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Review Article

Process Analytical Technology for *Kupipakwa Rasayana*: Real-Time Thermal, Spectroscopic and Off-Gas Monitoring

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Abstract

Kupipakwa Rasayana preparation depends on the sequence of heating, observation, bottle closure and cooling, not simply on the highest temperature reached. Experienced practitioners assess fumes, flame and neck deposits to judge the progress of the process. These observations are valuable, but they are difficult to compare consistently across operators and manufacturing sites. This narrative review examines how process analytical technology (PAT) could support these decisions through thermal measurements, spectroscopy and off-gas monitoring. Published characterization studies of *Rasasindura* provide evidence of changes in mercury sulfide phases and particle characteristics during processing. They do not, however, establish a validated real-time control system. A proposed framework therefore begins with synchronized temperature records and documented classical observations, followed by at-line Raman analysis, selective gas measurements and correlation with final-product tests. Near-infrared spectroscopy may be more useful for moisture and herbal processing media before heating than for direct monitoring of mercury sulfide conversion. Important limitations include optical interference, unrepresentative sampling, sensor fouling and the possibility that instrumentation changes the bottle environment. Mercury exposure monitoring and engineered containment must be addressed independently of product characterization. Formulation-specific validation is needed before any sensor signal can guide closure, heating or batch release. PAT should initially strengthen process understanding and traceability; real-time release remains a longer-term objective requiring reliable analytical models, independent validation and regulatory acceptance.

Keywords: *Kupipakwa Rasayana*; *Rasasindura*; process analytical technology; Raman spectroscopy; thermal monitoring; mercury.

Introduction

Kupipakwa Rasayana is a group of *Rasashastra* preparations made by heating processed ingredients in a prepared glass bottle, or *Kupi*. Several formulations use mercury and sulfur; others include additional metals or mineral ingredients. Their identity depends on the prescribed preparation sequence and the location from which the finished material is collected.[1]

In practice, the difficult decisions concern transitions: when one heating stage has ended, whether fumes and deposits have changed as expected, and when bottle closure is appropriate. Published work on *Rajata Sindura* shows that traditional observations can be recorded alongside a temperature schedule rather than left entirely to memory.[2] Such documentation is a useful starting point, but it does not by itself establish which measurements predict acceptable product quality.

Process analytical technology (PAT) addresses this question by linking timely measurements of materials and process conditions to manufacturing decisions. The US Food and Drug Administration describes it as a framework for understanding and controlling manufacture, not as a requirement to install a particular instrument.[3] This review examines how that approach could be adapted to *Kupipakwa Rasayana*, with emphasis on thermal monitoring, spectroscopy and off-gas analysis. Its purpose is to propose a testable research framework, not a validated manufacturing procedure.

Scope and approach of the review

This is a focused narrative synthesis of the supplied manuscript and selected supporting literature. The cited *Rasasindura* and *Rajata Sindura* studies were checked against accessible journal or bibliographic records. Targeted web searches through 5 September 2026 used combinations of *Kupipakwa Rasayana*, *Rasasindura*, *Kajjali*, process analytical technology, thermal analysis, Raman, near-infrared and off-gas monitoring. FDA, ICH, EPA and NIOSH sources were consulted for analytical-development, validation and exposure-monitoring principles.

Priority was given to directly relevant characterization studies and authoritative methodological guidance. Incomplete references that could not be reliably identified were not retained. Classical terminology is discussed through published pharmaceutical descriptions; no new translation or verse-level textual analysis was undertaken. This was not an exhaustive database search, systematic review or meta-analysis. No new batches, patients, animal experiments or sensor datasets were studied. Proposed applications are distinguished throughout from measurements already reported in the literature.

What the material studies establish

Biswas and Bellare found predominantly beta-HgS with residual sulfur in the studied *Kajjali* and alpha-HgS in *Rasasindura*. Their thermal experiments, performed in air at a heating rate of 10°C/min, identified a sulfur-related event near 318°C and marked material loss at higher temperatures. The authors interpreted confinement and vapour transport as important to final-product formation.[4] These laboratory observations are useful mechanistic clues, but neither the reported temperatures nor the proposed pathway can be transferred unchanged to a production bottle. Atmosphere, sample mass, geometry and heating rate differ.

