

## Application of Multivariate Statistical Quality Control In Pharmaceutical Industry

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### ABSTRACT

In univariate quality control charts, only one of the process variables is observed, while multiple variables are observed simultaneously in multivariate quality control charts. Thus, the relations between variables are taken into account. Our application is for painkiller tablets whose characteristic properties are weight, hardness and thickness. These variables have correlation to each other and they were used in implementation of the Hotelling's  $T^2$  multivariate quality control. Out of control values were decomposed by MYT procedure in order to determine cause of signal.

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## 1. Introduction

There have been many studies regarding quality under different terms such as examination, statistical quality control, total quality control and total quality management in the literature. In the past, it used to come to mind only related simple measurement and examination proceedings when quality control was considered; however, today, these applications are replaced by statistical process control techniques which can be used for every kind of problem solving and which take place not only as last product but also at production stage.

In the analysis of examined events, univariate statistical analyses which are valid under restrictive assumptions were replaced by multivariate analyses enabling to deal with more than one feature all together regarding an examined topic or event. The most important

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restriction regarding univariate analyses is the fact that many factors within the event are kept under control empirically and each time only effect of a single factor is examined. On the other hand, multivariate analyses are used for various purposes in applications because of the fact that it is dealt with the analyses of more than one feature.

## 2. MULTIVARIATE STATISTICAL QUALITY CONTROL

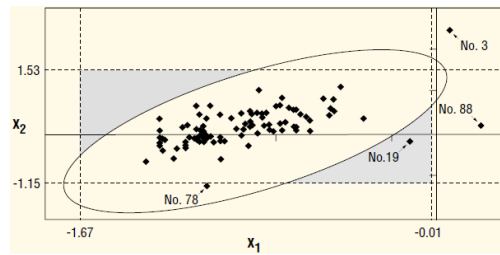
Multivariate statistical process control requires the use of multivariate statistical methods in order to develop industrial process production and quality. Multivariate control methods have many advantages when compared to univariate control methods, because multivariate control methods not only examine single variable effects but also control the relationship among variables by considering all examined variable groups. Therefore, multivariate methods are more sensitive than univariate control process against variation in the variable or its relationships.

Main method of forming multivariate control schemas is based on Hotelling  $T^2$  statistics. Hotelling developed a control method whose context is related with statistical distance and named it as Hotelling  $T^2$  statistics. This statistics possesses the same function with Student-t distribution. Hotelling  $T^2$  was developed through adapting from univariate chartssimilar to Multivariate Cumulative Sum (MCUSUM) and Multivariate Exponentially Weighted Moving Average (MEWMA) charts. Hotelling  $T^2$  chart is the most commonly used multivariate control schema. MCUSUM and MEWMA charts have not become widespread due to the fact that they are not known by the users and these require more complex calculations [1].

### 2.1 Univariate and Multivariate Control Zone

While Shewhart's control zone in Figure 1 is within rectangular box,  $T^2$  control zone is in the form of eclipse. 3 uncontrolled points are determined for all zones; however it is not agreed on which 3 points are uncontrolled. While observation No:3, No:78 and No:88 signal for box zone, observation No:3, No:19 and No:88 produce uncontrolled signal. For instance  $X_1$  variable is out of process limits and this causes signal according to the result acquired through decomposing  $T^2$  value which is calculated for observation 88 in the right side of control eclipse. In addition, when observation 19 is within the shewart rectangle, it is outside of  $T^2$  eclipsezone. This indicates that there may be an error stemming from the relationship between  $X_1$  and  $X_2$  Moreover, observation 19 is high value for  $X_1$  variable while it is low for  $X_2$  variable. Observed values of these two variables should be in a direct proportion relationship. There should be positive correlation among the variables; a high valued variable

is in conformity with the other variable. Multivariate control techniques are pretty sensitive to these kinds of signal situations. However, this type of sensitiveness cannot occur in univariate control variables due to the fact that analysis is carried out only with single variable [3].



**Figure 1.** Eclipse Control Zone

Forming and examining two independent control charts individually is another method used. However, this means examining lots of charts as well as interpreting the relationship of these charts in a wrong way. Because, variables are addressed independently in Shewart charts and effects of other variables are ignored.

