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Optimizing Performance of Tablet's Direct Compression Process Using Fuzzy Goal Programming

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Abstract**—**This paper aims at improving the performance of the tableting process using statistical quality control and fuzzy goal programming. The tableting process was studied. Statistical control tools were used to characterize the existing process for three critical responses including the averages of a tablet's weight, hardness, and thickness. At initial process factor settings, the estimated process capability index values for the tablet's averages of weight, hardness, and thickness were 0.58, 3.36, and 0.88, respectively. The L_9 array was utilized to provide experimentation design. Fuzzy goal programming was then employed to find the combination of optimal factor settings. Optimization results showed that the process capability index values for a tablet's averages of weight, hardness, and thickness were improved to 1.03, 4.42, and 1.42, respectively. Such improvements resulted in significant savings in quality and production costs.

Keyword**—**Fuzzy goal programming, control charts, process capability, tablet optimization.

I. Introduction

THE pharmaceutical industry is a vital segment of the health care system, which is regulated heavily as any mistakes in product design or production can be severe, costly and even fatal. The compressed tablet is the most popular dosage form in use today. Dolocet is a combination drug, an effective analgesic and antipyretic with a mild effect on the stomach. It is provided in tablet form. The Dolocet solid-dosage tablets are manufactured by compressing a powder formulation into a die. This processing technique is known as direct compression. It offers simplicity, economy, and the potential for high-volume output.

Typically, the tablet quality can be described by several quality characteristics including: (*i*) average weight; the dosage form of a drug is traditionally composed of two ingredients: the active pharmaceutical ingredient (API) which is the drug itself and is a measure of the effectiveness of a drug and the excipient, which is the substance of the tablet or the liquid the API is suspended in. API is used to measure the effectiveness of a drug. The upper and lower specification limits of the tablet weight are 617.4 mg and 642.6 mg. It is preferred that the average tablet weight at nominal, Nominal-The-Best (NTB) type response, (*ii*) average hardness in units of Kilopond (Kp). An acceptable hardness is required and tablet strength testing is necessary for both, research and development of new formulations and for quality control. The lower specification limit for the tablet hardness is 6 Kilopond (Kp), which is considered the larger-the-better (LTB) type response, and (*iii*) Average thickness, which is important for packaging; the uniformity of the thickness indicates that the tablet press is performing well. Variation in the thickness will affect the tablets weight and hardness. The upper and lower specification limits of the tablet thickness are 3.99 mg and 4.41 mg, respectively; hence, the average tablet thickness is considered the nominal-the-best (NTB) type response [1].

The robust design proposed by Taguchi has been only found efficient for optimizing a single response of main interest [2]-[4]. Several approaches have been proposed to optimize process performance with multiple responses [5]-[7]. Nevertheless, determining precise targets for multiple quality responses is often a difficult activity for a process/product engineer [8]-[10]. Therefore, several formulations of goal programming (GP) models were introduced for solving the fuzzy GP (FGP) problems taking into account the decision-maker's (DM's) preferences [11]-[14]. An effective FGP technique is the weighted additive model, which considers all shapes of membership functions, with the objective to minimize the weighted deviations from the imprecise fuzzy values for all quality responses and process factors [15]-[19]. FGP has been utilized for optimizing process performance in many business applications [20]-[21].

In reality, determining the combination of optimal factor settings for tablet manufacturing processes to improve multiple quality responses is a real challenge. This paper, therefore, aims at optimizing the performance of direct compression process for multiple quality characteristics using statistical techniques and weighted additive model in fuzzy goal programming.

II. Process Performance at Initial Factor Settings

A. Control Charts

A control chart is one of the primary monitoring techniques of Statistical Process Control (SPC). Control charts plot the averages of measurements of quality characteristic in samples taken from the process versus the sample number. The chart has a center line (CL) as well as upper and lower control limits (*UCL* and *LCL*, respectively). At initial factor settings, the $\bar{x}-s$ charts for averages a tablet's weight, hardness, and thickness are shown in Fig. 1.

Obviously, the control charts indicate that the process is in statistical control for the three quality responses.

