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Methodology Article

Application of Shewhart Control Charts in the Inspection of Pharmaceutical Manufacturing Process

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Abstract: Control charts, also known as Shewhart Control charts, are used to determine if a manufacturing process is in a state of statistical control. This article illustrates the use of charts to evaluate pharmaceutical manufacturing process variability. According to the characteristics and control requirements of quality parameters, several types of typical parameters were introduced to illustrate the detection results and create the control charts in order to confirm whether the production was under control. Expedite the operator discovering the process variation caused by special factors, and taking corrective actions so that the products consistently complied with the regulatory specifications and production instructions.

Keywords: Pharmaceutical Manufacturing, Statistical Control, Shewhart Control Charts

1. Introduction

The control chart theory has been proposed for decades. Although it is available in various manufacturing industries, it is rarely used in drug manufacturing. This may be related to the use of pharmacopoeia or other legal standards as the products quality control practices in most countries around the world. Although this control method is indispensable, it is only limited to judge whether the samples meet the standards. In order to control the production process, the control chart has its irreplaceable advantages.

Drug production process control is an important strategy for enterprises to ensure product quality, it is necessary to conduct effective, real-time and on-line detection on specific indicators. In order to timely determine whether the intermediate can flow into the next process or not, some parameters need to analysis periodically to keep the process in stable state, such as the moisture of intermediate of solid dosage preparation, weight variation of granules or capsules, Oxygen residue in the top air portion of large volume parenteral solutions (LVP) containers, etc. If judgment of quality only depends on the specification, it is hard to know the trends of quality variance and the causes, and make it difficult to discover the potential factors compromised quality. The advanced in-place monitoring equipment, combined with control charts plotted by computer, can enable the operator timely find out the quality affecting causes (assignable causes), quickly eliminate the impact factors, to ensure the normal production.

2. Types, Plotting Methods and Judging Standard of Control Charts

Control charts, one type of basic tool of quality control [1], there are mainly two types of it: variables control charts and attributes control charts, each type include two categories: The standard value has been given or hasn't been given. As to what type or category of charts should be chosen, depending on the quality attribute, monitoring method, the characteristics of the parameters and control requirements of the product etc.

2.1. General Plotting Steps and Judging Criteria for Control Charts

In general, control chart plotting should base on the data

type (variables or attributes) and control chart type and size of sample etc., design sampling data, including amount of sampling unit [2] or sampling groups and the sample size per group, through the processing of data, calculate the center line and control limits, then plot the control charts, then identify whether the production process is in statistical control or not.

There are two judging criterion to the control chart, one is the criterion of stability, the other is the criterion of un-stability. In drug production, the control chart is used to analyze whether the process is in-control, the principle of judgment generally based on the following points:

2.1.1. Cases of Process in Statistical Control

i. The points on the control chart must be between the upper and lower control limits of the control chart.

ii. The points within the control limits, distributed without defects, that is, in the case of no abnormal arrangement.

2.1.2. Cases of Process Out of Statistical Control

When occur either of the following situation:

i. The distribution of the control point falls out of the upper or lower control limits, or falls on the control limit, component of result, which, in the course of a number of test results or measurement results for the same characteristic or quantity, varies in an unpredictable (random) manner [3].

ii. The points fall within the control limit are not randomly arranged. For example, control points are frequently close to or concentrated near the center-line, or control points are periodically changing, and so on. Whether there is any abnormality in the distribution of judgment points, often based on eight standard tests for special causes, or rules for lack of control [4-5].

2.2. Control Charts Suitable for Drug Production Process Control

Several kinds of control charts are selected below to describe the data processing and plotting methods.

For the purposes of this article, the following symbols apply.

μ_0 A given value of standard value

σ_0 A given value of standard deviation

$\bar{X}$ Average of the samples or Subgroup average

R Subgroup range: difference between the largest value and smallest value of a subgroup

R_m Moving rang: difference between two adjacent values (calculation of absolute value)

$\bar{R}$ Average of the R values for all subgroups or average of R_m

$\overline{Me}$ Average of the median of subgroups

$\bar{\bar{X}}$ Average of the subgroup averages

C_L: Center line

U_{CL}: Upper control limit

L_{CL}: Lower control limit

A, d_2, D_1, D_2, D_3, D_4, E_2, A_2, A_4 Coefficient for calculating control limit of control chart (Values or calculation formula are all obtained from Coefficient tables or the relevant statistical literatures)

USL: Upper Specification Limit

LSL: Lower Specification Limit

$\hat{\sigma}$ Estimated process standard deviation value

2.2.1. The Mean Chart ($\bar{X}$) and Range (R) Control Chart (the Process Parameter Values Have been Given) are Applied to the Weight Control of the Capsule Filling Process

In the filling process of capsule, the weight variation must be control [6]. For one type of β-Lactam antibiotics, the Cefalexin Capsules [Strength 0.125g (Calculated as $C_{16}H_{17}N_3O_4S$)], according to the testing result of intermediate, each capsule ought to reach the expected weight of 187.5 mg. The standard deviation set for the process is 2.7 mg. Considering the rapid operation of automatic capsule filling machine, in addition to the necessary sampling of QA, operators are required to sample regularly. In the past, they only focused on whether the sampling results within the allowable deviation range, it's difficulty to grasp the abnormal trends of weight variation timely, if we design the sampling steps, such as the number of subgroups and sampling interval, put the results of each time as a subgroup, calculate the average and range of subgroups, then we can plot control charts to see if the filling process is under control, according to this, operators are required to take 5 samples periodical to detect their weight of filling respectively. The average ($\bar{X}$) and the range (R) of 5 capsules are automatically calculated through a pre-designed spreadsheet with statistical functionality, in which 25 sets of data are selected to form 25 subgroups with a size of 5, the ($\bar{X}$) and (R) for all subgroups are calculated, as shown in Table 1.

