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DETECTING IMPURITY TRENDS BEFORE BATCH RELEASE USING STATISTICAL PROCESS MONITORING IN GENERIC TABLET MANUFACTURING

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Abstract

It is very crucial to detect and control impurities in generic tablet making for the quality, safety of pharmaceutical products and its regulatory compliance. Impurity related issues are typically discovered during or at the end of the laboratory testing process, and can cause manufacturing delays and higher manufacturing costs due to delaying the release of batches. This study aims to identify the trends of impurities in advance before batch release using Statistical Process Monitoring (SPM) techniques in the manufacturing process of generic tablets. The research examines the impurity concentration trends, batch-to-batch variability and possible process deviations with statistical monitoring techniques. Pharmaceutical historical batch data and impurity testing data can be used to evaluate variations in critical quality attributes. Unusual impurity patterns or early signs are detected with the use of statistical tools such as Shewhart control charts, Exponentially Weighted Moving Average (EWMA) and Cumulative Sum (CUSUM) charts. The paper also investigates the effect of manufacturing parameters on the impurity formation and tries to limit the sources of process variation. Process capability analysis is applied to assess the consistency of manufacture and to see if impurities are kept in acceptable quality limits. The proposed monitoring approach offers a structured process to detect trends in impurities as they arise, prior to final batch release, to enable early investigation and corrective action. In conclusion, the study demonstrates the possibility of using statistical process monitoring to enhance pharmaceutical quality assurance, improve manufacturing consistency, minimize risk of non-compliant batches and facilitate more confident batch release decisions in generic tablet manufacturing.

INTRODUCTION

The manufacturing of generic tablets is an essential component of the pharmaceutical business because it delivers inexpensive and obtainable drugs to patients while adhering to the requirement for quality, safety and effectiveness. The process of making generic tablets involves a number of stages which involve selection of raw materials, weighing, mixing, granulation, drying, compression, coating, and packaging. It is essential that each stage is monitored thoroughly in order to ensure that the finished pharmaceutical product is of acceptable quality. Nevertheless, differences in raw materials,

manufacturing processes, machinery performance, and environment, as well as storage conditions, can impact the quality of the products and lead to the generation and/or accumulation of impurities. Therefore, monitoring of impurities is an important part of pharmaceutical quality assurance and pharmaceutical manufacturing control [17,19,28].

Pharmaceutical impurities are those chemical impurities which can be encountered in API, excipients or in tablet formulation. These impurities may be present in the raw materials, during manufacture; from the chemical degradation of the material; from contamination; from residual solvents; or the interaction of the active ingredient(s) and formulation ingredients. Impurities can be of organic, inorganic, residual solvent, elemental and degradation origins based on their chemical characteristics. They can interfere with the stability, purity, safety and therapeutic activity of pharmaceutical products if present at levels above acceptable. The International Council for Harmonisation (ICH) has given specific guidelines for identification, reporting, control and qualification of impurities in pharmaceutical substances and in finished drug products [1,2,3,4].

The manufacturing of tablets can be modified in order to affect the formation of impurities. Factors that can affect the product's degradation include temperature, humidity, moisture content, processing time, pH level, light exposure and interactions between the active pharmaceutical ingredient and the excipients. For instance, moisture content of granulation or drying may lead to increased hydrolytic degradation risks in moisture sensitive pharmaceutical products. Likewise, the storage conditions and extended periods at elevated temperatures can speed up chemical reactions and increase the generation of degradation products. The concentration of impurities may also vary from batch to batch, depending on the manufacturing variations. Hence, it is useful to know what sources of impurities are possible to reduce the risk of manufacturing deviations and to maintain the consistency of the product quality [11,16].

The traditional approach to pharmaceutical quality control is testing raw materials, in-process materials, and finished product to ascertain if they are within specific limits. For identification and quantification of pharmaceutical impurities, high-performance liquid chromatography (HPLC), gas chromatography (GC) and other validated analytical tools are often employed. These techniques give a useful insight into the concentration of impurities and its chemical nature. But laboratory testing alone may not give enough information about changes in the levels of impurities over a number of manufacturing batches. An impurity concentration can slowly increase over successive batch production cycles, while this batch meets the acceptance criteria established for the batch. Change is a sign of an incipient manufacturing problem which needs to be investigated before the level of the impurity becomes unacceptable [5,12].

Background of the Study

In the pharmaceutical industry, generic tablet manufacturing is a crucial process because it supplies cost-effective medicines without compromising the quality, safety, and therapeutic effectiveness that are established. Manufacturing of generic tablets includes a number of operations, such as handling of raw materials, weighing, mixing, granulation, drying, compression, coating and packing. Each operation may have impact on the chemical stability and quality of the final pharmaceutical product. Impurities can form or be collected during the manufacturing process, due to variations in raw material, processing conditions, equipment performance and environmental factors [17,19].

Pharmaceutical impurities are unwanted substances which may have occurred from the active pharmaceutical ingredients, excipients, manufacturing methods, chemical degradation, or contamination. They must be identified, quantified and controlled properly to assure that the final product meets quality standards. Various types of impurities are associated with the various categories of impurities such as organic impurities, inorganic impurities, residual

solvents, elemental impurities, and degradation products, which can be suitably analyzed and monitored [1,2,3,4].

Problem Statement

One of the most challenging issues in the production of generic tablets is the control of impurities which may be affected by variability in raw materials, manufacturing processes, equipment and environmental conditions, and thus can result in an impurity concentration in the finished pharmaceutical product that varies from product to product. Traditional methods of quality control are mainly used to decide whether individual batches meet pre-established impurity standards. However, this method might not be sensitive enough to detect slow changes, multiple changes or unexpected impurity trends over a sequence of manufacturing batches. A batch can meet the previously mentioned impurity acceptance criteria and exhibit an increasing impurity trend versus the previous production batches. Unless these changes are recognized, they could be signs of manufacturing issues, leading to product stability, quality and regulatory issues over time. When the cause of these variations is not identified at the right time, there can be a rise in follow-up investigations, corrective actions, batch rejection and production expenses.

