visible) particles or the particles detected using visual aids^{3,4}. While quantitatively establishing TUPs, this earlier study did not fulfil the investigational component as expected by the regulatory authorities.

In our work, we demonstrate that discolored particles and white particles of MCC are similar in terms of physical and chemical attributes, and they are just visibly different (color differences). Overall, this study highlights that the bulk MCC retained its quality even in the presence of small amounts of TUPs. Based on this MCC example, a brief methodology is outlined for more robust and comprehensive characterization of TUPs. In conjunction with other approaches, such as the IPEC Guidance^{3,4}, the current investigations should help excipient suppliers, their clients, and regulatory authorities have better insights on TUPs in excipient batches and the implications on batch quality, safety and appropriate disposition of these important materials.

MATERIALS AND METHODS

Microcrystalline cellulose (Sample) was sourced internally from Sigachi Industries Ltd. Microcrystalline cellulose internal standard (Standard) was procured from Sigachi Industries limited, Dahej (Gujarat). Technically Unavoidable Particles (TUPs) were obtained by isolating brown colored/ charred particles from the Sample. All other chemicals and solvents used were of suitable grade.

Methods for estimation of Technically Unavoidable Particles:

A range of techniques were used for investigating the physical and chemical similarity of TUPs to that of Sample (and Standard) as follows:

Counting visually different particles:

A wet method was followed for this analysis. 10 g of each test article was added to 100 ml of water in a beaker and stirred well. Samples were observed visually under artificial or natural light against a bright background⁶.

Scanning Electron Microscopy (SEM):

Test materials were mounted on double-faced adhesive carbon tape. Surface morphology of the Sample and TUPs, with reference to the Standard, was studied with a scanning electron microscope (Make: Phenom US, Model: ProX G6 Desktop). SEM instrument light optical imaging mode at comparable magnifications (25 – 30X) was used to obtain real life images of the test article.

Differential Scanning Calorimetry (DSC):

DSC thermograms of Sample, Standard and TUPs were obtained using a differential scanning calorimeter (Make: Perkin Elmer US, Model: DSC 6000), operated with Pyris Manager program software. The instrument was equipped with an intra cooler. Accurately weighed quantities of samples (3 – 5 mg) were analyzed in hermetically- sealed, pin-holed aluminum crucibles. The samples were heated at a constant rate of 10 °C/minute over a temperature range of 30 – 350°C. They were held for 1 minute at 350°C and cooled from 350°C to 32°C at 10°C/minute. An inert atmosphere was maintained by purging nitrogen gas at flow rate of 20 mL/minute. The instrument was calibrated for temperature and heat flow using indium and zinc standards, respectively.

Powder X-Ray Diffraction (PXRD):

PXRD profiles of the Sample, Standard and TUPs were recorded using a powder X-ray diffractometer (Make: Bruker Corporation Germany, Model: AXS D8 Focus P-XRD). The samples were irradiated with monochromatic Cu K radiation (1.542 Å) and analyzed between 5 – 50 °(2θ). The voltage and current of 40 kV and 40 mA were used, respectively. The step width 0.5 second/per minute and increment 0.0498169, respectively were used.

Fourier Transform Infrared spectroscopy (FT-IR):

FT-IR spectra were obtained using a FT-IR spectrometer (Make: Shimadzu Corporation Japan, Model: IR Spirit). About 2 – 3 mg of the sample was finely ground with dry KBr and pressed into pellets using a hydraulic press. The resulting materials were mounted on the sample cell and spectra were scanned over the wavenumber range of 4000 – 400 cm⁻¹ at 45 scans per spectrum.

Elemental analysis using Scanning Electron Microscopy with integrated energy dispersive spectroscopy (SEM-EDS):

Test materials were mounted on double-faced adhesive carbon tape. Surface morphology of the Sample and TUPs was studied with a scanning electron microscope (Make: Phenom US, Model: ProX G6 Desktop) in electron optical imaging mode at comparable magnifications (600 – 700X) with reference to the MCC standard. The images were obtained using bright field illumination mode, an electron optical thermionic source (CeB6), at acceleration voltages 15 kV, with an Energy dispersive spectroscopy (EDS) detector and Backscattered electron detectors. EDS specifications include a ultra-thin silicon nitride (Si3N4) X-ray window, energy resolution Mn Kα ≤132 eV, a multi-channel analyzer with 2048 channels at 10 eV/ch processing capabilities with an input count rate of 5319 cps.