Table 1. *Monitoring data of weight variation during capsules filling process (n=5).*

No.subgroups	Average weight of Subgroups ($\bar{X}$) (mg)	Range of subgroups (*R*)	No.subgroups	Average weight of Subgroups ($\bar{X}$) (mg)	Range of subgroups (*R*)
1	188.6	6.5	16	185.4	4.8
2	185.4	5.2	17	185.3	4.2
3	187.3	7.0	18	188.5	5.9
4	186.9	5.3	19	188.2	8.5
5	188.2	4.1	20	186.6	4.0
6	188.1	7.4	21	185.8	6.2
7	189.9	8.9	22	187.7	5.5
8	186.7	6.5	23	188.3	6.8
9	186.0	4.2	24	185.9	7.8
10	188.1	8.2	25	188.5	5.3

No.subgroups	Average weight of Subgroups ($\bar{X}$) (mg)	Range of subgroups (*R*)	No.subgroups	Average weight of Subgroups ($\bar{X}$) (mg)	Range of subgroups (*R*)
11	187.2	7.0			
12	185.0	7.7			
13	187.8	7.6			
14	188.8	5.4			
15	188.6	7.7			

Because the standard value has been given (μ_0=187.5, σ_0=2.7), using the formula for control limits of Table 1 [7], and the value of the factor A, d_2, D_2, D_1 of Table 2 [7] for n=5, the mean control charts and range control charts can be calculated and plotted.

Control chart for average, $\bar{X}$:

Center line $C_L=\mu_0=187.5$mg

$$U_{CL}=\mu_0+A\sigma_0=187.5+(1.342\times2.7)\approx191.1\text{mg}$$

$$L_{CL}=\mu_0-A\sigma_0=187.5-(1.342\times2.7)\approx183.9\text{ mg}$$

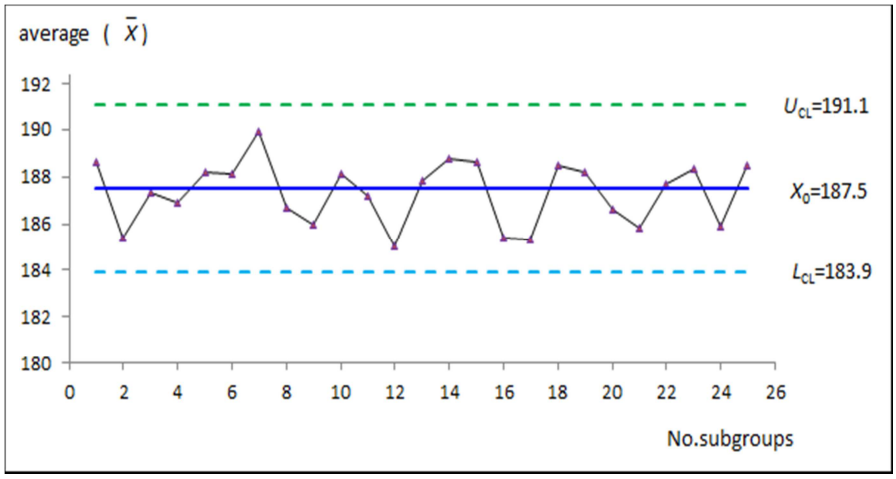
Control chart for moving ranges, R:

Center line $C_L=R_0=d_2\sigma_0=2.326\times2.7\approx6.3$ mg

$$U_{CL}=D_2\sigma_0=4.918\times2.7\approx13.3\text{ mg}$$

$L_{CL}=D_1\sigma_0=0\times2.7$ (since $n<7$, L_{CL} is not shown)

The control charts are plotted in Figure 1, which indicate that the filling process of the capsule is in statistical control.



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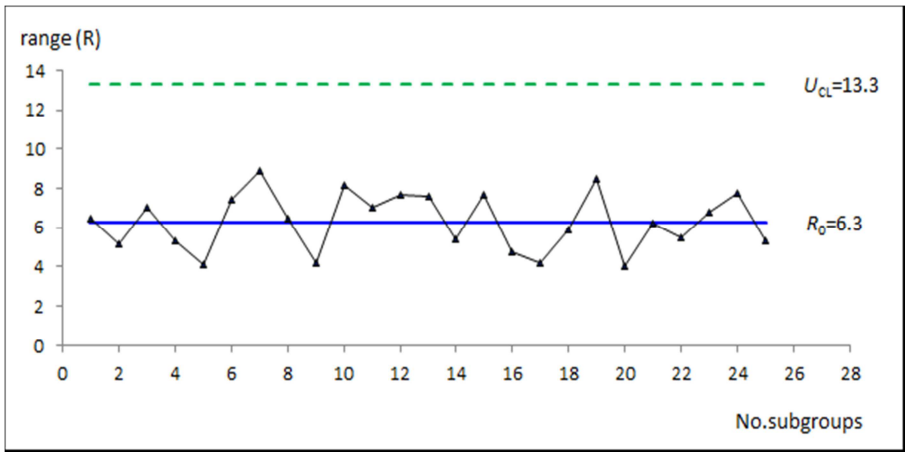

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Figure 1. *X (a) and R (b) charts of the weight of capsule filling in Table 1.*

2.2.2. Individuals (X) and Moving Range (R_m) Control Chart (Cases Where Standard Values are Not Given) Applied to the Assay of Active Pharmaceutical Ingredient (API) and Moisture Monitoring of Intermediate

In the process of tablet production, the intermediate (particles) needs to be mixed before tablet compression. In order to control the reasonable moisture of particles and tablets weight, the blended intermediate need to be sampled for detecting the moisture and assay of API.

