Evaluation of Quality Characteristics and Process Stability for Pharmaceutical Dosage Form Using Attribute Control Charts

Essam Eissa M*1, Mohsen Abdoh A2

1Quality Compliance Department, HIKMA Pharma, City, Giza, Egypt.
2Quality Assurance Department, HIKMA Pharma, City, Giza, Egypt.

*Corresponding Author: Email: mostafaessameissa@yahoo.com

Abstract: Objective: Monitoring of manufactured product characteristics and manufacturing process stability are important criteria in the pharmaceutical industry that affect medicinal dosage forms safety and quality. One of the most important tools to accomplish that is by using the control charts. However, selection of the control charts based on data type is important for appropriate visualization of the system and product efficiency. Methods: The discrete nature of data (count and percent) directed the analysis toward the use of attribute charts using commercial statistical software package. The following study demonstrated the application of Laney-modification of U charts for analysis and trending of five in-process control (IPC) and quality control (QC) properties of selected product of oral solid dosage form film coated tablet (FCT). Results: All trended results of 31 batches of Fluoroquinolone tablet failed to follow normal, binomial and/or Poisson distribution with the exception of the assay of active pharmaceutical ingredient (Levofloxacin) which passed both normality and Poisson distribution tests at significance level α = 0.05. Histograms showed the pattern of data distribution with outliers being observed with dissolution test, bulk and finished product output yields. The presence of freak points in the manufactured batches were confirmed by application of Laney U΄ control charts. Conclusion: The application of Laney modification was useful to correct for over- or under-dispersion of the results - as indicated by Sigma Z values - especially when they did not follow the required distributions.

Keywords: Attribute charts, in-process control, quality control, film coated tablet, dissolution, disintegration, Yield.

Introduction

Quality control charts provides useful and handy tool for improvement projects and cost reduction through the last four stages of the basic DMAIC road map (i.e. in measure, analyze, improve and control phases after define step) [1]. Application of control charts for variable data has been demonstrated by some investigators with pharmaceutical products manufacturing of tablets [2-4].

However, data with discrete nature are more suited for attribute type of control charts [5]. The currently presented study aimed to investigate the application of attribute control charts with some quality control (QC) and in-process control (IPC) monitoring discrete results that may fail to follow specific pattern of data distribution. The present work also focused on detecting any out-of-control (OOC) behavior between studied batches of manufactured antimicrobial orally administered film coated tablet (FCT), even if there was not any out-of-specification results could be detected.

Materials and Methods

Materials

Non-sterile oral solid product was manufactured in class D area in the production plant of a pharmaceutical plant. The dosage form is FCT with Levofloxacin (Fluoroquinolone) 500 mg as hemihydrate active pharmaceutical ingredient (API). Results were gathered from database of both QC and IPC from the main company server. Statistical analysis was done at α = 0.05. Normality test and distribution fitting were generated using XLSTAT Version 2014.5.03. Histograms and attribute control charts were drawn using Minitab17.1.0. The study assesses the process and the quality retrospectively to assess the adequacy of the implemented measures.
Methods

Results Collection and Source

Process batch record (PBR) was used as source for the gathered results from 31 manufactured products. All records were handled and reviewed by trained and qualified quality assurance (QA) officers before any further processing could be conducted. All methods of analysis and testing were validated and approved according to regulatory requirements and performed as specified per compendial guideline using calibrated and validated instruments [6]. Monitoring of compliance to good manufacturing practice (GMP), good laboratory practice (GLP) and good documentation practice (GDP) was performed by both QA and compliance departments officers. Selected parameters were chosen to be inspected from PBR namely: relative potency assay of API, fraction dissolved after 45 minutes, disintegration after compression and before coating and determination of the bulk and finished product yield (i.e. recovered fraction from the theoretical amount).

Data Processing

In order to establish suitable criteria for selection of control charts, the following steps were followed:

- Review of the type of data to decide which broad class of control charts to use (either variable or attribute).
- Distribution analysis of the results to identify if data could follow (or at least approximately follow) specific distribution such as normal, binomial and/or Poisson [7].
- Histogram drawing will aid visualizing the profile of the monitored process or quality characteristic [7].

