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Short communication

SEM/EDS analysis as a complementary tool for continuous improvement of cefixime granules for oral suspension

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ABSTRACT

The aim of this study was to evaluate scanning electron microscopy (SEM) combined with energy-dispersive X-ray spectroscopy (EDS) as complementary analytical tools for supporting continuous improvement in pharmaceutical granule manufacturing. Pilot-scale cefixime granules for oral suspension were prepared as defined process scenarios, including placebo, reference, intermediate, stress-exposed, and optimised batches. SEM was used to compare granule morphology, surface integrity, and agglomeration behaviour, whereas EDS provided qualitative and semi-quantitative information on localised elemental composition, with emphasis on sulfur as an API-related marker and oxygen-to-sulfur trends as surface-sensitive indicators of process- or stress-related variability. Intermediate and stress-exposed batches showed increased surface roughness, microstructural deterioration, and higher oxygen-to-sulfur ratios, whereas reference and optimised batches showed more uniform morphology and comparable elemental profiles. The findings indicate that SEM/EDS can provide useful material-level insight into process-related variability and may support root-cause investigation and process refinement. Overall, SEM/EDS is proposed as a complementary, localised, and semi-quantitative approach for supporting continuous improvement in pharmaceutical granule manufacturing.

Keywords: continuous improvement, SEM/EDS analysis, cefixime granules, pharmaceutical manufacturing, process variability

INTRODUCTION

Pharmaceutical manufacturing has progressively shifted from end-product testing toward science- and risk-based process control, where product quality is achieved through process understanding, lifecycle management, and continuous improvement rather than retrospective inspection (1–6). In solid oral dosage form manufacturing, wet granulation

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and drying are among the most variability-prone unit operations. Changes in liquid addition, mixing efficiency, drying conditions, or environmental exposure may affect granule morphology, residual moisture, dissolution behaviour, and content uniformity (7–12). Therefore, continuous improvement activities benefit from analytical tools capable of identifying material-level manifestations of process variability (13–15).

Scanning electron microscopy (SEM) enables direct visualisation of granule morphology, surface integrity, agglomeration behaviour, pores, cracks, and surface defects, while energy-dispersive X-ray spectroscopy (EDS) provides qualitative and semi-quantitative information on localised elemental composition (16–20). Although SEM/EDS is well established for solid-state and microstructural characterisation, its use as a complementary decision-support tool for continuous improvement in pharmaceutical granulation remains less extensively described.

Cefixime was selected as a model active pharmaceutical ingredient because of its sensitivity to moisture, temperature, and degradation-related structural changes. As a third-generation cephalosporin containing a β-lactam core and sulfur-bearing functional groups, cefixime may undergo hydrolytic or oxidative degradation under unfavourable processing or storage conditions (21–26). The presence of sulfur in the cefixime molecule enables the use of sulfur-related EDS signals as useful API-associated markers for comparative assessment of localised surface distribution and process-related heterogeneity (16, 19–21).

The aim of this study was to evaluate SEM and EDS as complementary, localised, and semi-quantitative analytical tools for supporting continuous improvement in pilot-scale manufacturing of cefixime granules for oral suspension. By comparing granule morphology and relative elemental trends across defined process scenarios, this short communication illustrates how SEM/EDS can provide material-level insight into process-related variability and support root-cause investigation and process refinement in pharmaceutical granule manufacturing.

EXPERIMENTAL

Materials and sample description

A structured panel of pilot-scale batches of cefixime granules for oral suspension was prepared to represent defined process scenarios relevant to pharmaceutical granulation and drying operations (8–11). The batches were designed to reflect controlled differences in process execution and environmental exposure rather than formulation development or commercial batch release evaluation.

The investigated formulations contained cefixime trihydrate as the active pharmaceutical ingredient in API-containing batches, together with a conventional excipient platform for oral suspension granules, including saccharide-based diluents, binders, suspending agents, flavouring components, and, where applicable, sodium benzoate as preservative (11, 12). Exact quantitative composition data are not disclosed due to industrial confidentiality considerations. However, all investigated batches were prepared using the same qualitative formulation framework, except where explicitly stated, to enable comparative SEM/EDS evaluation.