Considering that some products may produce dozens of batches continuously in a certain production cycle, in order to understand whether the process control condition in the

production period is in stable, it is necessary to examine some key quality indicators of intermediates, such as moisture and API assay, the former not only affect the smoothness of the tablet process, but also affect the tablets hardness, the dissolution performance and stability, while the content of API in the particles is a decisive factor for the weight of tablet to be pressed. By monitoring the content of moisture and API assay, plotting Individuals and moving range control chart, we can know whether the process control is reasonable and stable.

Tables 2 and 3 show the results of moisture (%) and assay of API ($mg.g^{-1}$) of 20 consecutive batches of intermediate of Phenoxybenzamine Hydrochloride Tablets(one type of α -Adrenergic receptor inhibitor)(Strength 10mg). considering that each batch number is eventually mixed before sampling, only one sample is taken for detection in each batch and the moving range for successive batches is used as the basis for calculating the control limits.

Table 2. *Moisture results of 20 consecutive batches of intermediate (particles) samples.*

Batch number	Moisture (X) (%)	Moving rang (R_m)	Batch number	Moisture (X) (%)	Moving rang (R_m)
1	4.3		11	4.4	0.3
2	2.8	1.5	12	2.9	1.5
3	3.5	0.7	13	3.7	0.8
4	4.0	0.5	14	3.0	0.7
5	3.9	0.1	15	3.1	0.1
6	2.6	1.3	16	4.5	1.4
7	3.3	0.7	17	3.5	1.0
8	3.1	0.2	18	4.2	0.7
9	4.3	1.2	19	3.2	1.0
10	4.1	0.2	20	4.0	0.8

Calculation of $\bar{X}$ and $\bar{R}$:

$$\bar{X}=(4.3+2.8+\ldots+4.0)/20\approx3.62$$

$$\bar{R}=(1.5+0.7+\ldots+0.8)/19\approx0.77$$

Control chart for moving ranges, R:
Center line $C_L=\bar{R}=0.77$

$$U_{CL}=D_4\bar{R}=3.267\times0.77\approx2.52$$

$L_{CL}=D_3\bar{R}=0\times0.77$（since $n<7$, L_{CL} is not shown)

The values of the factors D_3 and D_4 are obtained from Table 2 [7] for n=2. Since the range chart exhibits a state of statistical control, the plotting of the control chart for individuals can be carried out.

Control chart for individuals, X:
Center line $C_L=\bar{X}=3.62$

$$U_{CL}=\bar{X}+E_2\bar{R}=3.62+(2.66\times0.77)\approx5.67$$

$$L_{CL}=\bar{X}-E_2\bar{R}=3.62-(2.66\times0.77)\approx1.57$$

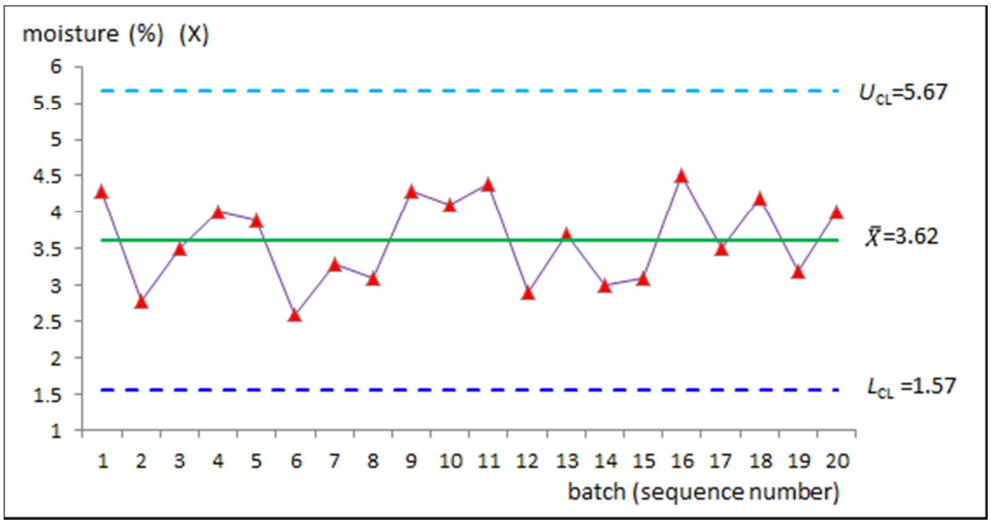
The formula for control limits are obtained from Table 3 [7], and the value of the factor E_2 calculated as follows:

$E_2=3/d_2=3/1.128\approx2.66$ (the value of the factor d_2 are obtained from Table 2 [7] for n=2).

The control charts are plotted in Figure 2, which indicate that the process is in statistical control.

Table 3. *Test results of API assay of 20 consecutive batches of intermediate (particles) samples.*

Batch number	assay (X) ($mg.g^{-1}$)	Moving rang (R_m)	Batch number	assay (X) ($mg.g^{-1}$)	Moving rang (R_m)
1	86.6		11	85.2	2.0
2	84.7	1.9	12	87.0	1.8
3	85.1	0.4	13	86.8	0.2
4	87.3	2.2	14	85.1	1.7
5	87.8	0.5	15	87.2	2.1
6	85.5	2.3	16	84.8	2.4
7	84.9	0.6	17	85.8	1.0
8	86.0	1.1	18	85.5	0.3
9	86.4	0.4	19	86.8	1.3
10	87.2	0.8	20	85.9	0.9