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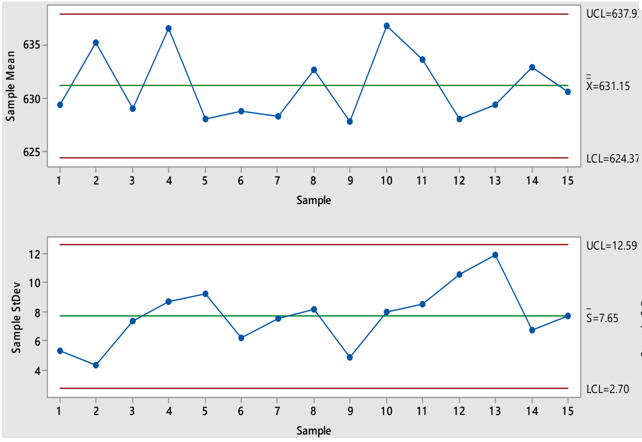
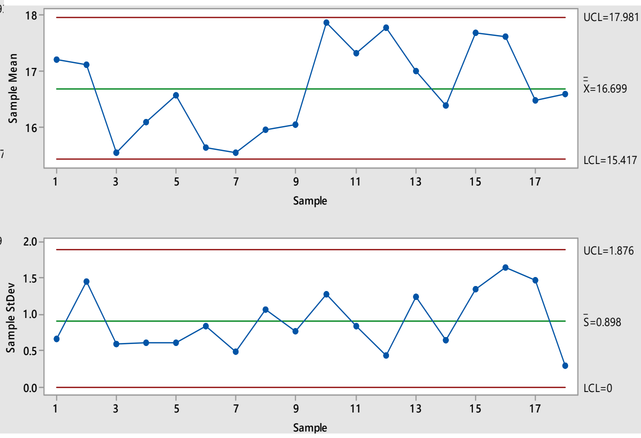
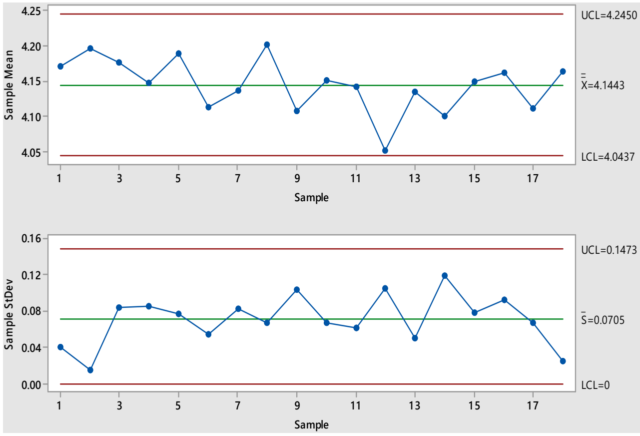


(a) Weight



(b) Hardness



(c) Thickness

Fig. 1 The $\bar{x}$ –s charts for average tablet at initial factor settings

B. Process Capability Analysis

Capability analysis is used to assess whether a process is statistically capable to meet a set of customer desired product specifications. In practice, the process standard deviation, σ , is unknown and is frequently estimated by:

$$\hat{\sigma} = \frac{\bar{s}}{c_4} \tag{1}$$

where c_4 is a constant related to the sample size, while $\bar{s}$ is the *CL* value in the *s* chart. The actual process capability index (C_{pk}) attempts to take the target, *T*, into account. The C_{pk} estimator, $\hat{C}_{pk}$, can be expressed mathematically by:

$$\hat{C}_{pk} = \min\left\{\frac{\hat{\mu} - LSL}{3\hat{\sigma}}, \frac{USL - \hat{\mu}}{3\hat{\sigma}}\right\} \tag{2}$$

where $\bar{\bar{x}}$ is the process mean estimated by the *CL* value of $\bar{x}$ chart. Further, the multivariate process capability (MC_{pk}) is a criterion for selecting an optimal design is known as MC_{pk} and is used as a capability measure for a process having multiple performance measures. MC_{pk} is a proposed system capability index for the process which is the geometric mean of performance measure of C_{pk} values.

$$MC_{pk} = \left(\prod_{1}^{m} C_{pk}\right)^{1/m} \tag{3}$$

where *m* is the number of quality characteristics. For the tablet's weight, 15 samples were taken; each of size 12. While, for each of the tablet's hardness and thickness, 18 samples were taken; each of size 10. The estimated *UCLs and LCLs* of the $\bar{x}$ charts for average tablet weight, hardness, and thickness are displayed in Table I. The estimated means, standard deviations, and $\hat{C}_{pk}$ values calculated and are listed in Table II.