Anonymised batch codes were assigned to ensure confidentiality. The investigated batches were defined as follows: P–0, placebo batch without API and preservative; P–S, pla-

cebo batch containing sodium benzoate; R–1, reference API-containing batch manufactured under standard controlled process conditions; X–1, API-containing batch exhibiting typical in-process variability; A–1, API-containing batch exposed to elevated temperature and humidity; and N–1, optimized API-containing batch produced after targeted process adjustments.

Cefixime trihydrate was selected as a model API because of its sensitivity to moisture and thermal stress (21–26). Its β-lactam structure and sulfur-containing functional groups make it suitable for comparative SEM/EDS evaluation of process-related microstructural and surface elemental changes (16, 19–21). The investigated batches were not intended to represent a statistically powered process-validation study, but rather a structured set of representative process scenarios for exploratory and comparative SEM/EDS assessment.

SEM/EDS instrumentation and operating conditions

Scanning electron microscopy coupled with energy-dispersive X-ray spectroscopy was used to characterise the microstructural and localised elemental properties of the investigated cefixime granules (16–20). SEM was applied to assess granule morphology, surface integrity, agglomeration behaviour, microcracks, and localised surface features, whereas EDS was used as a qualitative and semi-quantitative tool for evaluating selected elemental signals associated with the formulation matrix and API-containing batches (16, 19, 20).

SEM analysis was performed using a field-emission scanning electron microscope, FESEM TESCAN MIRA LMU, equipped with an Oxford Instruments EDS detector, Aztec Ultra Max 40. SEM imaging was conducted under high-vacuum conditions at accelerating voltages of 5–15 kV. Lower accelerating voltages were used for surface-detail visualisation, whereas higher accelerating voltages enabled assessment of deeper topographical features and fracture surfaces (16–18). Magnifications between 150× and 3000× were applied to allow both general morphological evaluation and detailed inspection of localised microstructural features.

EDS microanalysis was performed at a working distance of approximately 10 mm, consistent with recommended analytical geometry for X-ray collection in SEM/EDS analysis (16, 19, 20). Representative EDS point spectra and corresponding semi-quantitative elemental compositions were acquired with emphasis on sulfur, which served as an API--associated elemental marker due to its presence in cefixime and absence from the placebo matrix (19–21). Carbon and oxygen signals were recorded as contextual indicators of the organic matrix and surface chemistry, but were not considered specific markers of API content or distribution. Oxygen-to-sulfur trends were interpreted only as relative, surface-sensitive indicators of process- or stress-related variability, rather than absolute compositional descriptors (19, 20).

Spectral acquisition times of 30–60 s were applied, with automatic peak deconvolution used to resolve overlapping emission lines. Due to the localised and surface-sensitive nature of SEM/EDS analysis, the obtained data were interpreted comparatively and semi-quantitatively, rather than as statistically representative bulk compositional measurements of the entire pilot-scale batch (19, 20).

Sample preparation for SEM/EDS analysis

Granules were handled under minimal mechanical stress to preserve their original morphology, in accordance with general sample preparation principles for SEM analysis

of particulate and non-conductive materials (16–18). Each batch was gently homogenised by rolling and tapping, and approximately 10–20 mg of sample was lightly dispersed onto aluminium SEM stubs pre-coated with conductive carbon adhesive tabs.

Because pharmaceutical granules have low intrinsic electrical conductivity, all samples were sputter-coated with a thin gold layer of approximately 5–10 nm using a Quorum Q150R ES sputter coater (16–18). The coating was applied to minimise beam-induced charging, reduce image drift, and support stable SEM imaging of non-conductive pharmaceutical materials. It did not interfere with the interpretation of sulfur-related EDS signals used as API-associated markers (16, 19, 20).