Mukhi and colleagues also identified alpha-HgS and an approximately 1:1 atomic Hg:S ratio in their *Rasasindura* sample, with nanoscale particles detected by microscopy.[5] These findings support phase and composition testing. They do not show that every batch has the same properties. Conversely, Gokarn and colleagues reported cubic HgS in *Rajata Sindura*, prepared over 33 hours.[2] That contrast argues for formulation-specific targets; it does not establish that added silver alone caused the phase difference. Table 1 separates the available findings from the proposed PAT uses.

Table 1. Evidence supporting the proposed monitoring framework

Evidence source	Reported contribution	Unresolved PAT question
Kajjali/*Rasasindura* study	Phase, thermal and particle characterization	Can a real-time signal predict the final phase?
Rasasindura characterization	Alpha-HgS and Hg:S characterization	How reproducible are attributes across batches?
Rajata Sindura standardization	Documented processing; cubic HgS reported	Which model is appropriate for this formulation?
General pharmaceutical PAT	Measurement-based process understanding	Can the approach transfer to a hot, coated *Kupi*?

Sources: published studies and FDA guidance.[2,3,4,5]

Defining the process before selecting sensors

The first task is to specify the product and its intended quality attributes. ICH Q8(R2) provides a useful distinction between material attributes, process parameters and quality attributes.[6] For this application, the mercury-to-sulfur ratio and *Kajjali* moisture are starting-material characteristics; heating rate and closure timing are process variables; phase composition and residual elemental mercury are potential product attributes. A parameter becomes critical only when evidence shows that its variability can affect a relevant quality attribute. Until then, these should be described as candidate variables.

Risk assessment should prioritize variables according to their potential consequences and the uncertainty surrounding them, following the general principles of ICH Q9(R1).[7] Bottle geometry, coating, batch load, sensor location and exhaust draw deserve attention alongside the nominal temperature schedule. These factors may change heat or mass transfer even when the furnace display looks normal. The framework is an adaptation of general pharmaceutical principles, not a claim that FDA or ICH guidance specifically approves these formulations. Table 2 outlines the proposed relationships.

Table 2. Candidate material and process variables

Category	Examples to document	Proposed quality link
Material attributes	Identity, Hg:S ratio, residual sulfur, moisture	Starting state and reproducibility
Equipment attributes	*Kupi* geometry, coating, furnace position	Heat transfer and deposition pattern
Heating parameters	Rate, holds, spatial temperature differences	Transformation and volatilization
Closure and cooling	Closure event, integrity, cooling history	Confinement and crystallization
Sampling conditions	Probe position, extraction flow, sample delay	Representativeness of analytical signals

Thermal monitoring and classical observations

A sensible first installation would record calibrated temperatures continuously at reproducible external locations, together with furnace operation and operator observations. The objective is to describe the temperature history experienced by the system. Furnace, bottle-wall and neck temperatures are not interchangeable. If an internal measurement is needed, it should first be assessed in a purpose-designed research setup because insertion can alter sealing, heat transfer and contamination risk.

The record should capture heating ramps, holding periods, transitions, closure and cooling, rather than only the maximum reading. Comparing several batches may reveal reproducible patterns or unexpected delays. An observed band of successful profiles is a reference envelope, not yet a validated design space. Its limits should be challenged against final-product results before they are used to authorize corrective actions.

Classical *Paka Lakshana* should be recorded independently, with predefined descriptions and timestamps. Video can help document visible changes, but lighting, background, lens deposits and camera position must remain controlled. Visible plume intensity is not a measure of mercury concentration, and flame colour alone does not identify gas composition. Agreement between observers should be assessed before their annotations are used to train a model. Table 3 gives examples of candidate pairings; these are hypotheses rather than established equivalences.