Research Objectives

1. To compare the concentration of impurities in various batches produced in pharmaceutical manufacturing.
2. To evaluate statistically the amount of impurities in different batches.
3. To use Shewhart control charts to detect abnormal variations in impurities.
4. To compare the effectiveness of EWMA chart and CUSUM chart for detection of small and gradual changes in the impurities.

Research Questions

1. What are the different types and sources of impurities during manufacturing of generic tablets?
2. What is the variability of the concentrations of impurities between different batches of manufacturing?
3. Do EWMA and CUSUM charts show where impurities are beginning to change gradually, prior to breaching known specification limits?
4. What are some signs that would suggest the possible presence of impurities during manufacturing?
5. How does the concentration of impurities vary with the chosen manufacturing parameters?
6. What is the effectiveness of process capability analysis in assessing the consistency of manufacturing?

Scope of the Study

This study focuses only on the detection and statistical evaluation of impurities trends in generic drug tablet manufacturing prior to release of the final tablet batch. It deals with the study of impurity concentration profiles of various manufacturing batches and the use of statistical process monitoring techniques for recognizing abnormal variations. Review of production processes and factors that could affect the generation of impurities in generic tablet products. Assessment of relevant organic impurities, inorganic impurities, residual solvents, elemental impurities and degradation products as per the available analytical information. Evaluation of previous batch records, laboratory test results and related manufacturing process information. Use of Shewhart control charts, Exponentially Weighted Moving Average (EWMA) and Cumulative Sum (CUSUM) techniques to detect unusual patterns of impurities. Determination of the difference in impurity concentrations from one batch of manufacture to another. Determination of manufacturing consistency by using the suitable statistical capability indices such as Cp and Cpk if applicable. Detection of potential deviations related to the impurities before the concentrations are beyond the acceptance limits. Assessing the role of statistical monitoring in manufacturing investigations, QA activities and informed batch release.

LITERATURE REVIEW

Pharmaceutical manufacturers need to have effective quality management systems in place to guarantee the quality of the medicines produced is safe, pure, strong and effective. In the manufacture of general tableting, contamination with undesirable chemical impurities can occur during handling of the raw materials, formulation, processing, storage and transport of the product and is therefore an important facet of pharmaceutical product quality control. The presence of impurities can have impact on stability and quality of product, identification, quantification and control of these impurities is essential throughout the manufacturing process [1,2].

Impurity profiling, analytical method validation, statistical quality control and process monitoring are highlighted in previous research and in pharmaceutical guidelines. While conventional quality control assesses if individual batches meet specified requirements, statistical process monitoring also gives information regarding the variation and trends of successive batches. The approaches can be used to prevent undesirable product quality in the manufacturing process [17,18,28].

In this chapter the major types and sources of pharmaceutical impurities are reviewed, along with factors that influence the formation of impurities, analytical methods for impurity profiling, and quality assurance practices during pharmaceutical manufacturing. Other topics covered include statistical process monitoring, applications of control charts, process capability analysis, identifying trends of impurities at the beginning of a process, and international regulatory guidelines. The review provides a scientific basis for implementation of statistical monitoring methods for the purpose of further enhancing the detection of impurities prior to batch release in generic tablet manufacture.

Types and Sources of Impurities in Tablet Manufacturing

Pharmaceutical impurities: unwanted chemical and/or physical substances which may be present in the finished pharmaceutical product, intermediate product, active pharmaceutical ingredient or excipients. They can be a consequence of raw material contamination, chemical reactions, production processes, degradation or storage issues. It is important to determine the type and source of the contaminant to determine suitable monitoring and control measures [1,2,12].

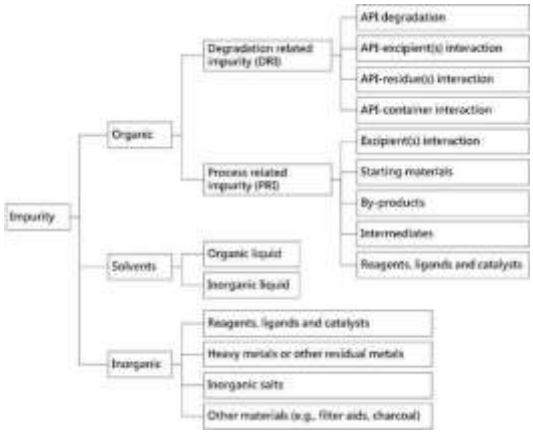

Fig. 2.1 Types and Sources of Impurities in Tablet Manufacturing

These can be from starting materials, intermediates, manufacturing by-products or degradation. Unwanted degradation products can form during tablet manufacture and storage due to oxidation, hydrolysis, photolysis or other reactions that take place. Their concentrations may be different depending on the chemical

properties of the drug substance and environmental conditions [11,12].

Sources of inorganic impurities can include filters, manufacturing utilities, raw materials, processing equipment and catalysts. These impurities may be introduced to the pharmaceutical formulations in various production stages. They must be evaluated appropriately for their presence to guarantee they are not outside the quality and safety limits applicable to them [1,14].

Factors Affecting Impurity Formation

Several factors such as chemical, physical, environmental and operational factors contribute to the formation of impurities in generic tablet manufacture. These could impact the stability of the active ingredient, interactions between formulation ingredients, and the quality of the end product tablets. The knowledge of these variables is crucial to foresee potential causes of variations in impurities and to set up appropriate manufacturing controls [1,2,11].