Given the moisture sensitivity of cefixime and related β-lactam antibiotics, samples were equilibrated in a desiccator for at least 2 h before sputter coating to reduce surface moisture and minimise preparation-related artefacts (21–26). After coating, each stub was inspected under a stereomicroscope to verify appropriate particle dispersion and coating uniformity. Representative fields of view were acquired from different areas of the prepared stubs at selected magnifications. The resulting SEM and EDS observations were interpreted as localised, comparative microstructural and semi-quantitative elemental assessments (19, 20).

RESULTS AND DISCUSSION

SEM and EDS analyses were performed under controlled analytical conditions to enable comparative evaluation of the investigated pilot-scale batches of cefixime granules for oral suspension. The EDS-derived elemental trends, particularly the oxygen-to-sulfur (O/S) ratio, were interpreted in a comparative and semi-quantitative manner, focusing on relative differences between batches rather than absolute elemental composition. This interpretation is consistent with the known limitations of EDS for quantitative analysis of light elements such as carbon and oxygen in complex organic pharmaceutical matrices (16, 19, 20).

Sulfur was selected as the primary API-associated elemental marker because it is present in the cefixime molecule and absent from the placebo excipient matrix. Carbon and oxygen signals were recorded as contextual indicators of the organic matrix and surface chemistry, but were not considered specific markers of API content or distribution. Accordingly, oxygen-related signal variations and O/S ratios were interpreted only as relative, surface-sensitive indicators of process- or stress-related variability, particularly when evaluated together with SEM-derived morphological observations (19, 20).

SEM imaging revealed distinct batch-dependent differences in granule morphology, surface integrity, and agglomeration behaviour (Fig. 1). The placebo batch without API and preservative (P–0, Fig. 1a) showed compact particles with predominantly smooth and continuous surfaces, limited surface roughness, and no visible microcracking or structural collapse. This batch served as a structural and elemental baseline for distinguishing excipient-related features from API- or preservative-associated effects.

The placebo batch containing sodium benzoate (P–S, Fig. 1b) also displayed compact granules with relatively smooth surfaces and coherent agglomerate formation. Localised surface features consistent with crystalline domains were observed and were interpreted as preservative-associated surface characteristics rather than evidence of microstructural deterioration. Given the expected low preservative concentration and the localised nature