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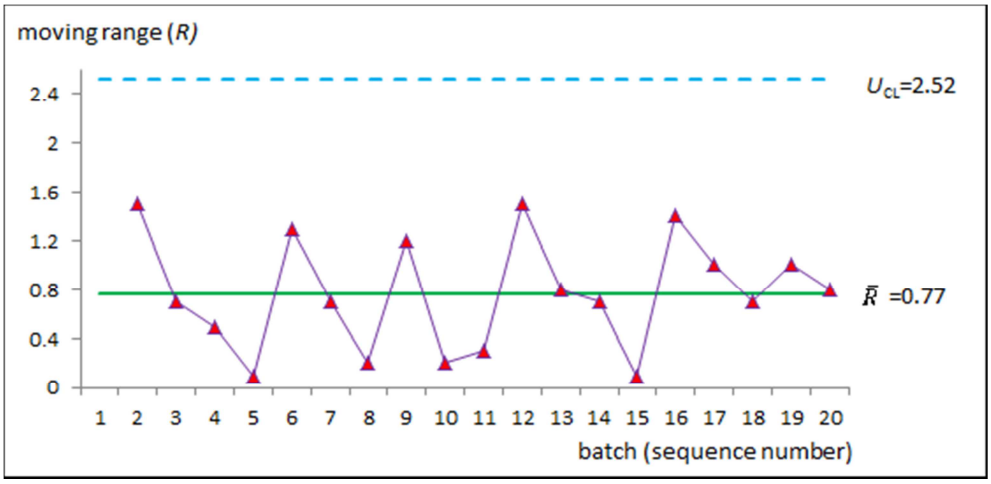

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Figure 2. *X(a)and R (b) control charts of particles moisture data in Table 2.*

Calculation of $\bar{X}$ and $\bar{R}$

$$\bar{X}=(86.6+84.7+\ldots+85.9)/20\approx86.1$$

$$\bar{R}=(1.9+0.4+\ldots+0.9)/19\approx1.3$$

Control chart for moving range, R:

Center line $C_L=\bar{R}=1.3$

$$U_{CL}=D_4\bar{R}=3.267\times1.3\approx4.2$$

$L_{CL}=D_3\bar{R}=0\times1.3$ (since $n<7$, L_{CL} is not shown)

The values of the factors D_3 and D_4 are obtained from Table 2 [7] for n=2. Since the moving range chart exhibits a state of statistical control, the plotting of the control chart for individuals can be carried out.

Control chart for individuals, X:

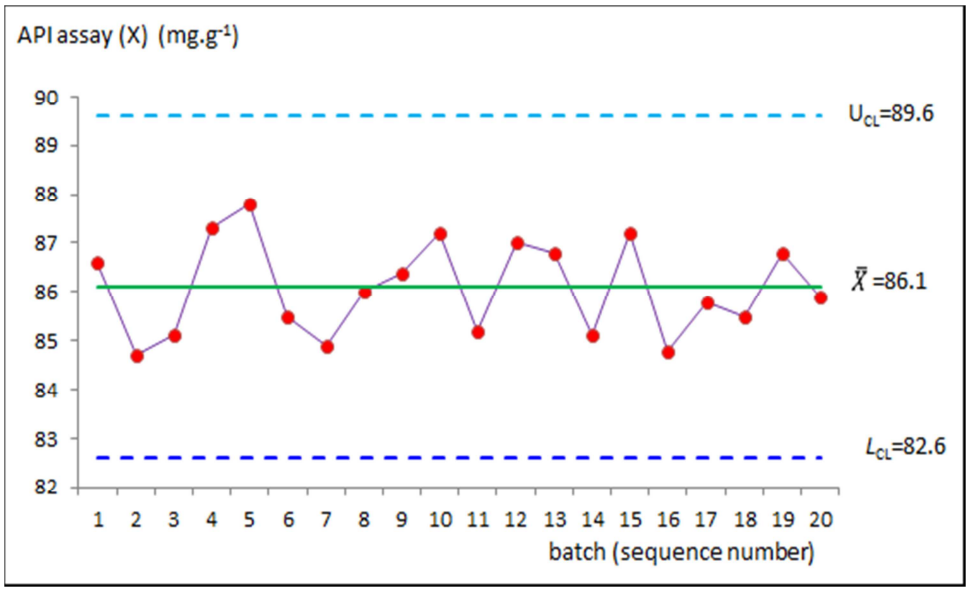
Center line $C_L=\bar{X}=86.1$

$$U_{CL}=\bar{X}+E_2\bar{R}=86.1+(2.66\times1.3)\approx89.6$$

$$L_{CL}=\bar{X}-E_2\bar{R}=86.1-(2.66\times1.3)\approx82.6$$

The formula for control limits and the value of the factor E_2 are calculated in the same way as Figure 2. The control chart is shown in Figure 3.

From Figure 2 and Figure 3, the individuals and moving range control charts of moisture and assay monitoring data can be seen, each of the 20 consecutive points are within the control limit, the state is stable, the distribution of points without sudden variation tendency, two control charts show that the production process is in a stable status. Indicates no factors affecting moisture and assay, and the production process can ensure that the moisture and assay of API meet the quality specification.



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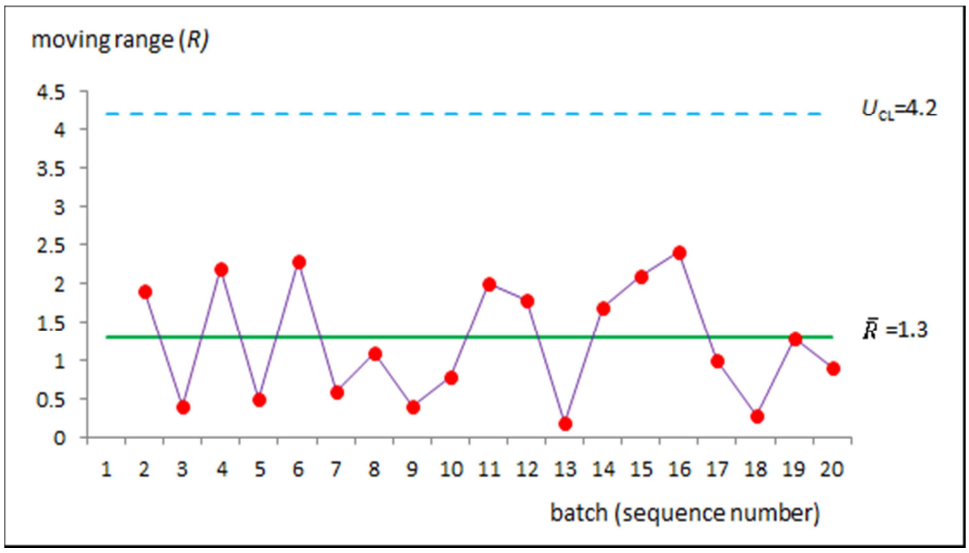