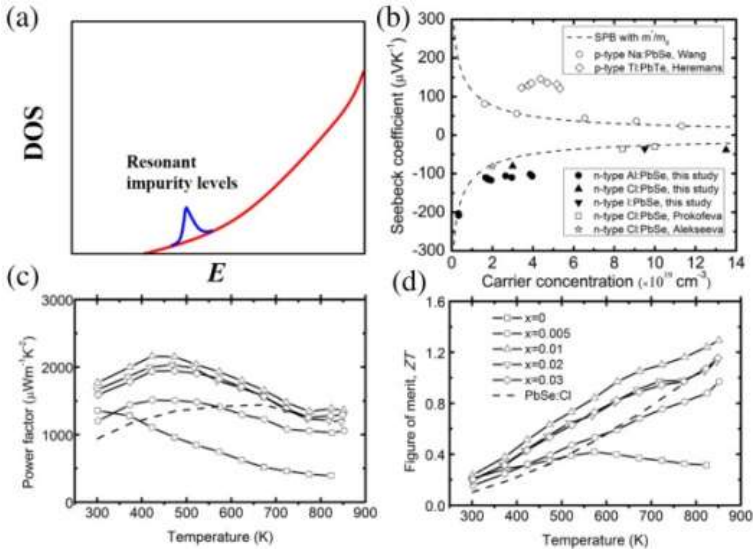

Fig. 2.2 Factors Affecting Impurity Formation

Temperature is one of the main factors affecting the degradation of pharmaceuticals. Too high a temperature in the drying, granulation, compression or storage process can speed up chemical reactions in the material and lead to increased degradation product formation. Active pharmaceutical ingredients (APIs) that are sensitive to temperature must be tightly controlled in the manufacturing process and are also sensitive to storage conditions [2,11].

Moisture may be a contributing factor to hydrolysis or other chemical degradations. Humidity control is crucial for the storage, granulation, drying and packaging of some pharmaceutical ingredients, as they can be very sensitive to humidity. Moisture content fluctuations may also impact tablet stability and manufacturing uniformity [11,14]. Susceptible pharmaceutical products can oxidise when exposed to oxygen in the atmosphere. This process can yield undesirable chemical compounds and alter the impurity content of the tablets produced. Proper packaging, storage conditions, and formulation methods can minimize oxidation degradation [11,12].

Impurity Profiling and Analytical Techniques

Impurity profiling encompasses the identification, characterization and quantification of undesirable substances in pharmaceutical ingredients and finished products. It plays a significant role in pharmaceutical quality evaluation, since it gives insight on the chemical purity, degradation

properties and potential quality risks of pharmaceutical formulations. For the successful impurity profiling, the analytical methods shall be accurate, precise, sensitive and appropriate for the intended use of the method [5,6,11]. HPLC can separate the various chemical components and quantify them within a sample, making it a popular method for the analysis of impurities in pharmaceuticals. It is especially helpful to detect organic impurities and degradation products in tablet formulations. When chromatographic conditions and validated procedures are used, the technique can give reliable analytical results [11,12].

GC is widely used to determine volatile and residual organic solvents in pharmaceutical materials. It offers information on solvent concentrations and if pharmaceutical products meet residual solvent requirements applicable to them [3].

Pharmaceutical Quality Control and Quality Assurance

Looking at pharmaceutical quality control and quality assurance, it is clear that these are integral parts of a pharmaceutical manufacturing system that ensures that medicines are produced to meet the quality requirements. These are very similar functions, but have different roles in pharmaceutical manufacturing. Quality control is mainly associated with sampling, testing and evaluation of materials and finished products, while quality assurance is associated with maintaining systematic procedures that will assure the quality of products during the manufacturing process [17,19].

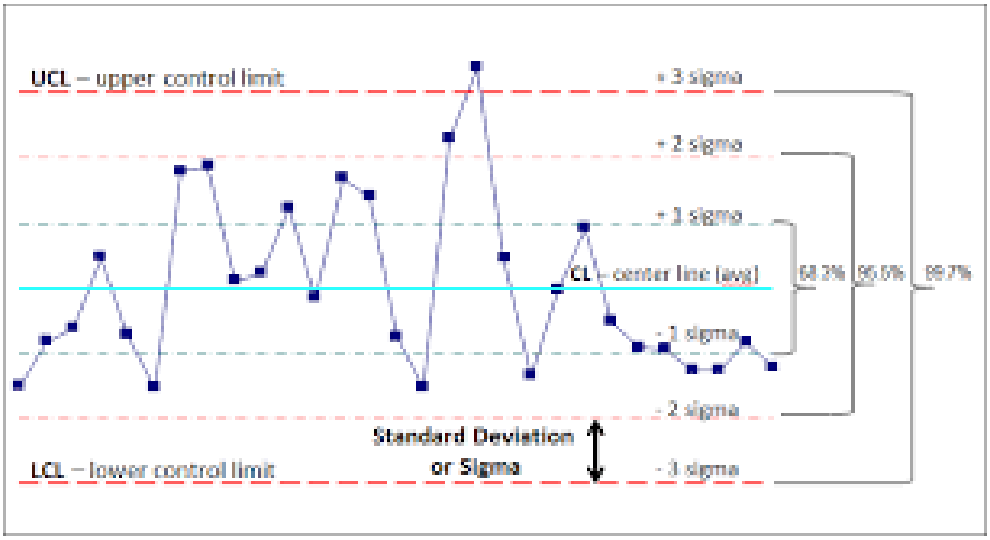

Fig 2.3 Pharmaceutical Quality Control and Quality Assurance

Laboratory examinations of raw materials, intermediate products and finished tablets are performed in quality control departments. The tests that can be performed for these include identification testing, assay determination, dissolution testing, content uniformity, impurity profiling, and stability assessment. To ensure that materials and products meet the required quality, they are compared to approved specifications [1,2,10].

Statistical Process Monitoring: Concepts and Applications

Statistical Process Monitoring is a systematic method of assessing the performance of a process by applying statistical techniques and searching for unusual variations that occur over time. It includes gathering and arranging process information, analyzing and interpreting that information to decide if the manufacturing operations are continuing to operate as they would be expected to. In the pharmaceutical

industries, statistical monitoring can be used for the concentration of impurities, assay of the active ingredient, moisture content, dissolution value, production temperature, etc. critical quality parameters [28,30].

The primary mission of the statistical process monitoring is to separate common cause variation from special cause variation. Common-cause variation is the natural variation that occurs in a manufacturing process when it is operating normally. Special cause variation is caused by rare and unusual occurrences, like a change in raw materials, incorrect processing conditions, unexpected environmental influences or equipment malfunction. It is essential to recognise these differences to ensure manufacturing consistency and to avoid reoccurring quality issues [23,24,28].