Table 3. Pairing classical observations with measurable records

Traditional checkpoint	Candidate record	Interpretive caution
Mridu Agni to *Tivra Agni*	Temperature–time profile	Ranges are formulation- and setup-specific
Fume and flame changes	Video plus selective gas analysis	Appearance does not identify chemical species
Shita Shalaka observation	Timestamped image; at-line deposit analysis	A local deposit may not represent the bed
Neck deposition	Image sequence and sample spectrum	Window fouling may resemble deposition
Bottle closure	Event log and associated sensor history	No single signal presently validates closure
Self-cooling	Recorded cooling curve	Instrumented and ordinary setups need comparison

Spectroscopy: start with accessible samples

Raman spectroscopy is a plausible candidate because it can provide solid-state information rapidly and can be used in pharmaceutical process monitoring.[8] For *Kupipakwa Rasayana*, the practical first question is whether a reproducible spectrum can be obtained from a safely collected, representative sample. Direct viewing through hot glass should not be assumed to work. Coatings, glass background, fluorescence, thermal radiation and deposits can obscure the signal.

A proposed feasibility study would compare independently characterized sulfur and HgS reference materials with *Kajjali* and accessible deposits. XRD should confirm the identity of reference phases. Mixtures spanning the intended range would be needed for quantitative calibration; a match to one reference spectrum is only an identification result. Elemental mercury should not be treated as a conventional molecular Raman reference or quantified by the absence of a Raman peak. It requires an appropriate mercury-specific method.

Laser power, acquisition time and sample temperature also need qualification. A spectrum is unreliable if the measurement itself changes the material. At-line analysis after controlled sampling may therefore be more informative than an unstable in-line probe. Any improvement in analytical speed must be balanced against sampling delay and the possibility that the sample changes while cooling.

Near-infrared (NIR) spectroscopy has a different role. General pharmaceutical literature describes its use alongside Raman for rapid process measurements.[9] NIR may be useful for moisture after *Bhavana* or variability in organic processing media, provided it is calibrated against a suitable reference method. Its sensitivity to water, physical scattering and matrix changes requires careful interpretation.[10] It should not be presented as an

established direct assay of HgS phase purity. Table 4 compares the proposed measurement options.

Table 4. Measurement options and practical limits

Tool	Most plausible initial use	Main validation concern
Thermocouples/data logger	Continuous external thermal history	Calibration, placement and thermal lag
Camera	Document fumes, flame and deposits	Lighting and progressive lens fouling
At-line Raman	Identify phases in accessible deposits	Sampling bias and laser-induced change
NIR	Pre-heating moisture or media uniformity	Matrix-dependent calibration
Extractive FTIR	Selected infrared-active exhaust gases	Line losses, interference and response lag
Mercury-specific analyser	Workplace or exhaust Hg-vapour trends	Species response and aerosol exclusion

Proposed applications; Raman and NIR capabilities are informed by pharmaceutical spectroscopy literature.[8,9,10]

Off-gas monitoring and occupational protection

Off-gas analysis could help identify when gaseous emissions change, but the emitted species should first be investigated rather than assumed. The furnace exhaust may combine bottle emissions, fuel combustion products and room air. A sample from that stream is therefore not automatically a direct measurement of the reaction inside the *Kupi*. Sampling position, dilution and flow must accompany every concentration record.

Naddour and colleagues used gas-analysis methods in research on sulfur protection for sensors in glass furnaces.[11] This is an adjacent engineering example, not evidence of a validated *Kupi*pakwa system. EPA Method 320 provides a methodological reference for extractive FTIR measurements of suitable vapour-phase compounds.[12] Adaptation would require checks for spectral interference, condensation, recovery, instrument range and transport delay. Ordinary gas-phase FTIR does not measure elemental mercury vapour; a separate mercury-specific technique is necessary.

