Multiresponse surface methodology to optimize the tablet’s quality characteristics

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Abstract. Response surface methodology is able to find the setting for input variables that optimize the response. When there is more than one response, the multiresponse surface methodology is used. To optimize these responses simultaneously, especially for quality characteristics, a hybrid method of Fuzzy Goal Programming (FGP) - Genetic Algorithm (GA) can accommodate it. In this research, the tablet's quality characteristics are the level of hardness, the level of friability, and the disintegration time of the tablet. The input variables that are considered to have a significant effect on the quality characteristics of the tablet are levels of binding agents, disintegrants, and the machine pressure on compression process. The use of FGP is based on the reason that this method provides flexibility especially when objective functions and constraints cannot be clearly defined, thus requiring fuzzy numbers as operators. This advantage is not owned by the basic method of common Goal Programming (GP). The use of GA is to find a global optimum solution because it implements a random system.

1. Introduction
Response Surface Methodology (RSM) was first introduced by Box and Wilson [1]. RSM includes experimental strategies for exploring experimental areas, modeling empirical statistics in order to gain an approximation of the relationship between responses and input variables (level of factors), and optimization methods to find the level of factors that optimize response values [2].

One of the problems in a decision is to select the condition of some input variables to get the optimum response in accordance with expectations. The simplest and easiest optimization is a single optimization. In fact, on real single optimization issues are rarely used because the problems encountered are very complex with the responses that need to be optimized are more than one. The optimization performed on multiple responses is called multiresponse optimization.

For multiresponse optimization, there are many complexities affecting response optimization. This complexity arises when an applied setting has optimized one response, not necessarily this setting will also optimize the other response. In fact, not infrequently the conflict between these responses. A workable idea to overcome this problem is to find a solution that is satisfying for all responses.

In the pharmaceutical industry, in order to be competitive and able to survive, it is necessary to achieve a high level of product quality. Since the quality of the product has multiple characteristics, it is necessary to develop a multiresponse surface methodology to optimize tablet manufacturing considering the tablet’s quality characteristics. The purpose of this paper is to get research ideas to address the gaps in existing research on this issue.
2. Multiresponse Surface Methodology

After data as the experimental results are obtained, then the first order model fitting (first order polynomial regression model) is applied. The first order model as in (1).

\[ \hat{y} = \hat{\beta}_0 + \sum_{j=1}^{k} \hat{\beta}_j x_j \]

If there is no serious lack of fit, then the steepest ascent method is used to approach the optimal point of the response. Myers and Khuri [3], also del Castillo [4] have developed the stopping rules used in carrying out this method. The steepest ascent method is described in detail by Khuri and Cornell [5], Box and Draper [6], as well as Myers et al. [2]. Otherwise, the second order model fitting is applied. The equation (2) shows the second order model.

\[ \hat{y} = \hat{\beta}_0 + \sum_{j=1}^{k} \hat{\beta}_j x_j + \sum_{j=1}^{k} \hat{\beta}_{jj} x_j^2 + \sum_{j=1}^{k-1} \sum_{j=1}^{k} \hat{\beta}_{jj} x_j x_j \]

or in matrix notation as in (3),

\[ \hat{y} = \hat{\beta}_0 + x^T \hat{b} + x^T B x \]

In the second-order model, the maximum point, the minimum point, or the saddle point, is identified using a stationary point approach and canonical analysis. If it is a saddle point, for a multiresponse problem, finding the level setting of factors (input variables) that will optimize all responses is usually difficult, since the settings that optimize one response may not necessarily optimize the other response. There are several strategies to solve the multiresponse problem, among them is by plotting contour plots or formulating them into constrained optimization problems. To solve a constrained optimization problem with two responses, Myers and Carter [7] introduced the Dual Response Systems (DRS). This algorithm is selecting a primary response as an objective function and the other response (secondary response) as constraint; and then identify the Lagrange multiplier to find solutions (the levels of the factors) that optimize the primary response function subject to the secondary response function being set equal to a particular value or at a certain value interval.