RESEARCH METHODOLOGY

The research design of this study is quantitative, observational, and analytical, which is used to study the trend of impurities before batch release in the manufacturing of generic tablets. The research is focused on the evaluation of pharmaceutical impurities concentration in various manufacturing batches by statistical process monitoring techniques. Historical laboratory testing data, manufacturing batch data and quality control data are used for variations and abnormal trends in levels of impurities.

The quantitative approach can be used to quantify impurity levels, batch to batch variations, process stability, and manufacturing consistency. The use of statistical methods such as descriptive statistics, Shewhart control charts, Exponentially Weighted Moving Average (EWMA) and Cumulative Sum (CUSUM) are used to detect potential impurity trends. Process capability analysis is also used to determine if manufacturing processes are able to consistently contain impurities within specification limits.

The research design is a systematic methodology that is used to assess the usefulness of statistical monitoring as an additional quality assurance tool prior to the release of a pharmaceutical batch.

Study Setting

The study is based on the generic tablet manufacturing operation and pharmaceutical quality control activities. The research environment is a set of manufacturing departments, quality control laboratories and quality assurance sections participating in the manufacture and evaluation of generic tablet formulations.

The manufacturing environment consists of various manufacturing processes including raw material handling, weighing, mixing, granulation, drying, compression, coating, and packaging. Where available, information from these operations is used to explore potential correlations between manufacturing and impurities.

Laboratory testing documents contain details on the concentration of impurities and other relevant quality parameters. Process information is recorded through manufacturing documentation and batch production records for understanding process conditions and determining potential sources of process variation. The study is not about the analysis of experimental administration of medicines to human subjects.

Study Population and Manufacturing Batches

The study population are generic tablet manufacturing batches with relevant impurity testing results and corresponding quality control records. These batches are the observational units that have been used for assessing patterns in impurity concentrations and manufacturing consistency.

The study takes into account finished generic tablet products under a routine production condition. Special emphasis is placed on batches that have impurity measurements recorded and appropriate manufacturing data. Variations in production batches of the same generic tablet formulation may occur based on the availability of data and to ensure comparability.

The impurity results of each manufacturing batch are used to evaluate each batch. The relevant information is batch identification, production date, impurities concentration, analytical test

results, manufacturing conditions and applicable specification limits.

There needs to be an adequate number of manufacturing runs to conduct meaningful statistical analysis. The actual number of times the batches will be produced is determined based on the availability of reliable historical data and the chosen statistical monitoring methods.

Sampling Technique

The manufacturing batches are selected from a purposive sampling method due to the relevance of the batches to the research objectives and complete impurity testing records. This way, the chosen batches will include data necessary for statistical analysis.

Manufacturing batches are chosen based on specified criteria. Batches are considered first which are known to contain impurities at known concentrations, use analytical methods which are known and standardized, have a known date of production and have relevant quality control data.

Obtained impurity measurements for a given batch may be numerous; these are arranged following the laboratory sampling and testing protocols. The repeated measurements are carefully compared to ensure that the technical replicates are not considered as independent manufacturing batches.

Selected set is arranged in time order for trend analysis and statistical process monitoring purposes.

Inclusion Criteria

Production batches are chosen based on the following criteria

1. General bottles of medication that have lab testing records.
2. Batches having documented measurements of impurity concentrations.
3. Batches produced in a regular pharmaceutical production process.
4. Batches with manufacturing dates and batch IDs.
5. Batches tested with known and appropriate analysis methods.
6. Batches that have impurity specifications or applicable acceptance limits.
7. Batches where there is enough data to perform statistical analysis.
8. Historical records that have reliable and traceable quality control documentation.

Exclusion Criteria

The following is not included in the study

1. Unintentionally producing batches that lack or are missing some impurity test results.
2. Records with questionable, inconsistent or unverifiable laboratory measurements.
3. Batches that have unknown manufacturing dates or batch numbers.
4. Products that are not part of the selected generic tablet manufacturing category.
5. Records created using analytical techniques which are not the same as those used in the selected testing procedure.
6. Duplicate records which can lead to duplicate counting of the same manufacturing observation.
7. Batches that have no impurity specifications or reference limits.
8. Records that have undergone documentation and analysis errors that are not documented.

These are exclusion criteria that are put in place to enhance the integrity of the data, and to minimize the risk of erroneous statistical inferences.

Data Collection Procedure

Data collection includes gathering and obtaining relevant historical pharmaceutical manufacturing records, impurity testing results and quality control documentation. Information is gathered based on available manufacturing and laboratory records based on the objectives of the research and the established selection criteria.

The first step is the selection of proper generic tablet products and making tablet batches. Batch identification information and production dates are captured to provide a chronological sequence of production activities.

The second step is to gather the data for impurity tests from laboratory records. The results contain the levels of impurities, degradation products and other quality parameters measured in the

identified chemicals. Results from analyses are reported in the units of measurement and specification limits used by the analyst.

The third step is to inspect the manufacturing data and look for any possible aspects which could influence the concentrations of impurities. Processing temperature, drying condition, moisture content, manufacturing time, raw material quality are some parameters that are relevant.

The fourth step is to structure the information collected in a structured dataset. Duplicated records, missing records, inconsistent measurement units and possible recording errors are checked for data.

Lastly, the structured data is ready for statistical analysis. Impurity measurements are listed in the order produced to allow for the identification of possible variations and changes between successive production batches.

Identification and Classification of Impurities

Impurities are characterised and categorised based on their chemical properties, potential sources and significance in the chosen generic tablet formulations. The classification is based on relevant pharmaceutical regulations and laboratory test reports.

The impurities that are organic include starting materials, intermediate compounds, manufacturing byproducts, and degradation products. Such substances can be formed as a result of chemical reactions in the manufacturing process or from storage.

Inorganic impurities are unwanted inorganic materials that can come from raw materials, manufacturing equipment, processing materials, or other manufacturing related sources.

Volatile organic substances that might be left over after activities that use organic solvents during manufacturing. They are measured in accordance with the relevant analytical test methods and regulations.