Mercury vapour, particle-bound mercury and other mercury species cannot be assumed to produce equivalent analyser responses. Workplace exposure assessment should therefore combine appropriate direct-reading instruments with a sampling strategy designed by an occupational hygienist. Area readings may reveal emission events but do not replace personal exposure measurements. NIOSH identifies inhalation and other exposure hazards for mercury compounds and lists dedicated measurement methods.[13]

For the proposed platform, loss of exhaust flow, analyser malfunction and a rising exposure signal should trigger a predefined safety response independently of any quality-prediction model. Capture systems, compatible gas treatment, contaminated filters, washings and spent adsorbents need an engineered waste-management plan. No universal alarm threshold or improvised scrubber design is proposed here. Applicable local requirements, species measured and averaging periods must be established before operation.

Closure, pressure and engineering fidelity

Closure changes the boundary conditions of the process and must be treated as a major recorded event. It should not be automated on the basis of a declining sulfur signal alone. That decline could reflect sample-line blockage, altered extraction or instrument failure rather than a genuine process endpoint. A future closure model would need several independent signals, explicit uncertainty limits and confirmation against the resulting product.

Pressure measurement is a research question, not a recommendation to modify and pressurize an ordinary glass bottle. Instrumented studies require qualified engineering design, compatible materials, containment and an independent hazard assessment. Their results must then be compared with the established pharmaceutical setup. A research reactor may improve access for sensors while changing precisely the vapour transport and condensation behaviour under study. Preserving process fidelity is therefore part of validation, not merely a historical preference.

Quality attributes and the limits of characterization

A chemical identity result and a safety conclusion answer different questions. Mercury sulfide differs toxicologically from more soluble mercury compounds, but chemical form alone does not establish safety at a given dose or duration.[14] This review does not assess clinical efficacy or recommend patient use. Occupational inhalation hazards also remain relevant even when a collected product is predominantly HgS.

Final-product testing remains essential during PAT development. XRD addresses crystalline phase identity; XPS is surface-sensitive; elemental methods measure composition rather than automatically identifying chemical species. “Not detected” must be accompanied by a method and detection limit. Similarly, electron microscopy may show small primary particles while a dispersion method measures much larger agglomerates. Those measurements should not be reported as interchangeable particle sizes. Table 5 sets out the proposed reference measurements and the limits of their interpretation.

Table 5. Reference tests for evaluating PAT predictions

Candidate attribute	Reference approach	What must not be inferred
Crystalline phase	XRD; validated quantitative analysis if needed	Absence of every amorphous or trace impurity
Surface chemical state	XPS with suitable standards	Complete bulk mercury speciation
Hg and S compositio n	Validated elemental assays and mass balance	Chemical form from total concentration alone
Residual elemental mercury	Validated species-appropriate assay	Absence based only on XRD or Raman
Residual sulfur	Validated selective chemical/thermal method	Specific sulfur content from total mass loss
Particle characteristi cs	SEM/TEM; justified dispersion-based sizing	Equivalence of primary and aggregate size
Yield and deposit location	Gravimetry and collection records	Acceptable safety or potency from yield alone

Proposed test panel informed by the characterization studies.[4,5]

Validation, data integration and release decisions

Analytical development should begin with the intended decision. A method for identifying an unusual spectrum has different requirements from one intended to estimate a phase fraction or support batch release. ICH Q14 and Q2(R2) provide complementary frameworks for defining analytical performance, developing procedures and validating their use, including spectroscopic applications.[15,16] For this proposal, each instrument must be qualified before its data are combined with other signals.

Time synchronization is particularly important. A gas analyser may display an event after a camera records it because of transport through the sampling line. Calibration records, raw data, preprocessing choices, missing values and sensor replacements should remain traceable. The proposed integrated record would retain temperature history, spectra, gas concentrations, video annotations, closure time and final-test results under one batch identifier.

Initial analysis should favour interpretable summaries over unnecessarily complex models. Candidate features include stage duration, thermal gradients, selected spectral ratios and gas-event timing. A multivariate model should be tested on entirely independent batches, not merely random spectra taken from the same batch. Otherwise, apparent accuracy may reflect repeated measurements of nearly identical material. Different raw-material lots, operators and equipment conditions should be represented where the intended model use includes them.