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Figure 3. *X (a) and R (b) control chart of API assay of particles in table 3.*

2.2.3. Median (Me) Chart and Range (R) Chart (Cases Where Standard Values are Not Given) Applied to the Control of Oxygen Residue

The production line of large volume parenteral solution (LVP) (infusion solution) operates quickly, because of the large output per batch, and the processing process is more stable than other dosage-form, we can use the median-range control chart to control the nitrogen filling process, although the median is also from a single sampling point, but it can show the distribution width of process output, predict the process change trends.

In order to ensure the stability of a type of LVP, Lysine Hydrochloride and Sodium Chloride Injection (one kind of amino acid nutrition solution, which can promote protein synthesis and metabolism in human body) (Strength 250 ml: Lysine Hydrochloride 3.0g and sodium chloride 2.25 g), according to the production process, it should be filled into the high purity nitrogen after the solution infused into the container to expel the oxygen away, so as to eliminate the oxidation to the solution. Therefore, it is necessary to detect the concentration of oxygen left in the space of the container after sealing on the automatic production line, according to the previous verification, the acceptable limit of oxygen should be less than 3.5%. The detailed operation is as follows: At the beginning, when the containers begin to infuse solution and fill into the nitrogen, 5 samples were taken from each of the 4 groups of nitrogen outlets, the tester insert the needle probe through the plug into the container to detect the oxygen content of the headspace. In the subsequent production process, repeat the above operation every half an hour, a total of 4 times (composed of 16 subgroups), plus the first 4 subgroups, a total of 20 subgroups including 100 samples. The test results are shown in table 4, by which a median chart was

established. The median and ranges are also given in the table.

Table 4. *Test results of oxygen residue of large volume parenteral solution.*

No. subgroups	oxygen residue (%)					*Me*	*R*
	X_1	X_2	X_3	X_4	X_5		
1	2.1	2.9	2.3	2.8	2.4	2.4	0.8
2	2.5	2.7	2.5	2.8	3.2	2.7	0.7
3	3.1	1.9	2.8	3.2	2.6	2.8	1.3
4	2.4	2.4	2.7	1.8	2.8	2.4	1.0
5	2.7	2.6	2.2	3.1	2.9	2.7	0.9
6	3.3	2.0	2.1	2.2	2.4	2.2	1.3
7	3.3	3.2	2.4	2.5	2.1	2.5	1.2
8	2.2	2.7	2.8	2.9	2.7	2.7	0.7
9	2.7	2.8	2.7	3.0	3.2	2.8	0.5
10	2.3	3.2	3.0	2.2	2.4	2.4	1.0
11	2.8	3.0	2.8	1.8	2.6	2.8	1.2
12	2.3	2.2	2.6	3.0	3.3	2.6	1.1
13	3.1	2.8	2.5	2.3	2.8	2.8	0.8
14	2.8	2.4	1.9	2.4	3.3	2.4	1.4
15	2.3	2.7	2.6	2.9	3.0	2.7	0.7
16	2.9	3.1	2.1	2.5	2.2	2.5	1.0
17	3.1	2.8	2.5	2.8	3.1	2.8	0.6
18	2.5	2.3	3.2	2.6	2.7	2.6	0.9
19	2.8	2.1	3.0	2.5	2.3	2.5	0.9
20	2.4	2.3	2.6	3.3	3.0	2.6	1.0

The averages of median and range for subgroups are calculated as follows:

Average of the median of subgroups ($\overline{Me}$)= (2.4+2.7 +…+2.6)/20≈2.6

Average range ($\bar{R}$)=(0.8+0.7+…+1.0)/20≈1.0

The range chart is calculated as follows:

Range chart

Center line C_L= $\bar{R}$ =1.0

$$U_{CL}=D_4\bar{R}=2.114\times1.0\approx2.1$$

$L_{CL}=D_3\bar{R}=0\times1.0$（since $n<7$, L_{CL} is not shown)

The value of the factors D_3 and D_4 are taken from Table 2 [7] for n=5. Since the range chart exhibits a state of control, the median chart lines can be calculated and plotted accordingly.

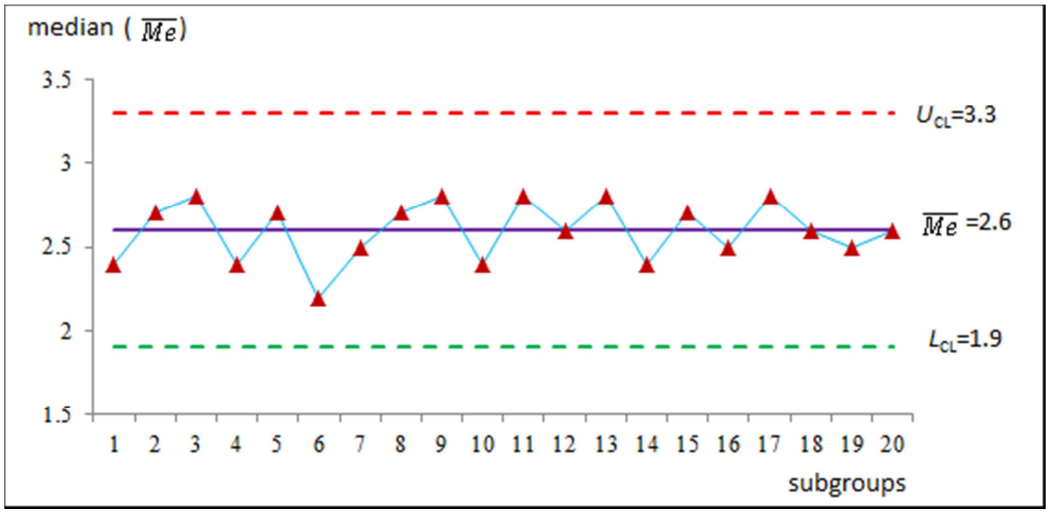
Median Control Chart:

Center line C_L= $\overline{Me}$ =2.6

$$U_{CL}=\overline{Me}+A_4\bar{R}=2.6+(0.691\times1.0)\approx3.3$$

$$L_{CL}=\overline{Me}-A_4\bar{R}=2.6-(0.691\times1.0)\approx1.9$$

The value of A_4 obtained from Table 4 for n=5. This chart shows that the process is exhibiting a state of statistical control.



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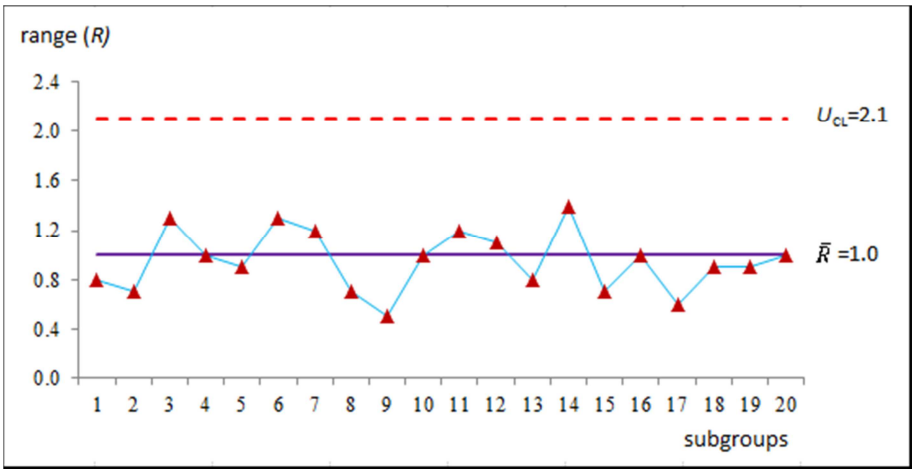

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Figure 4. *$\overline{Me}$ (a) and R (b) control chart of data in table 4.*

2.2.4. Mean ($\bar{X}$) Chart and Range (R) Chart (Cases Where the Standard Value Is Not Given) Are Applied to the Control of the Label Print Location

During the print of package information such as label batch number, production date and expiry date, the information must be printed to a specific blank space. It needs to control the offset of the print position by determining offset based on the horizontal center axis of the product lot number on the label.

For the printing position and the reference do not need to be completely at the same level, an acceptable deviation may exist, as long as the rational design of subgroups and sampling intervals combine with the measured offset value, use the mean and range chart can control the label printing process reasonably.

Set the sampling time interval and sample size, control the position and discreteness by the upper and lower specification limits, so that the print meets the requirements. The method is as follows: The measured offset value of the print position comparing to the specified reference are given in table 5. Take 4 printed label samples every 30min to form a subgroup till 20 subgroups in total, calculate the mean and range of subgroups at the same time. The specified upper specification limit (USL) is 2.3 cm and the lower specification limit (LSL) is 1.2 cm.

Table 5. *Offset value for label print location (n=4).*

No. subgroups	Offset value (cm)				Average of Subgroups $\bar{X}$ (cm)	Range of subgroups (*R*)
	X_1	X_2	X_3	X_4		
1	1.83	1.81	1.97	1.80	1.85	0.17
2	1.92	1.98	2.38	2.00	2.07	0.46
3	1.78	1.71	1.83	1.97	1.82	0.26
4	1.72	1.94	2.12	2.32	2.03	0.60
5	1.90	1.73	2.07	1.90	1.90	0.34
6	2.00	1.93	2.17	2.08	2.05	0.24
7	1.82	1.79	1.88	1.82	1.83	0.09
8	1.69	2.26	2.07	2.09	2.03	0.57
9	2.40	1.83	1.91	2.26	2.10	0.57
10	2.01	1.91	1.88	1.92	1.93	0.13
11	2.00	1.98	2.08	2.02	2.02	0.10
12	1.92	2.00	2.12	2.17	2.05	0.25
13	2.17	1.75	1.96	1.94	1.96	0.42
14	1.92	1.87	1.89	1.99	1.92	0.12
15	2.22	2.20	2.08	1.99	2.12	0.23
16	1.76	1.99	2.25	2.02	2.01	0.49
17	1.62	1.83	1.91	1.78	1.79	0.29
18	1.81	1.59	1.70	1.68	1.70	0.22
19	1.71	1.56	1.70	1.69	1.67	0.15
20	1.70	1.67	1.71	1.60	1.67	0.11

Calculation of $\bar{\bar{X}}$ and $\bar{R}$

$$\bar{\bar{X}} = \sum \bar{X}/20 = (1.85 + 2.07 + \ldots + 1.67)/20 \approx 1.93$$

$$\bar{R} = \sum R/20 = (0.17 + 0.46 + \ldots + 0.11)/20 \approx 0.29$$

Plot *R* chart first and evaluate control status.

R chart

Center line $C_L = \bar{R} = 0.29$

$$U_{CL} = D_4\bar{R} = 2.282 \times 0.29 \approx 0.66$$

$L_{CL} = D_3\bar{R} = 0 \times 0.29$ (since $n < 7$, L_{CL} is not shown)

The values of the factors D_3 and D_4 are obtained from Table 2 [7] for n=4. Because the R values in table 5 are within the control limits of the R chart (see Figure 5), the R chart shows that the process is exhibiting a state of statistical control, therefore, the $\bar{R}$ value can be used to calculate the control limit of the $\bar{X}$ chart.