### **Forming Hotelling $T^2$ Charts**

After examining the suitability of assumptions, first of all, reference data set should be formed and upper control limits of 1st and 2nd Phase charts of  $T^2$  statistics should be determined in order to form the charts. In a situation where main mass of parameters are unknown, this data set which requires to be estimated from a data set which does not include outlier observation is named as Past data set or Reference data set. We can estimate unknown  $\mu$  and  $\Sigma$  parameters in the applications  $\bar{X}$  and  $S$  values. These values are acquired by using Reference data set [4].

### **Forming 1<sup>st</sup> Phase $T^2$ Chart:**

1<sup>st</sup> Phase control methods find more approval  $T^2$  than 2<sup>nd</sup> Phase techniques in the literature. The purpose of the first phase is forming controlled reference data set, which is necessary for determining second phase control limit. It is assumed that reference data set follows multivariate normal distribution [10].

Tracy, Young and Mason [9] suggested 1<sup>st</sup> Phase charts which are practical under multivariate normal distribution.

1<sup>st</sup> Phase charts ground on extracting outlier observations from data set and it is also known as start-up phase.  $T^2$  statistics is an ideal method for determining deviation values and it is easy to apply, as well. If an observation exceeds upper control limit(UCL) which matches  $T^2$  statistics, this is extracted from data group.

In the situations where main mass parameters are unknown and multivariate normality is accepted,  $X \sim N(\mu, \Sigma)$

$$T^2 = (X - \bar{X})' S^{-1} (X - \bar{X}) \quad (1)$$

Distribution of  $T^2$  statistics used in the 1<sup>st</sup> Phase represents;

$$T^2 \sim \left[ \frac{(n-1)^2}{n} \right] B_{(\alpha; p/2, (n-p-1)/2)} \quad (2)$$

$B_{(\alpha; p/2, (n-p-1)/2)}$  beta distribution.

In this phase, upper control limit (UCL) of the charts is calculated as follows:

$$UCL = \left[ \frac{(n-1)^2}{n} \right] B_{(\alpha; p/2, (n-p-1)/2)} \quad (3)$$

Firstly, process starts to be cleaned by handling pre-data. If  $T_i^2 > UCL$  which is calculated for the examined  $X_i$  observation vector,  $i$ . observation vector is extracted from data set and new estimations are calculated with the remained data for average vector and covariance matrix. Secondly, data is handled one more time and similar procedures are applied. In this way, procedures continue until no any outlier observation remains. As a result, reference data set which is extracted from outlier observation is acquired.

### **Forming 2<sup>nd</sup> Phase $T^2$ Chart:**

Control process of 2<sup>nd</sup> Phase process starts. It is determined whether new observation vectors, which are selected from the process randomly, are under control or not by basing on main mass parameters estimated from reference data set in the 1<sup>st</sup> Phase. According to the 1<sup>st</sup> Phase, the greatest difference is the distributions used for the purpose of determination of UCL limits.

When the newly selected observation vector is calculated as  $X = (x_1, x_1, \dots, x_p)$ ,  $T^2$  value given with  $X$  is calculated as follows:

$$T^2 = (X - \bar{X})' S^{-1} (X - \bar{X})$$

$\bar{X}$  and  $S$  are the parameters which are estimated from reference data set. UCL of 2<sup>nd</sup> Phase  $T^2$  charts can be calculated as a function of  $F$  distribution. The given  $T^2$  statistics is upper control limit for  $\alpha$  while it is the size of  $n$  data set as,

$$UCL = \left[ \frac{p(n+1)(n-1)}{n(n-p)} \right] F_{(\alpha; p, n-p)} \quad (4)$$

New observations are drawn as graphics with the help of these formulas. When  $T^2$  values of new examined observation vectors exceed UCL, we can infer that observations are not in conformity with the main data set.

### 3. DETERMINATION OF UNCONTROLLED VARIABLES

In multivariate statistical processes, there are many situations that may cause signaling. An observation with  $p$  variable, which is outside the limits set beforehand depending on data status, may be uncontrolled. Similarly, a signal stemming from the relationship among one or more variables may be at variance with the previous data set. Moreover, the signal may have been formed with the combination of these two situations; while some variables cause error in an uncontrolled way, other may be in a situation, which shows resistance.