Solid state C13 Nuclear Magnetic Resonance (SS-NMR)

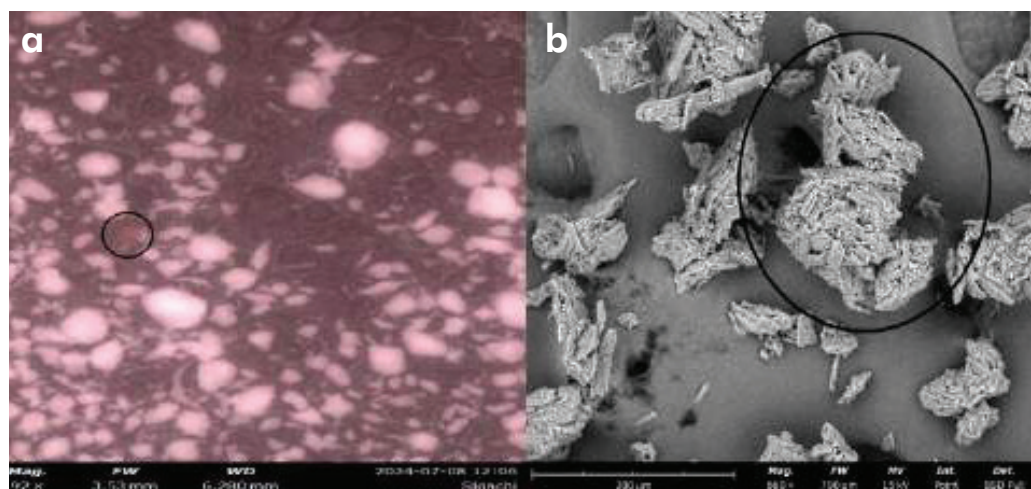
SS-NMR spectra were obtained using a NMR spectrometer with a solid state probe (Make: Bruker Corporation Germany, Model: AV-Neo 500) at 125 MHz resonance frequency for ¹³C, equipped with a CP-MAS probe, temperature: 298K, spinning rate: 14 kHz, Cross-polarization (CP) contact time: 2000 micro second and a recycle delay: 13.02s for the Sample and 31.28s for TUPs. Data points were sampled with an acquisition time: 0.0204800s; resulting total sweep width: 800 ppm. Chemical shifts were referenced externally against Adamantane. One thousand scans were carried out and added to get the total free induction decay (FID) signal. Then apodization, that is the FID is multiplied by an electromagnetic field with a decay time of 100Hz, was carried out to cut the noise in the spectrum and to increase the line width of the spectral lines. Such a signal is acquired in the time domain and a Fourier transformation is done to obtain NMR spectra.”

RESULTS AND DISCUSSION

Figure 1 shows various microscopic images of: the Sample, Standard and TUPs. In light optical imaging mode at lesser magnifications (Figure 1a), TUPs appeared as buff to brown colored material (encircled) against white colored particles of the bulk excipient. At higher magnification, and by using electron imaging mode (Figure 1b), TUPs showed no change in their

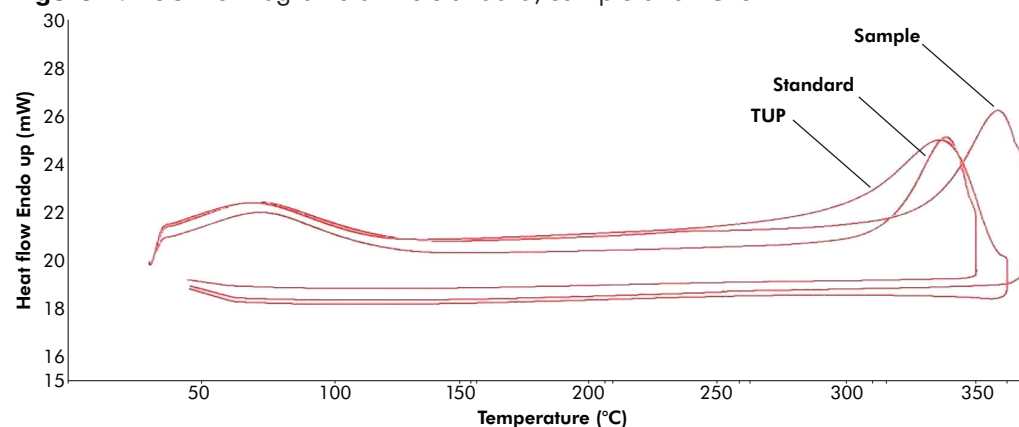
Figure 1.

(a) Light and (b) electron optical images of sample and TUP (encircled)



form or shape compared to the MCC standard. This indicated that such TUPs are just visibly different in color than the bulk excipient particles and that their surface morphology⁷ is unchanged even when they were obtained as a result of localized overheating and friction during the manufacturing process of microcrystalline cellulose.