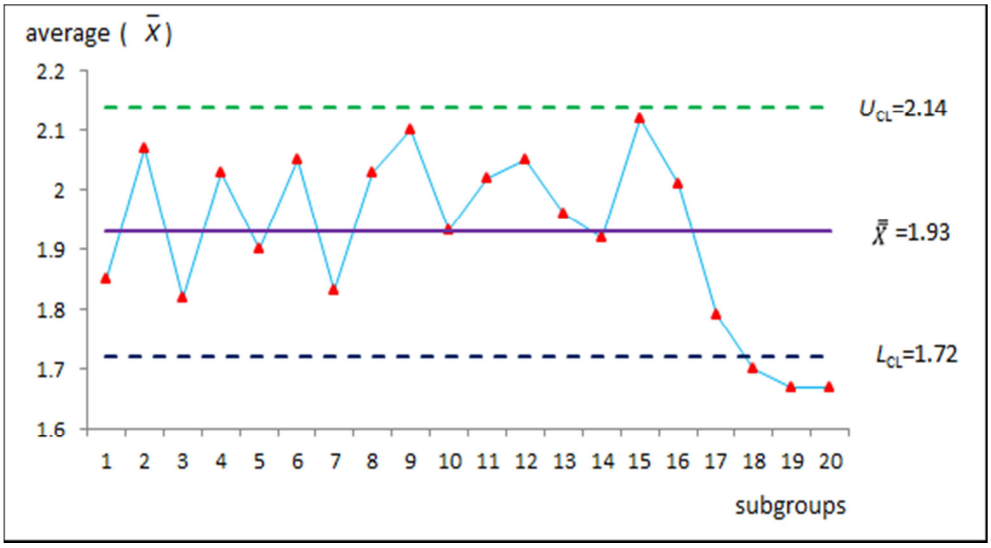
$\bar{X}$ chart

Center line $C_L = \bar{\bar{X}} = 1.93$

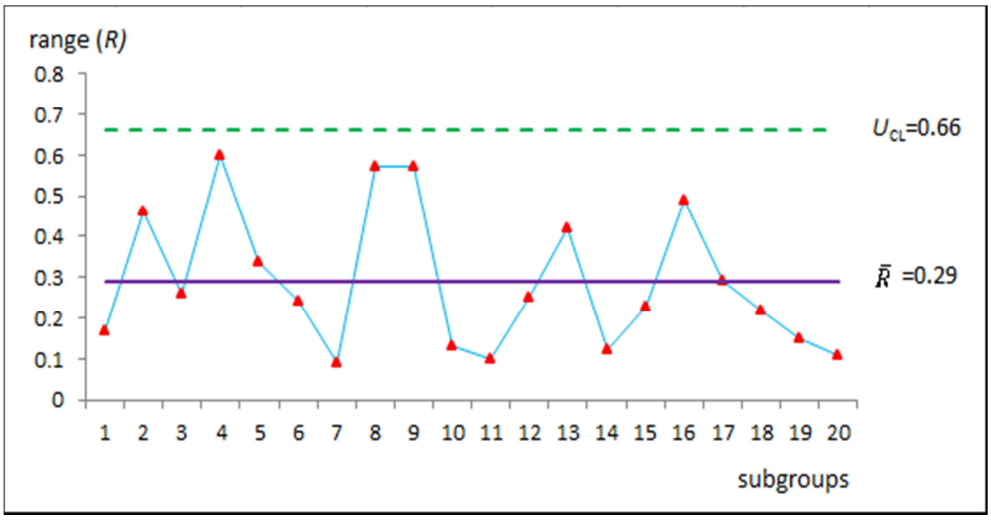
$$U_{CL} = \bar{\bar{X}} + A_2\bar{R} = 1.93 + (0.729 \times 0.29) \approx 2.14$$

$$L_{CL} = \bar{\bar{X}} - A_2\bar{R} = 1.93 - (0.729 \times 0.29) \approx 1.72$$

The values of the factors A_2 is obtained from Table 2[7] for n=4. $\bar{X}$ and *R* charts are drawn in Figure 5.



a



b

Figure 5. *$\bar{X}$ (a) and R (b) charts of data inTable 5, Offset value for label print location.*

2.3. Processing When an Exception Point Occurs in a Control Chart

When the control chart occurs anomaly in the distribution of one or more monitoring values, which conforms to the exception pattern described in the judgment criterion, it indicates that some assignable causes of variation may be operating, which must be diagnosed and corrected in order to eliminate the influencing factors and bring the process into normal state again. Ensure the production continuous compliance with quality standards and process specifications.

The following is illustrated by the unusual trend occurred in the print position control process of the package information print.

Check the mean $\bar{X}$ chart of the print position offset data in Figure 5, it can be observed that the number 18, 19 and 20

are falling outside their corresponding lower control limits. Indicates that there is one or some reason that affects the normal process of the operation, the reasons for these low values should be sought so that corrective action may be taken to prevent continuously. If the control limit is calculated based on the preceding data, action will be required from the 18th point.

By carefully troubleshooting the cause, it is found that there is a blot on the sensor of the printer, which affect the positioning function, and the printing is too close to the reference line, the printed information may overlap with the original scripts on the label.