#### 3.1 Mason Young Tracy (MYT) Decomposition Method

Hotelling  $T^2$  determines the variations in the process; but when the  $T^2$  statistics gives a warning, the most important problem is the process of determining the variables which one causes warning.

MYT is a method based on decomposition of  $T^2$  statistics in order to determine which variables or which relationships among the variables cause the problem within the process. Orthogonal decomposition of  $T^2$  statistics helps determination of the variables which cause deviation or signal.  $T^2$  statistics was divided into conditional and unconditional terms by using this method in Mason –Young- Tracy (MYT) decomposition method [12].

MYT decomposition method divides  $T^2$  statistics into 2 orthogonal (vertical) compounds which are known as conditional and unconditional terms and which are weighted equally [2].

MYT management is generally applied as follows in  $p$  variable process:

$X_i = (X_{i1}, X_{i2}, \dots, x_{ip})'$ .  $T^2$  statistics for observation vector

$T^2 = (X - \bar{X})' S^{-1} (X - \bar{X})$  in the formula  $X^{(p-1)} = (x_1, x_2, \dots, x_{p-1})$  and  $\bar{X}^{(p-1)}$  we shall decompose this  $(p-1)$  dimension vector as the average of  $(X - \bar{X})$  vector

$$(X - \bar{X})' = \left[ \left( X^{(p-1)} - \bar{X}^{(p-1)} \right) \left( x_p - \bar{x}_p \right) \right] \quad (5)$$

Similarly, variance-covariance matrix can be decomposed as follows:

$$S = \begin{bmatrix} S_{xx} & S_{xX} \\ S'_{xX} & S_p^2 \end{bmatrix}$$

$S_{xx}$  is the covariance matrix of first  $(p-1)$  pieces of variables. It is  $(p-1) \times (p-1)$  dimensional.  $S_{xX}$ , is a  $(p-1)$  dimensional vector showing covariance between  $p$  variable and other variables.  $S_p^2$ , is the variance value of  $p$  variable.

In this case,  $T^2$  statistics can be decomposed into two independent terms as follows,

$$T^2 = T_{p-1}^2 + T_{p,1,2,\dots,p-1}^2 \quad (6)$$

first term given in (6) is,

$$T_{p-1}^2 = \left( X_i^{(p-1)} - \bar{X}^{(p-1)} \right)' S_{XX}^{-1} \left( X_i^{(p-1)} - \bar{X}^{(p-1)} \right) \quad (7)$$

first  $(p-1)$  variable is used and it is a  $T^2$  statistics by itself. This term is named as unconditional term while the term in (6) is conditional term.  $\bar{X}^{(p-1)}$  is the sample average vector for the first  $p-1$  variable of  $n$  variant observation.

$$b_p' = S_{XX}^{-1} s_{xX} \quad (8)$$

As  $B_p$ ;  $x_p$  is dependent and other variables are independent, it is  $(p-1)$  dimensional vector including estimated values of regression equality coefficient.

As

$$\bar{x}_{p,1,2,\dots,p-1} = \bar{X}_p + b_p' (X_i^{(p-1)} - \bar{X}^{(p-1)}) \quad (9)$$

Sample average of  $p$ . variable  $\bar{X}_p$   $n$  observed as;

$$T_{p,1,2,\dots,p-1}^2 = \frac{(X_{ip} - \bar{X}_{p,1,\dots,p-1})^2}{s_{p,1,2,\dots,p-1}^2} \quad (10)$$

$T^2$  is calculated. On the other hand, estimation of the conditional variance is shown as

$$s_{p,1,2,\dots,p-1}^2 = s_p^2 - s_{xX}' S_{XX}^{-1} s_{xX} \quad (11)$$

Due to the fact that  $T_{p-1}^2$  which is the first term in (6) and unconditional terms as a  $T^2$  statistics, it can be decomposed into two components as unconditional and conditional terms [7].

$$T_{p-1}^2 = T_{p-2}^2 + T_{p-1,1,2,\dots,p-2}^2 \quad (12)$$

Here,  $T_{p-2}^2$  is the  $T^2$  statistics calculated for first  $(p-2)$  variables of  $x$  vector.