In industry, the quality of a product or process can have multiple quality characteristics and all of them have to be in "desirable" limit. Based on desirability function which is introduced by Harrington [8], Derringer and Suich [9] proposed a method to find the level setting of factors that provide the "most desirable" response values. For each response \( y_i(x) \), a desirability function \( d_i(y_i) \) assigns numbers between 0 (representing a completely undesirable value of \( y_i \)) and 1 (representing a completely desirable value of \( y_i \)), then the overall desirability is shown in (4).

\[ D = (d_1(y_1) \times d_2(y_2) \times \cdots \times d_q(y_q))^{\frac{1}{q}} \]

Desirability function approach requires clear upper and lower limits on the desired optimum results. The quality characteristic limit is sometimes not predetermined because the optimum response is the smallest (smaller the better/STB) value or the largest (larger the better/LTB) value. In order to avoid the determination of response value limits for multiresponse optimization, Hu, Teng, and Li [10] proposed Fuzzy Goal Programming (FGP). FGP is an extension of conventional goal programming, where the desired value of each response can be treated as a fuzzy goal.

Some heuristic approaches are used for a greater number of factors and/or the number of responses because conventional optimization techniques often fail to find a global optimum solution. Abbasi and Mahlooji [11] showed that in some cases, classical RSM does not perform well because: (1) there is a zonation step in classical RSM where the researcher has difficulties in determining the optimal direction, (2) there is no way to choose the right starting point, and there is a possibility to get stuck in local minimum/local maximum, and (3) in some cases there are indentations at some point which can not always be estimated in the second-order polynomial model.
Routara, Sahoo, Parida, and Padhi [12], Sivasakthivel and Sudhakaran [13] combine Genetics Algorithm (GA) and RSM to optimize machining process parameters. GA is one of the derivative-free stochastic optimization methods based loosely on the concepts of natural selection and evolutionary process. GA encodes each point in parameter (or solution) space into a binary bit string called a chromosome. Each point is associated with a fitness value that, for maximization, is usually equal to the objective function evaluated at the point. Instead of a single point, GA usually keeps a set of points as a population (or gene pool), which is then evolved repeatedly toward a better overall fitness value. In each generation, the GA constructs a new population using genetic operators such as crossover and mutation.

3. Tablet’s Quality Characteristics

The pharmaceutical industry produces various types of medicines to meet the public health needs. Basically, medicine is divided into three groups namely solid production (e.g. tablet), liquid production (e.g. syrup), and semisolid production (e.g. balsam). Tablets are the most widely used dosage form. Tablets are compact solid preparations, manufactured in a compressed or printed manner, in the form of a flat or circular tube, either flat or convex surface, containing one or more types of medicinal material (active substance) with or without additives.

Active substances are the medicine content which has been determined by pharmacists through various tests to cure the disease. Other substances of the tablet are the binding agent to provide adhesion to the mass of powders during granulation, disintegrant to aid the destruction of the tablet after ingestion, lubricant to reduce friction during the compression process and prevent the tablets from sticking to the mold, and diluent to fill the tablets to achieve a predetermined weight [14]. Based on the research of the tablet’s manufacturing process with wet granulation conducted by Nugroho and Shahab [15], it can be obtained fishbone diagram in Figure 1 which shows the considered input variables affect the quality characteristics of tablets. The tablet’s quality characteristics (three response variables) are the level of hardness, the level of friability, and the disintegration time of the tablet, while the factors (three input variables) are levels of binding agents, disintegrants, and the machine pressure on compression process.

4. Discussion

Table 1 shows the existing research and the gaps based on the results of the reviews that have been done.
Table 1. The Existing Research to Find a Global Optimum Solution in Tablet’s Manufacturing Process