Clean the sensor of the printer to eliminate the impacts and prevent similar situations from appearing again. Exclude the out-of-control points, that is, the value of the subgroup number 18, 19, 20 points, recalculate the control limit and plot the control chart. The values and control charts of $\bar{\bar{X}}$ and $\bar{R}$ are revised by the following formula (adopt the data of the first 17 subgroups only):

Revised statistical indicators:

$$\bar{\bar{X}}=\sum \bar{X}/17=(1.85+2.07+\ldots+1.79)/17\approx 1.97$$

$$\bar{R}=\sum R/17=(0.17+0.46+\ldots+0.29)/17\approx 0.31$$

Revised parameters of $\bar{X}$ chart:

Center line $C_L=\bar{\bar{X}}=1.97$

$$U_{CL}=\bar{\bar{X}}+A_2\bar{R}=1.97+(0.729\times 0.31)\approx 2.20$$

$$L_{CL}=\bar{\bar{X}}-A_2\bar{R}=1.97-(0.729\times 0.31)\approx 1.74$$

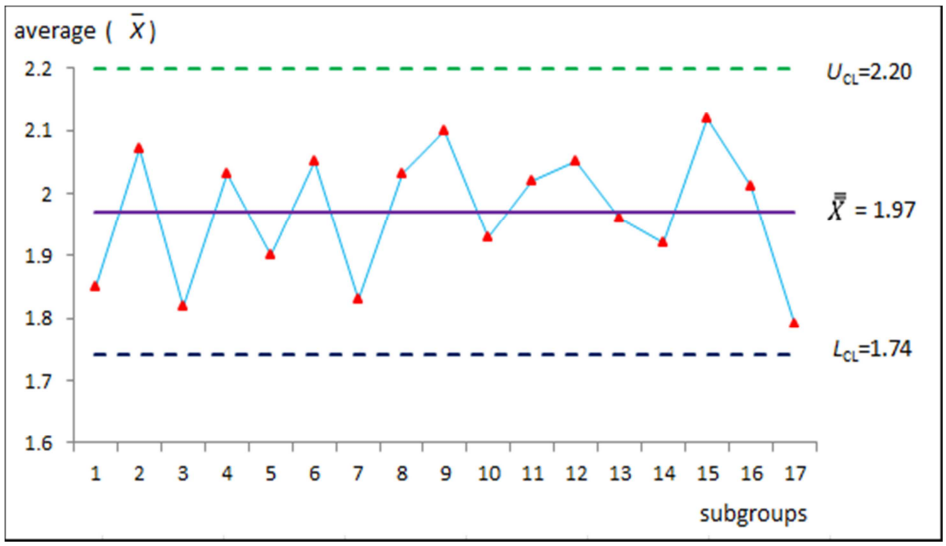
Revised parameters of R chart:

Center line $C_L=\bar{R}=0.31$

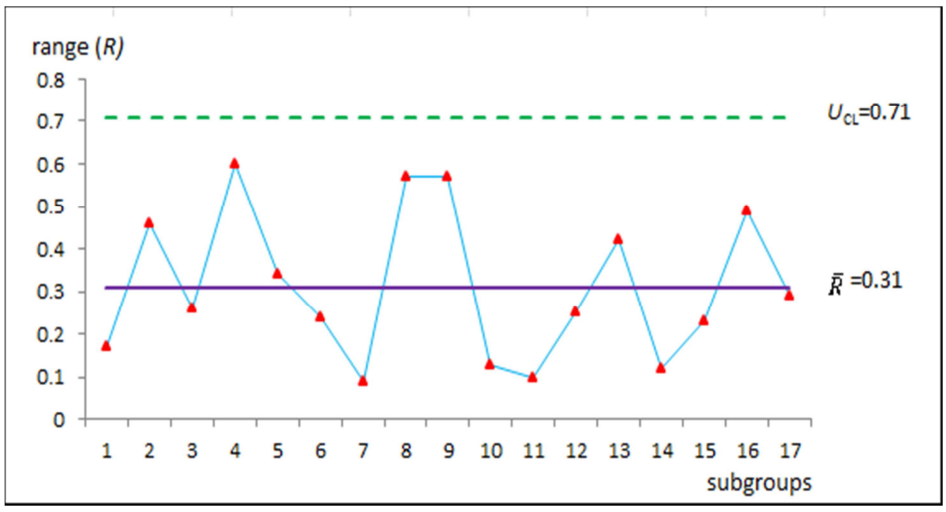
$$U_{CL}=D_4\bar{R}=2.282\times 0.31\approx 0.71$$

$$L_{CL}=D_3\bar{R}=0\times 0.31$$

The revised mean and range charts are shown below (Figure 6):



a



b

Figure 6. *Revised $\bar{X}$(a)and R (b) control chart in Table 5.*

After being revised, the charts exhibit a state of statistical control, by which the process capability can be evaluated.

Compute process Capability Index (PCI):

$$PCI=(USL-LSL)/(6\times \hat{\sigma}) \text{ [8]}$$

The value of $\hat{\sigma}$ calculated as follows:

$$\bar{R}/d_2=0.31/2.059\approx 0.15$$

The value of the factor d_2 is taken from Table 2, where n=4 [7]. Thus:

$$PCI=(2.3-1.2)/(6\times 0.15)\approx 1.2$$

Since PCI is greater than 1, the process capability index can be considered to achieve the expected results basically, considering some data exceed the upper limit of the prescribed specification (see Table 5), it is advisable to take action to adjust the central position of the process to a suitable value, and then establish the relevant parameters so as to keep the process in a better state of statistical control, generally, the minimum acceptable value of CPI is 1.33. In some cases, it's need to adjust the control limits scientifically based on the trends in monitoring data [9], especially in cases where we think the average may have been unduly influenced by extreme values [10].

In the intermediate control process, the plotted points fluctuated in the control chart, indicating that there may be identifiable causes (unnatural/controllable causes) exists, it is important to identify the causes timely, in order to eliminate the occurrence of abnormalities.

3. Conclusion

Shewhart control chart is widely used in manufacturing industry, in the pharmaceutical production process, there are many parameters that need to be controlled in-place so as to ensure conformity of intermediate or semi-product to specified specification or requirements. Based on the characteristics of the parameters and control requirements, each kind of parameter may find a suitable control chart for use.

Shewhart control chart can be used as a monitoring tool in pharmaceutical manufacturing process, which can reduce the reject ratio and promote the continuous improvement of products.

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