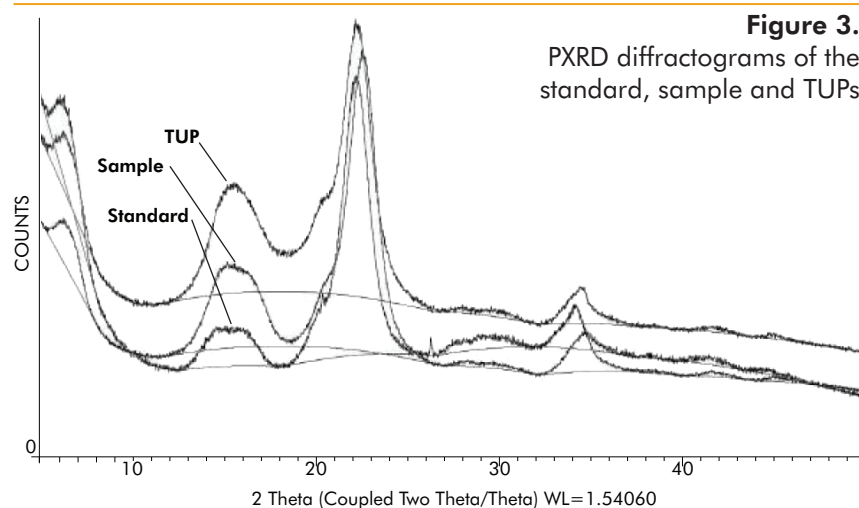
Such thermograms arising out of heating-cooling cycles served as a useful tool in assessment of polymorphic purity. Thus, the similar position, intensity and enthalpy of all of these thermograms suggested that microcrystalline cellulose existed in a similar polymorphic form in the TUPs and bulk MCC⁷. The insights gained from not by thermal analysis on the internal crystal habit

Figure 2. DSC thermograms of the standard, sample and TUPs

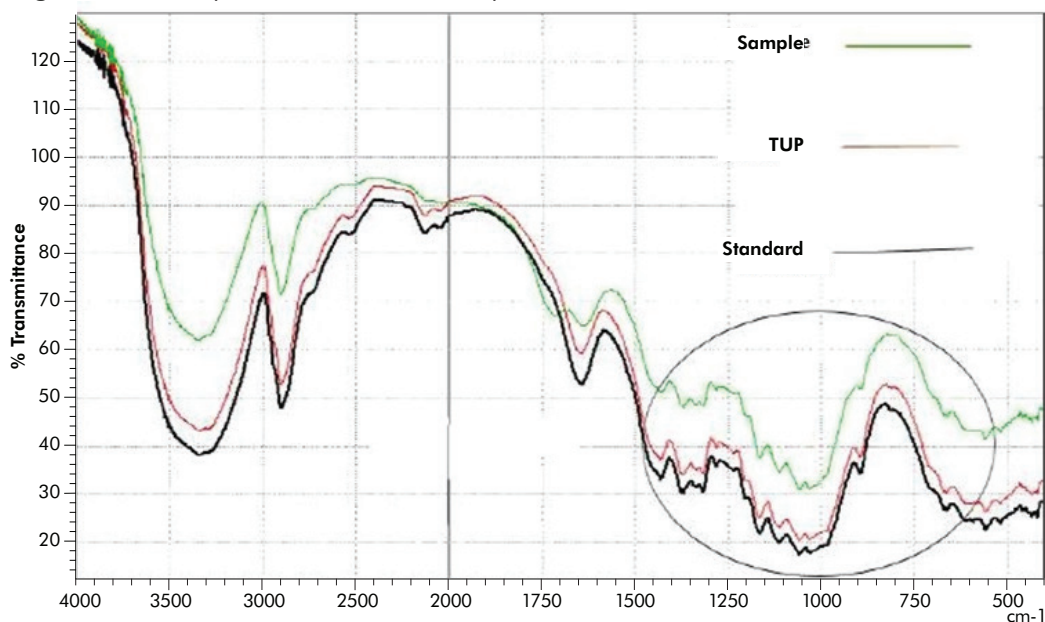
Thermal analysis of all the specimens using DSC (Figure 2) during the first- heating cycle, showed a broader endotherm in the temperature range of 80- 100°C corresponding to the loss of loosely bound water. The second sharp endotherm at temperatures greater than 275°C indicated melting of microcrystalline cellulose. During the second-cooling cycle, there was no thermal event, which was ascribed to the absence of any molecular re-organization in the specimens⁷.

were confirmed by the PXRD study.