| No | Research                                                                 | Proposed Method                                      | Gap                                                                 |
|----|--------------------------------------------------------------------------|------------------------------------------------------|----------------------------------------------------------------------|
| 1  | Response Surface Technique for Dual Response System [7]                  | Dual Response System                                 | • For two responses only                                             |
|    |                                                                          |                                                      | • Does not concern about the quality characteristics as responses   |
| 2  | Simultaneous optimization of several response variables [9]              | The useful class of desirability function            | Requires clear upper and lower limits on the desired optimum results |
| 3  | A fuzzy goal programming approach to multi-objective optimization problem with priorities [10] | Fuzzy goal programming                              | Does not concern to find a global optimum solution                   |
| 4  | Response Surface Methodology and Genetic Algorithm used to Optimize the Cutting Condition for Surface Roughness Parameters in CNC Turning [12], Optimization of Machining Parameters on Temperature Rise in End Milling of Al 6063 using Response Surface Methodology and Genetic Algorithm [13] | Genetic Algorithm for RSM                            | Does not concern on the Tablet’s Quality Characteristics            |
| 5  | Utilization of Response Surface Methodology for Modeling and Optimization of Tablet Compression Process [16], Use of Response Surface Methodology in the Formulation and Optimization of Bisoprolol Fumarate Matrix Tablets for Sustained Drug Release [17], Formulation and Evaluation of Immediate Release Table using Response Surface Methodology [18] | RSM to optimize the tablet’s quality characteristics | Using classical RSM                                                 |
| 6  | Multirespons Surface Optimization on Physical and Mechanical Properties of Drug Tablets with AHP-Fuzzy TOPSIS Method [19] | Hybrid AHP-Fuzzy TOPSIS for RSM                      | Does not find a global optimum solution                             |
| 7  | Application of Surface Response and Goal Programming Methods for Optimization of Physical and Mechanical Properties of Drug Tablets [20] | Goal Programming for RSM                             | Does not find a global optimum solution                             |

5. Conclusion
This review shows that multiresponse surface methodology in particular to optimize the tablet’s quality characteristics requires a new approach to conventional optimization techniques such as the Lagrange method and goal programming. Fuzzy goal program-ming combined with metaheuristic methods such as genetic algo-rithms can be applied successfully in setting the level of input variables as the global optimum solution.

References

[1] Box G E P and Wilson K B 1951 *J. R. Stat. Soc. Ser. B* vol. 13 no. 1 1–45
[2] Myers R H, Montgomery D C, and Anderson-Cook C M *Response Surface Methodology: Process and Product Optimization Using Designed Experiments 4th ed.* Hoboken (New Jersey: John)
[3] Myers R H and Khuri A I 1979 *Commun. Stat. - Theory Methods* vol. 8 no. 14 1359–1376
[4] del Castillo E, Fan S K, and Semple J 1997 *J. Qual. Technol.* vol. 29 no. 3 347–353
[5] Khuri A and Cornell J A 1996 Response Surfaces: Design and Analyses 2nd ed. R. (New York: Marcel Dekker Inc.)
[6] Box G E P and Draper N R 2007 Response Surfaces, Mixtures, and Ridge Analyses 2nd ed. Hoboken (New Jersey: John Wiley & Sons Inc.)
[7] Myers R H and Carter W H 1973 Technometrics vol. 15 no. 2 301–317
[8] Harrington E C 1965 J. Qual. Technol. vol. 21 no. 10 494–498
[9] Harrington G and Suich R 1980 J. Qual. Technol. vol. 12 no. 4 214–219
[10] Hu C F, Teng C J, and Li S Y 2007 A Eur. J. Oper. Res. vol. 176 no. 3 1319–1333
[11] Abbasi B and Mahlooji H 2012 Expert Syst. Appl. vol. 39 no. 3 3461–3468
[12] Routara B C, Sahoo A K, Parida A K, and Padhi P C 2012 Procedia Eng. vol. 38 1893–1904
[13] Sivasakthivel P S and Sudhakaran R 2013 Int. J. Adv. Manuf. Technol. vol. 67 no. 9–12 2313–2323
[14] Farmakope Indonesia 2014 Edisi V (Jakarta: Kementerian Kesehatan Republik Indonesia)
[15] Nugroho I A and Shahab A 2014 Prosiding Seminar Nasional Manajemen Teknologi XXI p. A-7-1--A-7-7.
[16] Garlapati V K and Roy L 2017 J. Young Pharm. vol. 9 no. 3 417–421
[17] Malakar J, Nayak A K, and Goswami S 2012 Int. Sch. Res. Netw. Pharm. 1–10
[18] Atram S C 2011 Asian J. Pharm. vol. 5 46–51
[19] Purwaning R D and Sunaryo S 2015 J. Sains dan Seni ITS vol. 4 no. 1 D85–D90
[20] Nugroho I A 2014 Aplikasi Metode Respon Permukaan dan Goal Programming untuk Optimasi Sifat Fisik dan Mekanik Tablet Obat Thesis (Surabaya: Institut Teknologi Sepuluh Nopember)