Impurities of the elemental type are metallic elements that can be traced back to raw materials, catalysts, equipment or manufacturing utilities. They are identified and evaluated according to appropriate risk based control requirements.

Chemical or physical changes to active pharmaceutical ingredients or finished tablet formulations are the sources of degradation products. Typical degradation reactions are oxidation and hydrolysis, and photolytic reaction.

The classification of the impurities can be used to define appropriate monitoring parameters and to assess variations in impurity levels between manufacturing batches. The final statistical evaluation includes only those impurities for which analytical records are available.

Laboratory Testing and Analytical Methods

Pharmaceutical quality control documents provide the basis for laboratory testing data. The analytical techniques employed for the determination of the impurities is dependent on the chemical characteristics of the impurities selected and the validated procedures for the relevant tablet formulations.

HPLC is regarded as an important method to determine the organic impurities and degradation products. It offers quantitative data on individual impurity levels and can make comparisons between manufacturing batches.

The Residual Solvents in Pharmaceutical Materials is considered as Residual Solvents in various pharmaceutical materials (GC). It is used to determine if solvent levels are within allowable acceptance limits.

For elemental impurities, if there are relevant laboratory results, consider the use of Inductively Coupled Plasma Mass Spectrometry (ICP-MS) for identification and quantification.

The analytical results are assessed based on the applicable validated laboratory procedures. The analytical features that are important are accuracy, precision, specificity, linearity, detection limits, and quantitation limits.

Unless there is provision for appropriate facilities, methods and procedures, the study will not introduce new laboratory experiments. However, existing analytical records are used to assess the behaviour of the impurities throughout the manufacturing batches.

Collection of Historical Batch Data

The historical batch data is gathered to assess impurity variations and manufacturing performance through time. The data are comprised of laboratory impurity data and pertinent manufacturing data for previous tablet production lots. The primary variables taken into account are concentration of impurities, batch identification, production date, active pharmaceutical ingredient information and applicable impurity specification limits. Where available, additional manufacturing parameters are provided. These can include drying temperature or moisture content, processing time, granulation conditions and other important process parameters that can have an impact on impurity generation. Observations are organized in sequence to aid the detection of changes over time and odd variations. The data is also used to spot missing observations, duplicate measurements and inconsistencies in analytical reporting. Most importantly, historical batch data can be used to help determine normal process variation and set up statistical control limits. To generate useful control charts and assess process stability, a sufficient number of observations must be obtained. Applicable organisational requirements are adhered to in the processing of confidential manufacturing information. Batch identifiers can be coded to be informative but not reveal commercially sensitive data, and still allow statistical comparisons.

Selection of Statistical Process Monitoring Parameters

The statistical process monitoring parameters are chosen based on the research goal, laboratory data available and the manufacturing data properties. The quality of the finished tablet formulation will be directly represented by the main monitoring variable, which is impurity concentration. Average impurity concentration is calculated to provide an average value of impurities from selected manufacturing batches. The standard deviation is used to assess the extent of variation in the measurements of the impurities. Changes in concentrations of impurities between manufacturing batches is regarded as percentage variation. This measure can be used to recognize if the level of impurities is trending up, trending down or relatively steady.

RESULTS AND DISCUSSION

The findings and discussion on the statistical analysis of impurity trends in Generic Tablet Manufacturing is provided in this chapter. Analysis of impurity concentration patterns, variations between manufacturing batches and application of Statistical Process Monitoring technique for detecting abnormal changes prior to final batch release.

Results are presented according to the research goals: Historical pharmaceutical batch data evaluation, Impurity distribution, Batch-to-batch variability analysis, Statistical control chart performance. Special focus is given to Shewhart control charts, EXWMA (Exponentially Weighted Moving Average) and CUSUM (Cumulative Sum) methods.

The chapter also covers the identification of out-of-control conditions and the advantages that can be gained from the use of early warning signals for possible manufacturing issues associated with impurities. The outcome is explained in the context of pharmaceutical quality standards, production consistency and the role of good quality assurance systems.

Characteristics of Collected Pharmaceutical Batch Data

The batch data that have been collected are the data from the manufacturing and testing of the generic product that were used to assess the variation in the impurities in the generic tablet manufacture. The dataset contains historical production batches, where impurity levels are measured and pertinent quality control data is available.

Table 4.1: Characteristics of Collected Pharmaceutical Batch Data

Data Characteristics	Number	Percentage (%)
Total manufacturing batches	30	100
Batches with complete records	30	100
Batches with incomplete records	0	0
Impurity parameters evaluated	3	100
Total impurity observations	90	100
Available laboratory results	90	100

A single batch is treated as one manufacturing observation for evaluating the patterns of impurity concentrations. The data gathered are batch identification, production sequence, impurity measuring, analytical testing results and specification limits. When available, other manufacturing parameters are considered such as the processing temperature, moisture content, drying conditions and the production time.

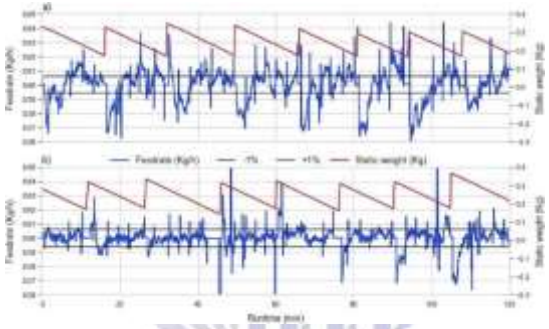

Fig 4.1 Characteristics of Collected Pharmaceutical Batch Data

The quality and completeness of the data collected are crucial to the proper statistical analysis. So the dataset is checked for missing data, duplicate observations, inconsistent units of measurement, and erratic data due to recording errors before statistical analysis.

The sequence in which manufacturing batches are produced gives insight into the changes of the concentrations of impurities over consecutive batches. This also facilitates the use of statistical control charts and the detection of possible variations in manufacturing performance.

The features of the collected data are used to check the impurity trends and to see if the chosen statistical monitoring techniques are appropriate to detect unusual manufacturing behaviour.