In this way, if we continue the possible MYT decompositions of  $T^2$  statistics;

$$\begin{aligned} T^2 &= T_1^2 + T_{2,1}^2 + T_{3,2,1}^2 + T_{4,1,2,3}^2 + \dots + T_{p,1,\dots,p-1}^2 \\ &= T_1^2 + \sum_{j=1}^{p-1} T_{j+1,1,\dots,j}^2 \end{aligned} \quad (13)$$

is acquired.

$T_1^2$  term in (13) is the square of univariate unconditional  $t$  statistics for the first variable of  $X$  vector and calculated with

$$T_1^2 = \frac{(x_1 - \bar{x}_1)^2}{s_1^2} \quad (14)$$

### **Control Limits of Conditional and Unconditional Terms**

Decomposed conditional and unconditional terms are compared with calculated critical values. It is accepted that unconditional and conditional terms show  $F$  distribution.

Unconditional terms in  $p$  variant situation

$$T_j^2 \cong \left( \frac{n+1}{n} \right) F_{(1,n-1)} \quad (15)$$

and conditional terms as  $k$  conditioned variable number

$$T_{j,1,2,\dots,j-1}^2 \cong \left( \frac{(n+1)(n-1)}{n(n-k-1)} \right) F_{(1,n-k-1)} \quad (16)$$

It is determined whether conditional and unconditional terms cause process to go out of control or not by means of UCLs (critical value). Unconditional terms are;

$$UCL_{unconditional} = \left( \frac{(n+1)}{n} \right) F_{(\alpha,1,n-1)} \quad (17)$$

conditional terms are;

$$UCL_{conditional} = \left( \frac{(n+1)(n-1)}{n(n-k-1)} \right) F_{(\alpha,1,n-k-1)} \quad (18)$$

compared with the above written formulas. It is understood that there is a signal stemming from  $j$  variable in the process in the situation of  $T_j^2 > \left( \frac{n+1}{n} \right) F_{(\alpha,1,n-1)}$  and existence of a signal in  $j$  variable process and in the situation of  $T_{i,j}^2 > \left( \frac{(n+1)(n-1)}{n(n-k-1)} \right) F_{(\alpha,1,n-k-1)}$   $i$  and  $j$  variables cause signal together [2].

### **Features of MYT Decomposition Method**

Decomposition of  $T^2$  statistics isn't single type. Since components of  $(x_1, x_2, \dots, x_p)$  vectors are  $p!$  permutation, we can disintegrate  $T^2$  value in  $p!$  different ways. For example,  $3!=6$  decomposition of  $T^2$  value is present for  $p=3$  variable [11].

$$\begin{aligned}
T^2 &= T_1^2 + T_{2,1}^2 + T_{3,1,2}^2 \\
&T_1^2 + T_{3,1}^2 + T_{2,1,3}^2 \\
&T_2^2 + T_{3,2}^2 + T_{1,2,3}^2 \\
&T_2^2 + T_{1,2}^2 + T_{3,1,2}^2 \\
&T_3^2 + T_{1,3}^2 + T_{2,1,3}^2 \\
&T_3^2 + T_{2,3}^2 + T_{1,2,3}^2
\end{aligned} \tag{19}$$

First terms are unconditional while others are conditional. It requires examination of  $p \times 2^{(p-1)}$  pieces of terms within all possible decompositions. In MYT decomposition, there is  $p \times (2^{(p-1)} - 1)$  different conditional term. It is reached  $T^2$  variable which gives signal with the calculation and aggregation of disintegrated terms. However, due to the fact that as the number of variable increases, calculation of all terms is difficult; the examination of decomposed terms is difficult, as well.

#### 4. MULTIVARIATE QUALITY CONTROL APPLICATION

Hardness, thickness and weight of the factors affecting painkiller tablets taken from the firms are taken as variables. Hardness is directly efficient with the distribution of the drug and its unit is newton. If the hardness of the drug is higher than optimum value, the drug stays in the stomach for some time and then enters into the intestine. It cannot disperse within the stomach in a desired way and active ingredient cannot show septicemia. If the hardness is lower than optimum value, some crushes are observed in the drug and sometime later, the drug disperses. Thus, hardness of the drug is selected as the quality variable. Thickness is in direct proportion with the amount of drug ingredient. Its unit is millimeter. Weight is the weight of one tablet of a drug and its unit is milligram. This is also another variable affecting quality. Three quality variables in our application and directional correlation coefficients calculated with 50 samples are shown in Chart 1 correlation matrix.