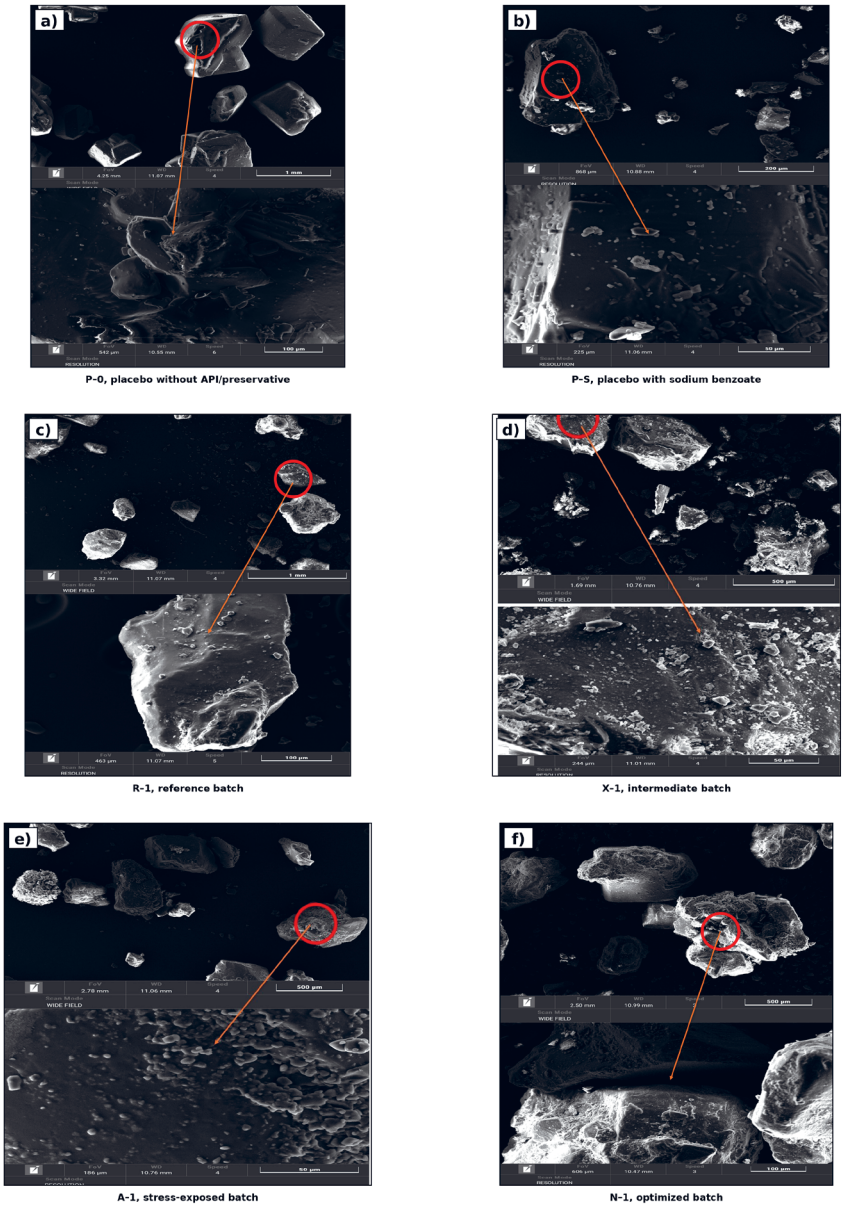

Fig. 1. Comparative SEM micrographs of the investigated pilot-scale cefixime granule batches: a) P–0, placebo batch without API and preservative; b) P–S, placebo batch containing sodium benzoate; c) R–1, reference API-containing batch produced under standard controlled process conditions; d) X–1, intermediate batch exhibiting process-related variability; e) A–1, stress-exposed batch; and f) N–1, optimised batch. Representative images are presented in a composite layout to facilitate direct visual comparison of granule morphology, surface integrity, and agglomeration behaviour.

of SEM/EDS analysis, these observations should not be interpreted as proof that sodium benzoate alone caused the observed morphology.

The reference API-containing batch (R–1, Fig. 1c), manufactured under standard controlled process conditions, showed uniform and mechanically coherent granules with smooth surfaces, well-defined particle boundaries, and limited structural defects. These features are consistent with balanced wet granulation, homogeneous binder distribution, and controlled drying conditions (8–10). In contrast, the intermediate batch (X–1, Fig. 1d) exhibited pronounced microstructural heterogeneity, including irregular agglomerate fusion, localised surface depressions, and increased surface roughness relative to the reference batch. These features suggest process-related variability, potentially associated with non-uniform liquid distribution, incomplete consolidation, or drying variability during wet granulation. However, SEM observations alone do not allow direct attribution to a specific unit operation.

The stress-exposed batch (A–1, Fig. 1e), subjected to elevated temperature and humidity, showed the most pronounced microstructural deterioration. SEM micrographs revealed surface roughening, pore enlargement, microcrack formation, and partial loss of granule compactness. These morphological changes are consistent with moisture- and temperature-associated structural alterations reported for cefixime and related β-lactam antibiotics (21–26).

Nevertheless, SEM should be regarded as a morphological tool and does not independently identify specific chemical degradation pathways. The optimised batch (N–1, Fig. 1f) displayed compact morphology and preserved surface integrity comparable to the reference batch, supporting the interpretation that targeted process adjustments contributed to improved material-level consistency relative to the intermediate batch. However, these findings should be interpreted as comparative SEM-based evidence rather than statistically validated proof of process robustness.