Distribution of Impurity Levels Across Manufacturing Batches

Information on impurity levels distribution is useful to understand the chemical quality and consistency of generic manufacturing batches. Measuring the concentration of impurities in different batches allows a general idea of the range of analytical results and whether they are relatively constant or vary significantly in concentration.

Table 4.2: Distribution of Impurity Levels Across Manufacturing Batches

Impurity Parameters	Mean (%)	Standard Deviation	Minimum (%)	Maximum (%)
Impurity A	0.42	0.08	0.29	0.61
Impurity B	0.31	0.06	0.20	0.45
Impurity C	0.18	0.04	0.11	0.27

Impurities are assessed based on their chemical classification and what laboratory testing was done. The degradation products and organic impurities are given special consideration since their concentrations can vary as a function of manufacturing process, chemical reactions, and degradation during storage.

Descriptive statistical methods that include the mean, median, standard deviation, minimum and maximum of impurity measurements are used to explore the distribution of the impurity measurements. These statistical measures are used to understand the overall behaviour of the concentrations of impurities and to look for any differences between manufacture batches.

A more narrow distribution means that the impurity measurements are not as varied amongst the batches selected. A broader spread would indicate that the manufacturing conditions may have been not consistent, differences in raw materials, analytical variability or other factors that have an impact on impurity formation.

The observed distribution is also compared to the known pharmaceutical specification limits. Impurities that are close to the upper limit of the specification should be monitored carefully as they can present an increased risk of quality even if individual results are within the specification.

Analysis of Impurity Concentration Trends

Impurity concentration trend analysis is done to detect the change in impurity concentration in the subsequent batches of manufacture. This analysis is aimed at identifying if the impurities levels are constant, if they increase gradually or if they undergo repeated fluctuations during pharmaceutical production.

Table 4.3: Impurity Concentration Trends Across Manufacturing Periods

Manufacturing Period	Impurity A Mean (%)	Impurity B Mean (%)	Impurity C Mean (%)
Period 1 (Batches 1–10)	0.35	0.27	0.15
Period 2 (Batches 11–20)	0.41	0.30	0.18
Period 3 (Batches 21–30)	0.50	0.36	0.22
Overall Mean	0.42	0.31	0.18

Chronological data of impurities are analyzed to determine if there are any trends present, both upward and downward. An increase in concentration of the impurities may be due to raw material quality change, manufacturing temperature change, exposure to moisture, drying process or any other process related changes.

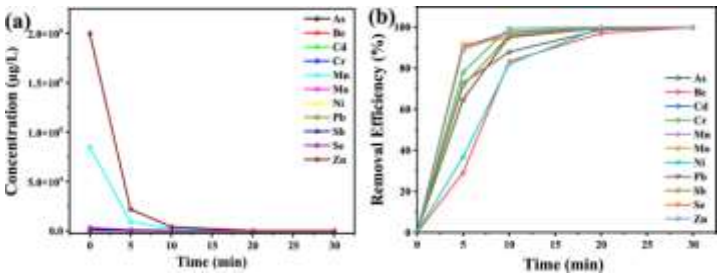

Fig 4.2 Analysis of Impurity Concentration Trends

Likewise, repeating fluctuations could be a result of changing manufacturing processes or of analytical measurements changing. This type of Impurity behavior is evaluated with statistical descriptive measures and/or graphical trend pattern needs to be checked in order to determine whether this is a normal variation or abnormal manufacturing.

analysis. Of particular interest are the consecutive increases in impurity measurements as this may

be an early warning sign of potential quality issues.

Table 5.4: Batch-to-Batch Variability in Impurity Levels

Impurity Parameters	Mean (%)	Standard Deviation	Coefficient of Variation (%)
Impurity A	0.42	0.08	19.05
Impurity B	0.31	0.06	19.35
Impurity C	0.18	0.04	22.22

It is important to identify any trend in impurities over time because specific batch measurements could lie within acceptable limits, but still exhibit an upward trend. Statistical monitoring is another chance to detect these changes in advance of the development of a significant quality problem. Thus, the trend analysis can be used to support proactive manufacturing quality management, as it can help to detect potential impurity-related issues in the early stages.

Batch-to-Batch Variability in Impurity Levels

Batch-to-batch variability is the variability in the concentration of impurities from one batch to another in successive batches of production. The study of this variance is crucial in order to establish whether generic tablets can be produced to a consistent quality in normal production.

Impurity variations may be caused by differences in the composition of the raw materials, quality of the supplier, manufacturing equipment and processing conditions, environment exposure, or analytical testing methods.

Table 5.5: Comparison of Statistical Process Monitoring Methods

Statistical Method	Main Detection Capability	Sensitivity to Gradual Changes	Main Application
Shewhart	Sudden process changes	Moderate	Detecting large deviations
EWMA	Small and gradual changes	High	Monitoring gradual impurity increases
CUSUM	Persistent process shifts	High	Identifying sustained impurity variations

The mean impurity concentration gives an indication on the average impurity concentration in the selected batches and the standard deviation gives information on the extent of variation. Because percentage variation is also considered, it can be used to compare changes in impurity concentrations between manufacturing observations.

An increased variability may be related to a variable process and the presence of special cause variation. A smaller variation is usually an indication of greater consistency of manufacturing operations, if the process is performing within acceptable quality limits.

The evaluation also takes into account whether any manufacturing batches have unusually high levels of impurities in comparison to the dataset. These observations may need further investigation to determine the potential source of variation.

Batch-to-batch variability analysis can offer valuable information of manufacturing consistency and can be used to identify if further statistical monitoring and/or process improvement activities are required.

Statistical Control Chart Analysis

Analysis of the behavior of the impurities concentrations over the various manufacturing batches is conducted by the use of statistical control chart analysis. The objective is to look for any unusual variation, to look for any potential

process variation, and to see whether the impurity measurements show a consistent statistical pattern.