**Table 1.**Correlation matrix of quality variables

	Hardness	Thickness	Weight
Hardness	1	0.385875	0.772833
Thickness	0.385875	1	0.195987
Weight	0.772833	0.195987	1

#### Forming of Reference Data Set and 1<sup>st</sup> Phase Control Charts

1<sup>st</sup> Phase process was applied for 50 observation in order to acquire reference data set in our study.

By using (3) and (1) numbered equations;

$$UCL = \frac{49^2}{50} \beta_{0,05;3/2,46/2} = 19.82$$

is found



UCL and this  $T^2$  values are compared; observations which  $T^2 \geq UCL$  are extracted from data group. If we draw  $T^2$  control graphic for these values, Figure 2 is acquired.

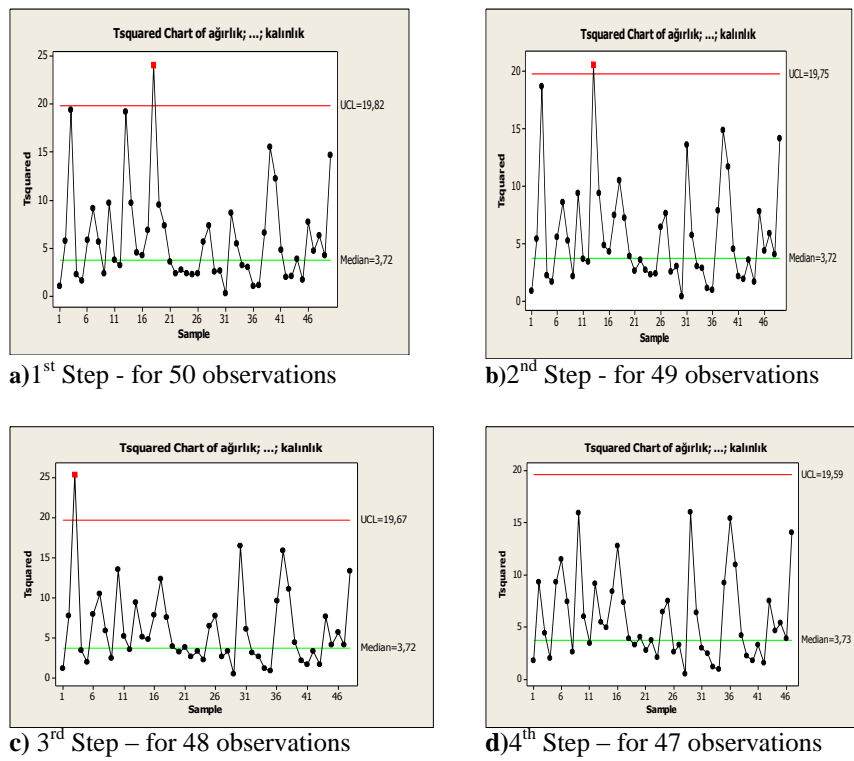


Figure 2. 1<sup>st</sup> Phase  $T^2$  control graph

Extracting values that exceed UCL from data group is repeated until no any uncontrolled situation occurs. In this situation, it is seen that all 47 observation values are smaller than control limits; that is, there is no uncontrolled situation and all samples in Figure d take lower values than UCL. Depending on the other steps and especially on the results of 4<sup>th</sup> step, it is observed that it is reached homogenous data set as reference data set. In this case, the first phase is completed.

With the remaining 47 samples, it is reached  $\bar{X}$  which is estimated for 2<sup>nd</sup> Phase procedures and estimated variance-covariance matrix.

**2<sup>nd</sup> Phase Control Chart**

After forming reference data set, the 2<sup>nd</sup> Phase is applied and this is the control phase. New samples are extracted randomly in order to control the process and variance-covariance matrix coming from reference data set and process average vector are used in acquiring  $T^2$  statistics of these new samples.