Model uncertainty, false acceptance and behaviour outside the calibration range deserve as much attention as correlation coefficients. Failed batches and deviations must be retained. If a sensor fails or the model encounters an unfamiliar condition, the system should revert to an approved fallback rather than infer normal operation. Changes to software, probes and calibration models should be controlled within a quality system, consistent with the lifecycle approach in Q10.[17]

A staged development path is preferable to immediate feedback control. FDA process-validation guidance emphasizes evidence across process design, qualification and continued verification.[18] Table 6 translates that principle into a proposed research sequence. The number of batches should be justified from expected variability and the intended prediction task; a large number of spectra does not compensate for too few independent batches.

Table 6. Proposed staged validation pathway

Stage	Evidence to collect	Decision gate
Observation	Synchronized sensors and independent *Paka* records	Measurements are reliable and non-disruptive
Characteriz ation	Intermediate and final reference tests	Signals have plausible material associations
Model developmen t	Multiple independent, varied batches	Performance criteria and uncertainty are defined
External validation	Batches excluded from model training	Predictions remain accurate in intended use
Limited feedback	Supervised actions within approved bounds	Quality improves without added safety risk
Continued verification	Drift, deviations and lifecycle records	Performance remains acceptable after change

Author-proposed pathway informed by analytical and process-validation guidance.[15,16,18]

Real-time release testing remains a longer-term possibility rather than a current outcome. It would require validated links between process measurements and all relevant release attributes, an approved control strategy and appropriate regulatory acceptance. A familiar temperature

profile cannot substitute for an unmeasured impurity, stability characteristic or other required quality test. Routine final testing should continue throughout early development.

Discussion

The strongest case for PAT is not that it makes *Kupipakwa Rasayana* modern, but that it can make important manufacturing decisions more transparent. A recorded observation can be reviewed; a synchronized analytical record can be compared across batches. Together, they may help explain why apparently similar heating schedules produce different outcomes.

The evidence is uneven. Material characterization supports the choice of candidate quality attributes, and general pharmaceutical literature supports the availability of rapid analytical tools. Neither establishes that a specific probe, spectral feature or gas peak is a valid endpoint in a *Kupi*. The central research gap is the missing relationship between time-resolved signals and independently measured batch quality.

Several practical errors could undermine an otherwise sophisticated system. A neck deposit may not represent the entire charge. An exhaust signal may be dominated by dilution. A camera may track window fouling rather than the process. A model trained only on successful batches may be unable to recognize failure. These problems favour a modest first platform with dependable thermal records, structured observations and exposure surveillance, followed by targeted analytical additions when their value is demonstrated.

This review is limited by its focused, non-systematic search, the small number of directly relevant material studies and the absence of an experimentally tested integrated platform. The proposed architecture also requires cost, maintenance and staff-training assessment. Formulation-specific validation is essential; conclusions for *Rasasindura* should not be extended automatically to *Makaradhwaja*, *Rajata Sindura* or *Tamra Sindura*. Most importantly, reproducible manufacture and demonstrated clinical safety are separate goals.

Conclusions

PAT offers a practical way to investigate the decisions already embedded in *Kupipakwa Rasayana* preparation. The immediate priorities are reliable thermal histories, clearly documented *Paka Lakshana*, appropriate exposure monitoring and reference testing of the finished material. At-line Raman, selective off-gas analysis and pre-heating NIR may add useful information after feasibility studies. Their signals must be validated before they guide closure, heating or release. A successful platform would preserve pharmaceutical identity while making manufacturing more reproducible, traceable and accountable; those benefits remain objectives to be demonstrated rather than established outcomes.

Declarations

Ethics approval and consent to participate: Not applicable. This narrative review reports no new human or animal research.

Consent for publication: Not applicable. No identifiable participant information is included.

Availability of data and materials: No new experimental datasets were generated. Supporting literature is identified in the references.

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