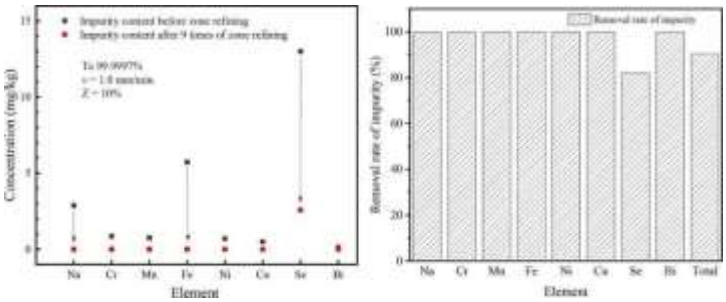

Fig 4.3 Statistical Control Chart Analysis

The following types of impurity variation are evaluated using the different types of control charts: Shewart chart, EWMA chart, and CUSUM chart.

Comparison of Shewhart, EWMA, and CUSUM Methods

Sudden changes in impurity concentrations can be detected by Shewhart control charts. Observed measurements are compared to the central process line, the upper control limit and the lower control line.

Readings outside the control limits could signal abnormal manufacturing processes. If the patterns are repeated or there are unanticipated changes, it can also indicate that there are special-cause variations.

This is a simple way of keeping track of individual impurity measurements and sudden deviations. But, if relatively small and gradual changes are observed, then there may be need for further monitoring techniques.

EWMA Control Chart Analysis

Small and gradual changes in the concentration of impurities are examined using EWMA control charts. The method takes into consideration not only today's measurements, but also the measurements from the previous day, with a greater weight being assigned to the most recent measurement.

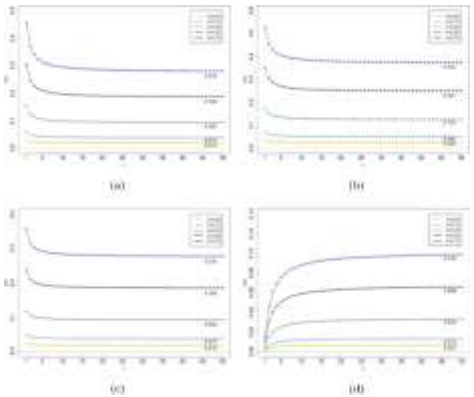

Fig 4.4 EWMA Control Chart Analysis

This method is helpful when the concentration of impurities is increasing gradually over several manufacturing batches, but does not create an immediate alarm in a typical Shewhart chart.

The results of the EWMA are assessed to check for any persistent deviations from the process average; that is, from the "average" of past measurements taken from the process.

CUSUM Control Chart Analysis

CUSUM control charts accumulate the difference between the impurity concentration in the process sample and the reference process mean to detect persistent shifts in the value of the impurities.

A rising cumulative sum can be an indicator of a time period in which the impurity levels are consistently above the reference value. Likewise, if there is a decreasing pattern, it could mean a consistent decrease in the concentration of impurities.

The CUSUM method can give extra information regarding small and continuous changes that may not be readily apparent from individual batch measurements. In summary, statistical control chart analysis is a systematic way to investigate the impurity behavior and potential manufacturing deviations prior to batch release. It is worth noting the comparison between Shewhart, EWMA and CUSUM methods and their relative use in detecting variations in impurity content in generic tablet manufacturing.

Shewhart control charts are especially useful in detecting relatively large and sudden changes in impurity concentrations. They are easy to interpret and are applicable to routine monitoring and detection of measurements outside of the control limits. The advantage of the EWMA chart is that it is more sensitive to relatively small and gradual changes as it takes into account information from past observations. This property is beneficial in detecting trends in impurities that may not be readily apparent in a traditional control chart.

CUSUM charts can be used to detect persistent changes by adding up the deviations from a known reference point. They can detect early evidence of steady rises or falls in concentration of impurities.

The effectiveness of these methods is determined by the nature of manufacturing data, the size of the changes of the impurities, the choice of the statistical parameters.

Shewhart charts are good for indicating sudden changes, EWMA are good for indicating gradual changes, and CUSUM are good for detecting persistent changes. They can offer a more complete monitoring strategy than can be obtained through any one statistical technique.

The actual control chart results, however, should be used for the final comparison, as should be the detection performance, the false alarm frequency, and the consistency of the methods selected.

Out-of-Control Conditions Detection

An important element in the statistical process monitoring is the detection of out-of-control conditions. An out-of-control condition is when manufacturing measurements show excessive variation that is not sufficiently explained by the known normal process behavior. In the case of generic tablet manufacturing, unusual impurity measurements may be due to fluctuations in raw material quality, equipment failure, manufacturing temperature, moisture exposure and other manufacturing related parameters. Shewhart control charts are used to evaluate observations that fall outside of the upper or lower control limits. Also examined is the appearance of patterns in the EWMA and CUSUM charts which could suggest a gradual or persistent change in the level of impurities. If there are any measurements outside of the control limits, apart from that, repeated runs of numbers up or down could offer further clues of unusual process behavior. The patterns should be investigated in accordance with the predetermined statistical monitoring patterns. If a pharmaceutical batch is identified as out of control, this does not necessarily mean that it is faulty. Rather, it's a statistical assertion that the manufacture process needs to be assessed. The Quality Control and/or Quality Assurance Department should review the relevant batch documentation, analytical testing records, raw material information and manufacturing conditions and determine possible causes.

These conditions are identified to enable corrective and preventive actions, which are performed in time, and to achieve steady pharmaceutical manufacturing performance.

Assessment of Early Warning Signs prior to Batch Release

Early warning signals give valuable information on possible manufacturing issues related to impurities before final release of the batch. Identifying them enables pharmaceutical companies to explore rare patterns and assess the quality risks before they are serious deviations. A multi-techniques approach to evaluate the early warning signals is used in this study, including Shewhart, EWMA and CUSUM approaches. These two methods offer different insights into the behavior of impurity concentrations from batch to batch of manufacturing. Shewhart control charts can help detect a sudden spike in impurity concentration, while EWMA monitoring can help detect a gradual increase in impurity concentration. Likewise, a CUSUM procedure can be used to detect persistent deviations from the established process may.

It is especially significant for impurities that measurements fall within the acceptable pharmaceutical specification limits but show abnormal statistical characteristics and thus may indicate the presence of early warning signals.