Table 2. Statistics determined with HDS(Reference Data Set)

	$X_1$	$X_2$	$X_3$
Average	902.198	175.915	6.931
Max.	920.9	193	7.04
Min.	891	157	6.87
Standard Dev.	6.633003	9.552668	0.032074

$\bar{X} = (902.198, 175.915, 6.931)$  process average vector of reference data, correlation matrix;

$$R = \begin{bmatrix} 1.000000 & 0.535903 & 0.838209 \\ 0.535903 & 1.000000 & 0.433163 \\ 0.838209 & 0.433163 & 1.000000 \end{bmatrix}$$

As it can be clearly seen from the correlation matrix, the relationship among quality variables increased in the last situation when compared with the first situation. Covariance matrix of reference data set is;

$$S = \begin{bmatrix} 43.06063 & 33.23386 & 0.174535 \\ 33.23386 & 89.31191 & 0.129896 \\ 0.174535 & 0.129896 & 0.001007 \end{bmatrix}$$

When the new data in Figure 2 chart is examined regarding 30 samples extracted for the 2<sup>nd</sup> phase randomly, it is seen that 3 of the 30 samples give uncontrolled signal when it is evaluated through comparing with UCL=9.021.

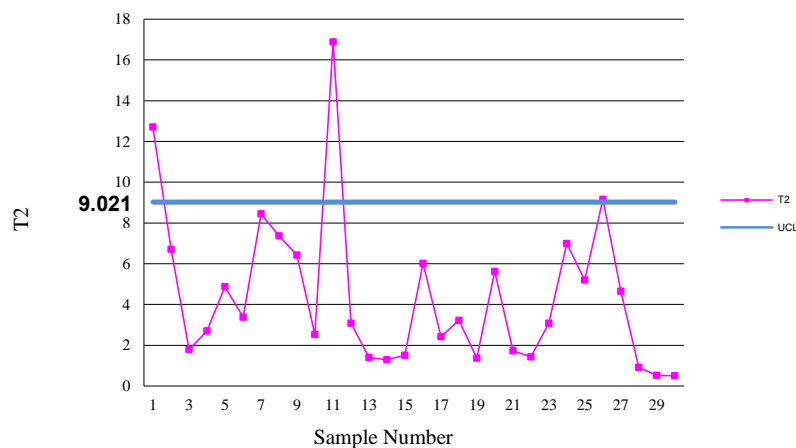


Figure 3.2<sup>nd</sup> Phase  $T^2$  control graph

### MYT Decomposition Management Application

When the decomposition of samples producing uncontrolled signal is realized, firstly unconditional terms ( $T_1^2, T_2^2, T_3^2$ ) are calculated. We compare critical values by calculating from equality (19);  $cv_{\text{unconditional}} = 4.133$  value  $T_i^2$  with unconditional value.

As it is known unconditional terms are calculated with the formula in equality 14. 3<sup>rd</sup> observation vector giving signal is calculated for the first term as  $X = (889.75, 184.5, 6.89)$ ;

$$T_1^2 = \frac{(x_1 - \bar{x}_1)^2}{s_1^2} = \frac{(889.75 - 902.19)^2}{6.63} = 3.598$$

and in other unconditional terms, in this way it is calculated as  $T_1^2 = 3.598$ ,  $T_2^2 = 0.825$ ,  $T_3^2 = 1.692$ .

Because all  $T_i^2 < cv_{\text{unconditional}}$ , the reason of this uncontrolled observation may be the relationship among the variables. It can be observed through examining conditional variables in order to find that signal comes from which variables or the relationship among variables.

Disintegration of conditional variables;

By using the equation in Part 3, we shall calculate  $T_{i,j}^2$  conditional terms  $T_{3,1}^2$  and  $T_{2,1,3}^2$  conditional terms. In order to calculate  $T_{3,1}^2$ , we need  $\bar{X}_{3,1}^{(p-1)}$  and  $s_{3,1}^2$ .