In Table I, the $\hat{C}_{pk}$ values are 0.58, 3.62 and 0.88 for the averages of tablet's weight, hardness, and thickness, respectively. As a result, the tableting process is capable regarding the average tablet hardness, because this value larger than the accepted level (1.33). However, it is found incapable for the averages of weight and thickness. Moreover, the calculated $\hat{M}C_{pk}$ value (= 0.333) is less than one. These results indicate that further process improvement is needed.

III. Process Optimization

Three main process factors are identified affecting the tablet quality, including: Feed Speed (x_1); the speed where the feeder delivers powder from the hopper to the die table. Head Pressure (x_2); which is the amount of force that is applied to compress the powder into tablets. Finally, the Turret Speed (x_3), which is the rotational speed of the die punch. The three factors are assigned each at three levels. The current settings for the tablet dosage are: Feed Speed = 23 rpm, Pressure =15 KN, and the Turret Speed=13 rpm. The L_9 array shown in Table III is selected for experimental design. Twenty samples are selected; each of size 10, 5 and 5 are taken for the weight, hardness and thickness, respectively. Each experiment is repeated three times. The averages of averages are calculated for the three responses and recorded in Table III. Let y_1, y_2, and y_3 denote the measured averages of weight, hardness, and thickness, respectively. To optimize process performance, the weighted additive model in fuzzy goal programming was utilized. The optimization procedure is described as follows:

Step 1: Formulate the mathematical relationship between each quality response and process factors.

The regression model for the average tablet weight (y_1) is formulated as follows ($R^2_{adjusted}=98.4$):

$$y_1=827+311.9x_1-324.6x_2-197.4x_3-6.84x_1^2+13.36x_2^2+11.1x_3^2-6.182x_2x_3$$

The regression model for y_2 is expressed as: ($R^2_{adjusted}=84$):

$$y_2=194+64.8x_1-60.6x_2-60.3x_3-1.6x_1^2+1.2x_2^2+2.32x_3^2+1.06x_2x_3$$

Finally, the regression model for y_3 is expressed as: ($R^2_{adjusted}=87.4$):

$$y_3=2.87+0.18x_1+1.54x_2-1.83x_3-0.073x_1x_2-0.07x_1x_3-0.012x_2x_3$$

TABLE I
Estimated Control Limits and Process Capability Indices

Response	*LSL*	*T*	*USL*	Process settings	*LCL*	*CL*	*UCL*	*LCL*	*CL*	*UCL*	$\hat{C}_{pk}$
Weight	617.4	630	642.6	Initial	624.3	631.14	637.93	2.7	7.65	12.59	0.58
	617.4		642.6	Optimal	628.5	632.29	635.74	1.08	3.81	6.54	1.03
Hardness	6	16	*	Initial	15.43	16.71	17.98	0	0.90	1.88	3.62
	6		*	Optimal	15.78	17.09	18.39	0	0.91	1.90	4.45
Thickness	3.99	4.2	4.41	Initial	4.05	4.15	4.25	0	0.07	0.14	0.88
	3.99		4.41	Optimal	4.10	4.16	4.23	0	0.04	0.09	1.42

TABLE II
Process Capability at Initial Settings

Quality characteristic	Mean	Standard deviation	$\hat{C}_{pk}$
Average weight (mg)	631.15	8.19	0.58
Average hardness (Kp)	16.70	0.07	3.62
Average thickness (mm)	4.14	1.18	0.88

TABLE III
Experimental Data

	x_1	x_2	x_3	y_1	y_2	y_3
1	22	12	14	4.286	18.70	643.370
2	22	13	15	4.228	13.64	619.727
3	22	14	16	4.218	16.40	632.620
4	23	13	14	4.236	17.62	641.980
5	23	14	15	4.172	18.26	632.600
6	23	12	16	4.284	18.96	632.350
7	24	14	14	4.286	17.20	647.360
8	24	12	15	4.192	17.36	628.020
9	24	13	16	4.160	16.82	623.190

Step 2: Choose the suitable membership function representing each response. That is:

a) For the average tablet weight, which is of NTB type response, the trapezoidal membership function, μ_{y_1}, is represented by:

$$\mu_{y_1}=\begin{cases} 0 & y_1 \le 617.4 \\ 1-\dfrac{630-y_1}{12.6} & 617.4 \le y_1 \le 630 \\ 1-\dfrac{y_1-630}{12.6} & 630 \le y_1 \le 642.6 \\ 0 & y_1 \ge 642.6 \end{cases}$$