EDS analysis provided complementary comparative information on localised elemental composition and surface-related stability differences among the investigated batches (Fig. 2). The presented EDS data correspond to representative point spectra and associated semi-quantitative elemental compositions. Therefore, they should be interpreted as localised and semi-quantitative observations, not as elemental maps or statistically representative bulk compositional data.

As expected, the placebo batch without preservative and API (P–0, Fig. 2a) exhibited a carbon-oxygen background with no detectable sulfur or sodium signal, confirming its suitability as a structural and elemental reference matrix. In the preservative-containing placebo batch (P–S, Fig. 2b), localised sodium signals were detected, while sulfur remained undetected, as expected for an API-free formulation. Because EDS is localised and surface-sensitive, sodium detection in P–S should be interpreted as evidence of sodium-rich surface regions associated with sodium benzoate, rather than as an indicator of high bulk preservative content (19, 20).

In the reference batch (R–1, Fig. 2c), sulfur-related signals were detected in the representative EDS spectrum, supporting API-related surface presence under controlled processing conditions. Sodium-related signals were negligible or close to the detection limit and were interpreted qualitatively only. Therefore, sulfur-related profiles, rather than sodium signals, were used as the primary API-associated elemental indicators. Trace non-formulation-related signals, where present, were not used for interpretation.

The intermediate batch (X–1, Fig. 2d) showed reduced and more variable sulfur-related signal intensity, consistent with the microstructural heterogeneity observed by SEM. This