McNeese (2009) demonstrated the possibility to apply individual-moving range (I-MR) charts, if Poisson or binomial assumptions have not been met. However, in order to apply I-MR chart, certain degree of normality must be ensured in data [8]. A modification of this approach is to use Laney modification in the attribute control chart, an option provided by Minitab software to correct for over-or under-dispersion in data [9].

Results and Discussion

As it was observed with some inspection characteristics, such as dissolution, disintegration and yields determination, it is more convenient to inspect some quality characteristic attributes as ratio or percent. Accordingly, quality control charts for discrete data would be more appropriately implemented in such instances. However, most data of the inspected characteristics failed to follow specific distribution pattern with exception of the relative assay potency at $\alpha = 0.05$, where it followed both normal and Poisson distribution as demonstrated in Table 1. Histograms that are illustrated in Figs. 1, 2 and 3 demonstrate the pattern of the distribution and help to visualize data profile in addition to the outliers. These outliers were evident with dissolution test, bulk and finished product yield.

Attribute control charts were applied accordingly but with Laney modification as could be visualized in Figs. 4, 5 and 6. An exception was the assay of API, where it passed both normality and Poisson distributions.

Table 1: Distribution analysis of data obtained from in-process control (IPC) tests and quality control (IPC) analysis of film coated tablet (FCT)

<table>
<thead>
<tr>
<th>Distribution Data Analysis</th>
<th>Assay of API*</th>
<th>Dissolution Rate</th>
<th>Disintegration</th>
<th>Bulk Product Yield</th>
<th>Finished Product Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normality Test Pass (at $\alpha = 0.05$):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson-Darling test</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Shapiro-Wilk test</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Binomial Distribution Test Pass (at $\alpha = 0.05$)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Poisson Distribution Test Pass (at $\alpha = 0.05$)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

\* Active Pharmaceutical Ingredient
Fig. 1: Histograms for assay of active pharmaceutical ingredient (API) and dissolution test in quality control (QC) after primary packaging.

Fig. 2: Histogram for the in-process control (IPC) disintegration test during manufacturing process at the compression phase of the tablet core.
So, I-MR chart was used also and it showed two more (27th and 29th batches) alarms predisposing the common one with Laney U’ chart (the last 31th batch). These two alarms provided early warning about drifts in the process [10] as shown in Fig. 4. However, it should be noted that both I-MR and Laney U’ charts have the same upper control limit (UCL) and lower control limit (LCL). Apart out-of-control (OOC) points that indicated that possible causes of excursions might be due extraneous factors not related to the process "denoted by 1", shifts in process mean "denoted by 2" indicated inadequate control on the manufacturing process with consequent product quality may be affected [11]. From the current work, it was sought that Laney modified attribute control charts may serve as better alternative of ordinary control charts when specific requirements for each - especially distribution pattern - are not met. Such predisposing conditions had been demonstrated by some authors for the commonly known classical control charts [12-14]. It is evident from Table 1 that real-world data may fail to follow the dedicated distributions appropriately. Accordingly, Laney control’ charts may be the best approach in such instances.

Fig. 3: Histograms for bulk and finished product yield from the manufacturing process showing outliers in the left side indicating significant mass loss
Fig. 4: Laney U’ chart for assay and dissolution tests as a part of quality control (QC) tests performed on semi finished film coated tablet (FCT) after packing in the primary packaging. Individual-Moving Range (I-MR) chart was used only for normally distributed assay data.
Fig. 5: Laney U’ chart for disintegration test performed during compression phase as a part of in-process control (IPC) through the manufacturing process of film coated tablet (FCT)

Fig. 6: Laney U’ chart for bulk core product after compression and finished product after coating yield of film coated tablet (FCT)
Conclusion
The currently adopted methodology to construct control charts is simple, time-saving and effective. Moreover, it is still important to access area of weakness and defect in addition to the process stability and quality of the product batch. However, whenever possible variable-type control charts are preferred to be implemented, if their requirements are fulfilled. While the product still meets the specifications, an extensive investigation is required to reveal sources of OOC causes, correcting and preventing them from occurrence in the future as part of preventive action/corrective action (CAPA) before any true out-of-specification (OOS) may occur.

References