Let $\omega^-_{y_1}$ and $\omega^+_{y_1}$ denote the negative and positive deviation from the weight target, then the corresponding constrains are:

$$y_1+\omega^-_{y_1}-\omega^+_{y_1}=630$$

$$\mu_{y_1}+\frac{\omega^-_{y_1}}{12.6}+\frac{\omega^-_{y_1}}{12.6}=1$$

$$\omega^-_{y_1},\omega^+_{y_1} \le 12.6$$

b) For the average tablet hardness, which is the LTB type, the membership function, μ_{y_2}, is defined by:

$$\mu_{y_2}=\begin{cases}0 & y_2\le 6\\ 1-\dfrac{17-y_2}{11} & 6\le y_2\le 17\\ 0 & y_2\ge 17\end{cases}$$

Let $\omega_{y_2}^{-}$ denote the negative deviation, the y_2 goal constraints are written as:

$$y_2+\omega_{y2}^{-}=17$$
$$\mu_{y_2}+\frac{\omega_{y_2}^{-}}{11}=1$$
$$\omega_{y_2}^{-}\le 11$$

c) For the average tablet thickness, which is of NTB type, the membership function, μ_{y_3}, is described by:

$$\mu_{y_3}=\begin{cases}0 & y_3\le 3.99\\ 1-\dfrac{4.2-y_3}{0.21} & 3.99\le y_3\le 4.2\\ 1-\dfrac{y_3-4.2}{0.21} & 4.2\le y_3\le 4.41\\ 0 & y_3\ge 4.41\end{cases}$$

Let $\omega_{y_3}^{-}$ and $\omega_{y_3}^{+}$ denote the negative and positive deviation from the thickness target, the y_3 goal constraints are then formulated as:

$$y_3+\omega_{y3}^{-}-\omega_{y_3}^{+}=4.2$$
$$\mu_{y_3}+\frac{\omega_{y3}^{-}}{0.21}+\frac{\omega_{y_3}^{+}}{0.21}=1$$
$$\omega_{y_3}^{+},\omega_{y3}^{-}\le 0.21$$

Step 3: Typically, the DM has no information about the exact values of x_1, x_2 and x_3. Let $\partial_{x_j}^{-}$ and $\partial_{x_j}^{+}$ denote the negative and positive deviations. Therefore, the trapezoidal membership function, μ_{x_j}; j=1,…, 3, is utilized to describe the three process variables as follows:

$$\mu_{x_1}=\begin{cases}0 & x_1\le 21\\ 1-\dfrac{22-x_1}{1} & 21\le x_1\le 22\\ 1 & 22\le x_1\le 24\\ 1-\dfrac{x_1-24}{1} & 24\le x_1\le 25\\ 0 & x_1\ge 25\end{cases}$$

$$\mu_{x_2}=\begin{cases}0 & x_2\le 13\\ 1-\dfrac{14-x_2}{1} & 13\le x_2\le 14\\ 1 & 14\le x_2\le 16\\ 1-\dfrac{x_2-16}{1} & 16\le x_2\le 17\\ 0 & x_2\ge 17\end{cases}$$

$$\mu_{x_3}=\begin{cases}0 & x_3\le 11\\ 1-\dfrac{12-x_3}{1} & 11\le x_3\le 12\\ 1 & 12\le x_3\le 14\\ 1-\dfrac{x_3-14}{1} & 14\le x_3\le 15\\ 0 & x_3\ge 15\end{cases}$$

Step 4: Assign weights to the deviations according to their relative significance to the DM. Then write the complete model as follows:

Minimize Z= $0.35(\omega_{y_1}^{-}-\omega_{y_1}^{+})+0.25\,\omega_{y2}^{-}+0.15(\omega_{y3}^{-}+\omega_{y_3}^{+})$

$$+0.1(\partial_{x1}^{+}+\partial_{x1}^{-}+\partial_{x2}^{+}+\partial_{x2}^{-}+\partial_{x3}^{+}+\partial_{x3}^{-})$$

Subject to:

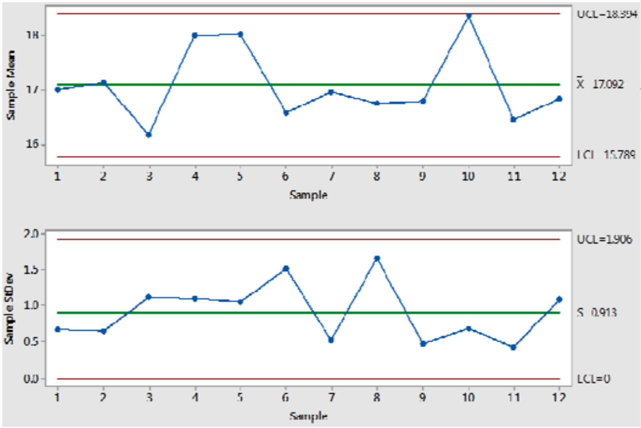
$$x_1+\partial_{x1}^{-}\ge 22,\qquad x_1-\partial_{x1}^{+}\le 24,$$
$$\mu_{x1}+\partial_{x1}^{+}+\partial_{x1}^{-}=1,\qquad 0\le\partial_{x1}^{+},\partial_{x1}^{+}\le 1,$$
$$x_2+\partial_{x2}^{-}\ge 14,\qquad x_2-\partial_{x2}^{+}\le 16,$$
$$\mu_{x2}+\partial_{x2}^{+}+\partial_{x2}^{-}=1,\qquad 0\le\partial_{x2}^{+},\partial_{x2}^{+}\le 1,$$
$$x_3+\partial_{x3}^{-}\ge 12,\qquad x_3-\partial_{x3}^{+}\le 14,$$
$$\mu_{x3}+\partial_{x3}^{+}+\partial_{x3}^{-}=1,\qquad 0\le\partial_{x3}^{+},\partial_{x3}^{+}\le 1,$$

The obtained optimal process conditions were found to be: Feed Speed of 24.28 (rpm), Pressure of 15.169 (KN), and a Turret Speed of 14.42 (rpm). The expected values for the weight, hardness, and thickness are calculated 630 mg, 17 Kp and 4.2 mm, respectively.

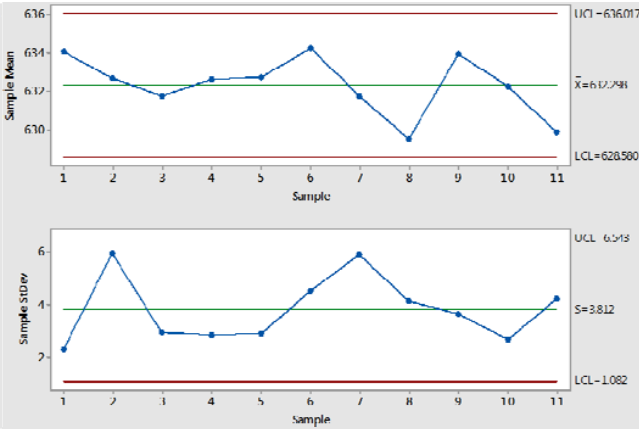
IV. Results

Validation experiments are conducted at the combination of optimal factor settings. Then, the $\bar{x}-s$ charts are established for the three quality responses as shown in Fig. 2. These charts are found to be in-control. Table II also displays the estimated *UCL*, *LCL*, and process capability values at the combination of optimal factor settings.

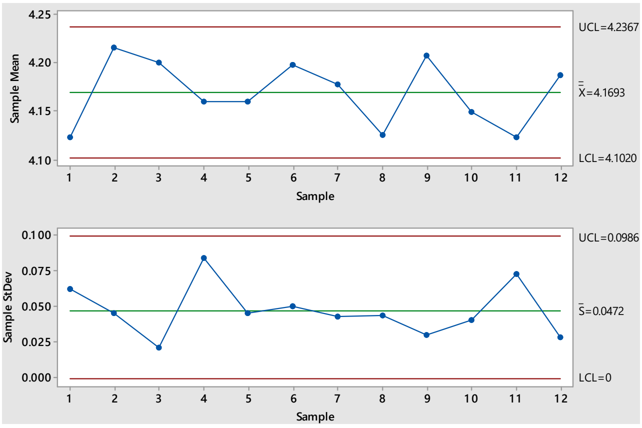
Utilizing the optimal factor settings; Feed speed = 24.28 RPM, Pressure = 15.16 KN, and Turret speed= 14.42 RPM, the $\hat{C}_{pk}$ values for the averages of tablet's of weight, hardness, and thickness are 1.03, 1.42, and 4.45, respectively. The calculated $\hat{MC}_{pk}$ is increased to 1.86. The corresponding improvement ratios were found to be 77.5%, 31.5%, and 61.3%, respectively. Such results will result in significant improvement in quality by reducing the percentage of nonconforming and thereby enhancing productivity.



(a) weight



(b) hardness



(c) thickness

Fig. 2 The $\bar{x}-s$ charts for average tablet at optimal factor settings

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