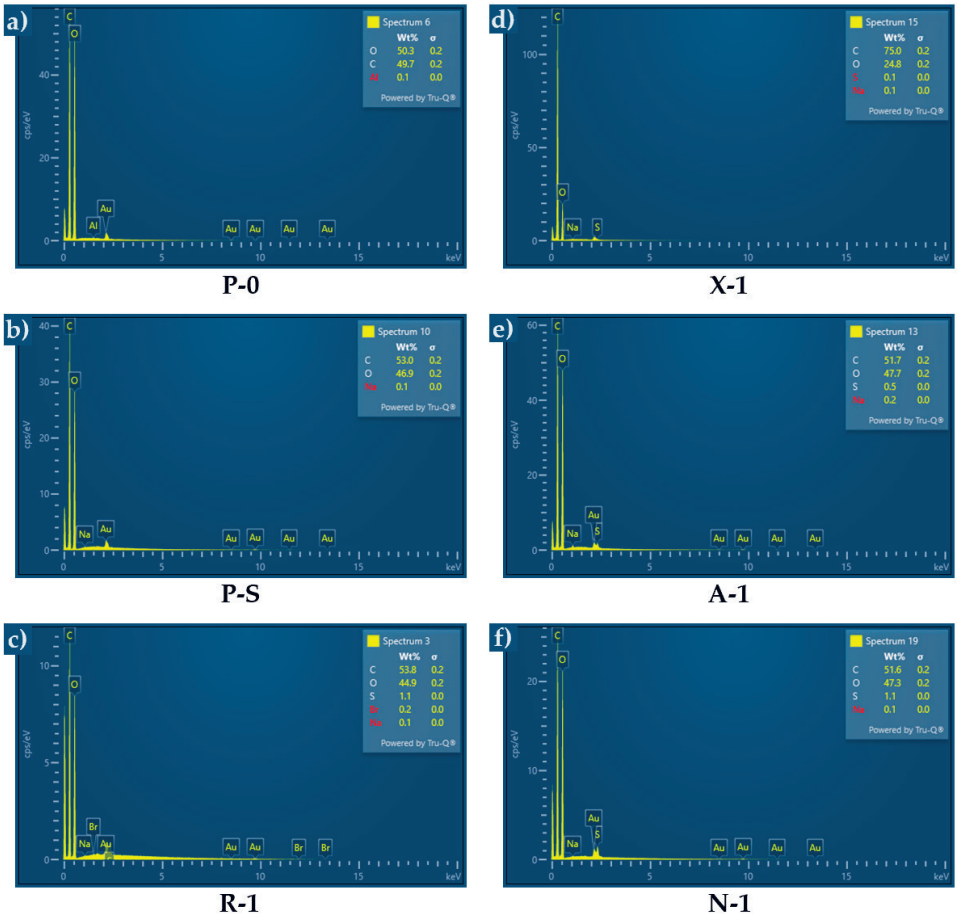

Fig. 2. Representative EDS point spectra and corresponding semi-quantitative elemental compositions of the investigated pilot-scale cefixime granule batches: a) P–0, placebo batch without API and preservative; b) P–S, placebo batch containing sodium benzoate; c) R–1, reference API-containing batch produced under standard controlled process conditions; d) X–1, intermediate batch exhibiting process-related variability; e) A–1, stress-exposed batch; and f) N–1, optimized batch. The spectra are presented as localised point EDS measurements and should not be interpreted as elemental maps or statistically representative bulk compositional data. Note: The EDS data are presented as representative point spectra with corresponding semi-quantitative elemental compositions. Abbreviations: EDS, energy-dispersive X-ray spectroscopy; API, active pharmaceutical ingredient; Wt%, weight percentage; σ, standard deviation; C, carbon; O, oxygen; S, sulfur; Na, sodium; Al, aluminum; Au, gold; Br, bromine; P–0, placebo batch without API and preservative; P–S, placebo batch containing sodium benzoate; R–1, reference API-containing batch; X–1, intermediate API-containing batch; A–1, stress-exposed API-containing batch; N–1, optimized API-containing batch.

suggests process-related heterogeneity affecting API-related surface characteristics rather than a change in the intended formulation composition. The stress-exposed batch (A–1, Fig. 2e) showed reduced sulfur-related signal intensity together with increased relative

Table I. Comparative summary of SEM-derived microstructural features, EDS-based elemental observations, and relative elemental ratios of the investigated pilot-scale cefixime granule batches

Sample	SEM morphology	Main EDS observation	O/S ratio	Na/S ratio	Interpretation
P–0	Compact placebo matrix; smooth surface; no visible microcracking	C/O background; no S or Na detected	–	–	Structural and elemental placebo reference
P–S	Compact placebo matrix with localised crystalline surface domains	Localised Na signal; no S detected	–	–	Sodium benzoate-associated surface domains; non-API-related heterogeneity
R–1	Smooth, compact granules with preserved surface integrity	Sulfur-related signal consistent with API-containing formulation; Na close to detection limit	40.8	0.09	Reference API-related surface profile under controlled processing conditions
X–1	Irregular surface topology and heterogeneous agglomeration	Reduced or variable sulfur-related signal	248.0	1.00	Process-related heterogeneity affecting API-related surface characteristics
A–1	Surface roughening, pores, microcracks, and partial structural deterioration	Reduced sulfur-related intensity with increased oxygen-related contribution	95.4	0.40	Stress-associated surface alteration
N–1	Compact morphology comparable to the reference batch	Sulfur-related profile comparable to R–1	43.0	0.09	Surface elemental profile comparable to the reference batch following process adjustment

Note: O/S and Na/S ratios were calculated from representative EDS point spectra and are used exclusively for comparative, semi-quantitative interpretation. They should not be interpreted as absolute compositional descriptors or statistically representative batch values. Abbreviations: SEM, scanning electron microscopy; EDS, energy-dispersive X-ray spectroscopy; API, active pharmaceutical ingredient; O/S, oxygen-to-sulfur ratio; Na/S, sodium-to-sulfur ratio; C/O, carbon-oxygen background; S, sulfur; Na, sodium; P–0, placebo batch without API and preservative; P–S, placebo batch containing sodium benzoate; R–1, reference API-containing batch; X–1, intermediate API-containing batch; A–1, stress-exposed API-containing batch; N–1, optimised API-containing batch