PXRD profiles of all the specimens, as exhibited in Figure 3, showed principal diffraction peaks at 5.9, 15.1 and 34.5° 2θ values, corresponding to the same crystalline form of microcrystalline cellulose. Additional peaks at 22.4, 29.9 and 41.5° 2θ values

**Figure 3.**

PXRD diffractograms of the standard, sample and TUPs

Figure 4. FT- IR spectra of standard, sample and TUPs

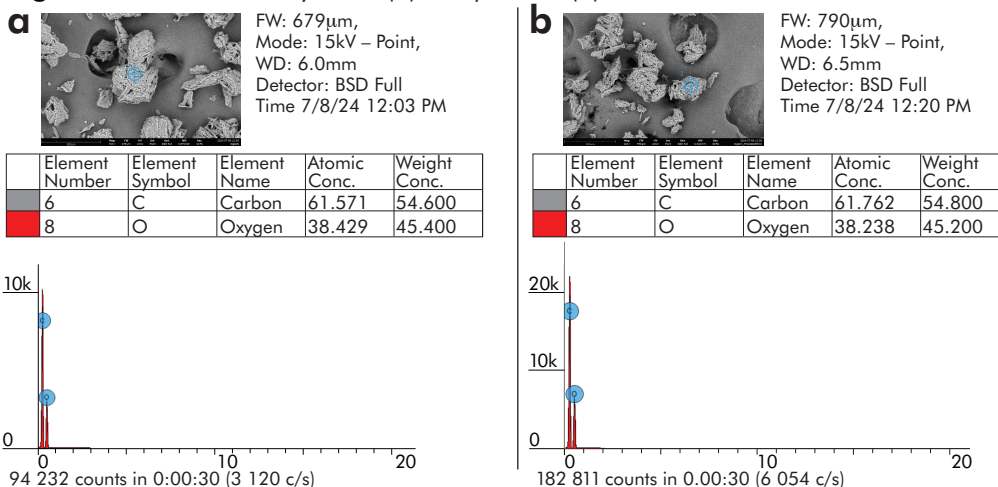
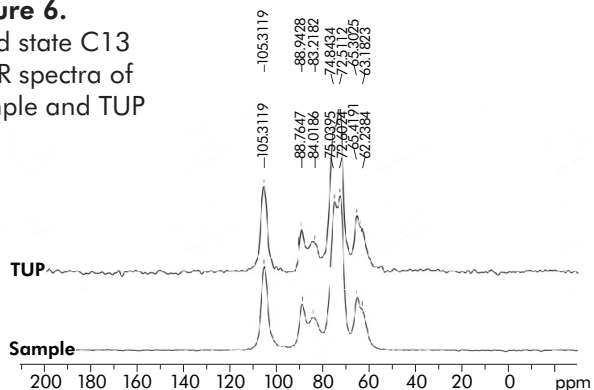
were of low intensity and diffuse. Characterization by these two techniques, DSC and PXRD, supported the view that TUPs were the same polymorph of MCC indicating that no polymorph conversion had taken place during generation of these materials during MCC processing.

Furthermore, FT- IR spectra of the Sample and TUPs were superimposable to that of the Standard (Figure 4). There were no additional peaks observed in the functional group

show that the elements present in the TUP specimens were qualitatively and quantitatively similar those present in Standard and Sample.

and fingerprint regions. This indicates that there was no alteration in the MCC molecular structure and functional groups in TUPs isolated following a spray drying process⁷. In other words, this analysis shows that TUPs are chemically similar to the MCC Sample and Standard.

A hyphenated technique, SEM-EDS, was used to detect the elements present on the surface of the test materials. Data generated (Figure 5)

Figure 5. Elemental analyses of (a) sample and (b) TUP**Figure 6.** Solid state C13 NMR spectra of sample and TUP

Superimposable SS-NMR spectra (Figure 6) provided further evidence that there was no change in chemical structure of the TUPs in comparison to the Sample. This confirmed that the different color (browning) of the TUP particles was not due to any significant change in the MCC chemical composition during spray drying process.

CONCLUSION

Microcrystalline cellulose was used as a surrogate excipient to explore ways to improve characterization of TUPs generated during manufacture of this excipient by spray drying. Results from SEM highlighted that TUPs were morphologically similar to the bulk excipient particles, with the only difference being that the former appeared discolored or charred. Comparable DSC thermograms for the TUPs and bulk excipient suggested unchanged internal solid-state structure of the TUPs that were putatively a result of overheating and friction during the MCC spray drying manufacturing process. Furthermore, the comparable diffraction patterns also indicate an unchanged crystal lattice, with the same polymorph for the TUPs.

The presence of superimposable FT-IR spectra in the fingerprint region, and quantitatively similar elemental composition from EDS, indicated chemical similarity between TUPs and the bulk excipient. The comparable chemical shift and intensity of principal peaks in SS-NMR spectra also confirmed their chemical 'sameness'. Hence, it was successfully established that technically unavoidable particles arising from normal MCC manufacturing conditions were only visibly different from the bulk excipient particles. In this study, the presence of such TUP particles did not affect purity of a bulk excipient, namely microcrystalline cellulose. In summary, this study provides a possible foundation for a testing framework to fulfil the investigational component to identify and characterize technically unavoidable particles in excipients, as expected by regulatory authorities.

REFERENCES

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