With the equality (9),

$$\bar{X}_{3,1}^{(p-1)} = 6.931 + 0.004(889.750 - 902.198) = 6.880$$

and equality (11), it is found as

$$s_{3,1}^2 = 0.001 - (0.174)(43.06)^{-1}(0.174) = 0.0003.$$

According to the equation in equality (10);  $T_{3,1}^2 = \frac{(6.89 - 6.88)^2}{0.0003} = 0.281$

Other conditional terms are calculated with the same method and shown in chart 3.

Critical value of conditional variables is found with equality (18) of first conditional variables for

$$k = 1.cv_c = \left[ \frac{48 * 46}{47 * 45} \right] F_{0.05;1,45} = 4.234 \text{ as the critical value.}$$

**Chart 3.**  $T_{i,j}^2$  Conditional Terms

$$T_{i,j}^2 = 7.971^* \quad T_{2,1}^2 = 5.198^* \quad T_{3,1}^2 = 0.281$$

$$T_{1,3}^2 = 2.187 \quad T_{2,3}^2 = 2.666 \quad T_{3,2}^2 = 3.533$$

$T_{1,2}^2$  and  $T_{2,1}^2$  values are higher than  $cv_c$  these cause signal.

Finally, we shall calculate  $T_{i,j,k}^2$  conditional terms, for  $T_{2,1,3}^2$ ,  $\bar{X}_{2,1,3}$  and  $s_{2,1,3}^2$ :

In the same equations;

$$\bar{X}_{2,1,3} = 175.915 + \begin{bmatrix} 0.836 \\ -16.057 \end{bmatrix} \left( \begin{bmatrix} 889.75 \\ 6.89 \end{bmatrix} - \begin{bmatrix} 902.197 \\ 6.931 \end{bmatrix} \right) = 166.160$$

$$s_{2,1,3}^2 = 89.311 - \begin{bmatrix} 33.233 \\ 0.129 \end{bmatrix} \begin{bmatrix} 43.060 & 0.174 \\ 0.174 & 0.001 \end{bmatrix} \begin{bmatrix} 33.233 \\ 0.129 \end{bmatrix} = 63.585$$

and

$$T_{2,1,3}^2 = \frac{(184.50 - 166.160)^2}{63.585} = 5.289$$

Remaining  $T_{i,j,k}^2$  conditional terms are calculated with the same method and shown in chart 3.

$$k = 2 \text{ for } cv_c = \left[ \frac{48 * 46}{47 * 44} \right] F_{0.05;1,44} = 4.336$$

**Table 4.  $T_{i,j,k}^2$  Conditional Terms**

$T_{1,2,3}^2 = 4.810^*$	$T_{3,1,2}^2 = 0.372$
$T_{2,1,3}^2 = 5.289^*$	

As a result, we observed in chart 3 that the reason of going out of control was the relationship between  $X_1$  and  $X_2$  variables. We shall check conditional and unconditional terms we examined together with  $T_{i,j,k}^2$  conditional terms in chart 4 by using the feature of MYT decomposition method in equality (19).

$$T^2 = T_1^2 + T_{3,1}^2 + T_{2,1,3}^2$$

$T^2 = 9.169 = 3.598 + 0.281 + 5.289$  is acquired through providing decomposition feature. This feature can be shown within other terms.

## 5. CONCLUSION

In statistical quality control studies, it must be determined which kind of quality control graphic should be used. If there is more than one quality character, control of these variables separately is wrong; at the same time, multivariate quality control techniques which can enable the control of the variables with each other should be used.

Observations composing of 50 samples regarding tablet variables in the first phase were acquired in order to form reference data set in the application. It was found that 47 of these formed reference data set as a result of four steps analyses. In the second phase,  $T^2$  graphic was drawn for 30 new observations and it was detected that three samples were uncontrolled. All uncontrolled points were caused from which variables or from which relationships among variables were determined with the calculation of unconditional and conditional terms in MYT decomposition method. The feature of MYT method and correctness of decomposed terms were also shown. This study can easily be applied to similar drug production processes.

When it is taken into consideration that many of the production processes or products are composed of more than one variable in real life, drawing only univariate  $\bar{X}$  graphics would be insufficient. Calculation of multivariate control methods is not easy when compared to Shewhart charts. Statistical packet programs are needed for these calculations. Graphic and calculation can be performed with the help of software regarding this topic. With these developments, process engineers will get the chance to keep lots of variables and observations under control during production.

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