oxygen contribution at the granule surface. This trend is consistent with surface-level oxidative or hydrolytic transformations reported for cefixime under humid and thermal stress conditions (21–26). The optimised batch (N–1, Fig. 2f) showed sulfur-related and carbon-oxygen background profiles comparable to those of the reference batch, supporting recovery of API-related surface uniformity after process adjustment. The combined SEM/EDS interpretation is summarised in Table I. Elevated O/S ratios in X–1 and A–1 were interpreted as indicators of process- or stress-related surface variability, whereas the O/S ratio of N–1 was close to that of R–1, supporting improved surface elemental consistency. Na/S ratios were reported only as supportive descriptors and were interpreted with caution due to the low sodium signal intensity and its formulation-specific origin. Overall, O/S and Na/S ratios were used exclusively as relative surface-sensitive indicators and should not be interpreted as absolute compositional descriptors or statistically representative batch values.

Process understanding and continuous improvement relevance

The combined SEM/EDS findings indicate that process-related variability in cefixime granules is reflected in both microstructural features and localised elemental trends. The intermediate batch showed heterogeneous agglomeration and reduced sulfur-related signal intensity, suggesting that relatively small deviations in wet granulation conditions may lead to detectable material-level variability. Such variability may be associated with non-uniform granulating liquid distribution, insufficient mixing efficiency, or suboptimal binder distribution (8–10).

Drying and environmental exposure also appeared to influence granule integrity. The stress-exposed batch showed surface roughening, pore enlargement, microcracking, and an increased O/S ratio, indicating enhanced relative oxygen contribution at the surface. In moisture-sensitive β-lactam antibiotics, insufficient moisture removal or excessive thermal exposure may contribute to hydrolytic or oxidative degradation pathways (21–26). Therefore, the SEM/EDS observations support the importance of controlled drying conditions, residence time, and environmental exposure during manufacture and storage.

Faster and more widely available methods, such as loss-on-drying, Karl Fischer titration, sieve analysis, assay testing, dissolution testing, FTIR, NIR, or Raman spectroscopy, remain more appropriate for routine release testing, in-process control, and identification of out-of-specification results (5, 28–30). SEM/EDS is not proposed as a replacement for these methods. Its value lies in providing localised morphological and elemental information that can support root-cause investigation when conventional bulk methods indicate variability but do not explain its material-level origin.

Taken together, the combined SEM/EDS findings support the use of this approach as a complementary, localised, and semi-quantitative tool for process understanding and continuous improvement in pharmaceutical granule manufacturing. The observed elemental ratios were interpreted only as comparative indicators, not as absolute compositional measures or statistically representative batch descriptors. Therefore, SEM/EDS should be used together with conventional quality control and process analytical methods, particularly when additional material-level information is needed to support root-cause investigation, interpretation of process-related variability, and future process refinement.

CONCLUSIONS

This study indicates that scanning electron microscopy (SEM) combined with energy-dispersive X-ray spectroscopy (EDS) can provide useful material-level insight into process-related variability in the manufacture of cefixime granules for oral suspension. Applied in a structured, comparative, and semi-quantitative manner, SEM/EDS enabled differentiation of batch-dependent differences in granule morphology, surface integrity, agglomeration behaviour, and localised elemental profiles.

Sulfur-related EDS signals served as useful API-associated markers, while comparative oxygen-to-sulfur (O/S) trends provided surface-sensitive information related to process- or stress-associated variability. The intermediate and stress-exposed batches showed more pronounced microstructural heterogeneity and altered relative elemental trends, whereas the optimised batch showed morphology and elemental profiles comparable to the reference batch.

Overall, SEM/EDS should be regarded as a complementary diagnostic approach rather than a replacement for conventional quality control methods. Its value lies in providing localised morphological and elemental information that may support root-cause investigation, process understanding, and future refinement of pharmaceutical granulation processes.

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Author's contribution. – Conceptualisation, I.M.; methodology and investigation, I.M., D.K., and A.M.; writing, original draft preparation, I.M.; writing, review and editing, D.K., A.M., and G.P.; supervision, D.M. and O.P. All authors have read and agreed to the published version of the manuscript.

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