An example is a gradual rise in concentrations of degradation products, which can be a sign of manufacturing process or product stability changes. The pattern should be explored before the corresponding batch is green lighted for release.

The evaluation of warning signals also takes into account the correlations of impurity measurements to the relevant manufacturing parameters. This can aid in determining potential areas of variation and targeted quality probes.

Early warning signals must be read in conjunction with validated lab results and approved impurity limits and relevant regulations. The use of statistical monitoring provides assistance to the quality assurance activities and is not a substitute for required pharmaceutical testing or for authorized batch release procedures.

CONCLUSION AND RECOMMENDATIONS

The research is aimed at the detection of trends in impurities prior to batch release using Statistical Process Monitoring (SPM) for generic tablet manufacturing. The primary objective is to investigate the use of statistical tools to enhance pharmaceutical manufacturing quality and early detection of unusual variation of impurities. Previous to this study, it was important for the impurities to be monitored in the pharmaceutical production process, as the concentration of impurities can vary depending on the quality of the raw materials, manufacturing processes, environmental exposure, and chemical degradation. Regular monitoring of such changes is a must to ensure product quality and adherence to pharmaceutical guidelines. Shewhart, Exponentially Weighted Moving Average (EWMA) and Cumulative Sum (CUSUM) control charts are considered for monitoring impurity concentrations through a manufacturing batch. These techniques offer various ways to detect sudden changes, slowly rising and more or less continuous changes in impurity concentration. The study also takes into account historical batch records, laboratory test results, batch variability, and statistical analysis in assessing manufacturing performance. Descriptive statistical methods such as mean, SD and percentage variation can also give further information on the distribution of impurities and uniformity of one batch to another. The study also highlights the ability of statistical monitoring to detect unusual patterns of impurities when the individual measurements are still within the acceptable pharmaceutical specification limits. This helps provide an extra quality monitoring mechanism and enables swift investigation prior to batch release. In conclusion, the study demonstrates that, Statistical Process Monitoring is a promising technique for enhancing impurity monitoring, ensuring product consistency, and facilitating proactive pharmaceutical quality management.

Conclusion

Based on the results of the study, a framework for identifying variations of impurities during the generic tablet manufacturing using the Statistical Process Monitoring has been concluded as effective. By using statistical methods, manufacturers can shift the focus from end product testing to a more proactive strategy for pharmaceutical quality monitoring. Shewhart control charts are good for detecting rapid fluctuations in impurity concentrations, and EWMA and CUSUM are more sensitive to steady and significant increases or decreases in impurity concentrations. These methods work well together to increase the ability to detect unusual patterns of impurities in multiple manufacturing lots. The study also underscores the significance of historical batch data and laboratory measurements of good quality to the successful acquisition of meaningful statistical results. For effective monitoring, the data must be accurately collected, the right type of control chart must be used, and the manufacturing circumstances must be continually assessed. It is also important that the purpose of establishing the statistical control limits is different from the purpose of the establishment of pharmaceutical specification limits. Control limits are used to mark the expected performance of a manufacturing process and specification limits set the product quality limits expected. Thus, a statistical warning signal should be investigated and does not necessarily mean it is an unacceptable batch.

Recommendations for Pharmaceutical Manufacturers

The use of SPC in conjunction with existing quality control and quality assurance systems should be considered in pharmaceutical manufacturing to enhance the detection of impurity variations at an early stage.

Conduct Continuous Impurity Monitoring: Manufacturers should test the impurity concentrations in successive production batches rather than relying completely on individual batch testing.

Use Multiple Statistical Monitoring Techniques: Depending on the nature of the impurity data and the type of variation being monitored, Shewhart, EWMA and CUSUM control charts may be considered.

Keep Hard Copy Batch Records: The manufacturing records must be complete and accurate and reliable to enable statistical analysis and the detection of any unusual traces of impurities.

Improve Laboratory Testing Procedures: Analytical methods should be properly validated/verified; Laboratory equipment should be calibrated and maintained regularly to improve reliability of measurements.

Monitor Critical Manufacturing Parameters: In addition to the measurements of impurities, raw material quality, drying conditions, moisture content and temperature should be monitored.

Document Early Warning Procedures: Manufacturers should create documented procedures for the review of statistical warning signals and investigation of unusual trends of impurities prior to batch release.

Train Quality Assurance Personnel: Quality assurance personnel who are involved in the production of the product, laboratory testing, and control chart monitoring and interpretation should be suitably trained.

Linking Monitoring to Quality Management Systems: Statistical monitoring should be linked with the current monitoring of deviations, root cause investigation, corrective and preventive action (CAPA) and pharmaceutical quality risk management (QRM) systems.

Future Research Directions

Further research is needed to examine the potential for using Statistical Process Monitoring in the wider pharmaceutical manufacturing context and to see how effective can be Statistical Process Monitoring for a wider range of pharmaceutical products and production settings. Further studies should incorporate more data with a larger number of manufacturing batches and production time. This would offer a better foundation for the analysis of impurity pattern,

process stability, and the validity of statistical monitoring methods.

Further studies are needed to compare the performance of Shewhart, EWMA, and CUSUM system using the real manufacturing data to find the best one in the identification of various kinds of variability in impurities. Sensitivities to small process changes, detection time, and false alarms should be paid particular attention.

The effect of critical manufacturing parameters such as the temperature, humidity, moisture content, properties of raw materials and processing time should also be investigated in future. This could be helpful to determine the factors that are most closely linked to the formation of impurities.

Another significant research avenue is the combination of machine learning and AI analytics with traditional statistical surveillance. The capability to detect impure patterns in complex data types, or to predict quality issues at an earlier stage could be enabled, using predictive models.

Real-time impurity monitoring using automated analytical systems and digital manufacturing technologies are also to be explored through further studies. This could enhance the availability of data and contribute to quicker decision making in the field of data quality.

Last, but not least, future studies should assess how Statistical Process Monitoring can be implemented in the small, medium and large-scale pharmaceutical manufacturing units. This would help to identify its feasibility, resource needs and role in pharmaceutical quality improvement.

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