Computer Optimization of Pharmaceutical Formulations II: Application in Troubleshooting

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Abstract □ The computer optimization technique presented in a previous paper was applied to a practical situation. The data generated by the set of statistically designed experiments and the subsequent computer analysis were used to indicate the directions necessary to improve various characteristics of a production tablet. Data from experimental size and production size batches are compared with computer predictions.

Keyphrases □ Computer optimization of pharmaceutical formulations—application in troubleshooting production tablet characteristics □ Formulation of pharmaceutical preparations—computer optimization, troubleshooting production tablet characteristics □ Pharmaceutical technology—application of computer optimization to troubleshooting characteristics of a production tablet

The previous paper in this series (1) described the general procedure used for computer optimization developed in these laboratories. The ability of the program to aid in the selection of a formulation with optimum properties was demonstrated.

The optimization technique can be useful in the development of a product by virtue of its capacity to generate a large amount of information and thus help the investigator understand his or her system. The present article reports on the practical application of such a program to another problem area in the pharmaceutical industry—troubleshooting.

The model system originally selected for the optimization study was a product formula. During the development of the optimization technique, it was learned that this product was experiencing some rejections in the production area for failure to meet a dissolution specification. Therefore, dissolution became the response of primary interest, but the objective was to increase the dissolution response without sacrificing other tablet properties.

For practical purposes, in this case a product that was already in production, the experimental range used to collect data for the optimization study was too large. That is, many possible solutions were located where the level of a given ingredient was outside the limits specified in the New Drug Application (NDA) for the product (2). Nevertheless, the results of the optimization procedure were useful because they pointed in the direction of an improved formulation.

Table I—Directions for Improvement from First Grid Search

Independent Variable		Qualitative Level
X_1	Diluent ratio	High
X_2	Compressional force	High[a]
X_3	Disintegrant level	High
X_4	Binder level	Low
X_5	Lubricant level	Low

[a] Maximum pressure set by punch specification.

Table II—Comparison of Tablet Responses

Response	Tablets from Production	Tablets from Experimental Lot (Formula at NDA Limits)
Disintegration time, min.	13.96	8.58
Hardness, kg.	3.80	5.40
Dissolution, % at 30 min.	35.18	67.16
Dissolution, % at 50 min.	60.00	82.02
Friability, %	0.14	2.065

Table III—Responses for Production Granulation Lubricated on Laboratory Scale (Only Levels of Disintegrant and Lubricant Vary)

Response	Production Levels for X_3 and X_5	NDA Limits for X_3 and X_5
Disintegration time, min.	16.04	10.12
Hardness, kg.	8.15	7.45
Dissolution, % dissolved at 30 min.	23.04	67.70
Dissolution, % dissolved at 50 min.	37.13	84.33
Friability, %	0.29	2.44

EXPERIMENTAL

The data utilized here are the same data discussed previously (1). The results of the 27 optimization experiments were analyzed according to the procedures outlined, and the predictions in this paper are based on the second-order regression equations generated[1]. Any additional measurements were carried out by the methods previously reported (1).

RESULTS AND DISCUSSION

The "grid search" program discussed previously (1) resulted in eight choices for an optimum formulation. Although they all contained ingredient levels unacceptable to the present very constrained problem, a trend was noted (Table I).

To test these predictions, it was decided to prepare a formulation with each variable set at its NDA limit in the direction specified by Table I. The method of preparation was identical to that for the 27 optimization experiments, *i.e.*, different from the production method. The initial interest was primarily in trends or qualitative results so that differences in batch size, equipment, lot numbers of material, and test methods were not of immediate concern.

The responses of primary interest for this formula as well as for a sample from production are shown in Table II. The dissolution response had indeed been improved by the changes.

For obvious reasons, as few changes as possible should be made in a production formula. The disintegrant level and the lubricant level, since they are added in the dry state at the end of the process, would be changed most easily.

[1] The predicting ability of individual equations is discussed in *Reference 1*.

Table IV—Computer-Predicted and Experimental Values for Tablet Responses

Response	Production Formula —Prepared on Laboratory Scale— Predicted	Experimental	Recommended Change —Prepared on Laboratory Scale— Predicted	Experimental
Disintegration time, min.	11.45	15.79	7.08	12.50
Hardness, kg.	5.97	5.00	7.30	5.48
Dissolution, % in 30 min.	37.80	26.34	66.26	64.99
Friability, %	0.91	0.46	1.06	1.07
Thickness, mm.	2.44	2.37	2.43	2.36
Porosity, ml./g.	0.0427	0.0418	0.0443	0.0440
Mean pore diameter, μ	0.7135	0.9926	0.6502	0.8488
Dissolution, % in 50 min.	57.18	47.51	82.96	82.57
Mean granule diameter, mm.	0.338	0.327	0.329	0.327
Weight uniformity, *RSD*, %	1.08	0.61	1.40	1.52
Thickness uniformity, *RSD*, %	0.78	0.42	0.79	0.59

Table V—Computer-Predicted and Experimental Values for Responses for Tablets Prepared in Production

Response	—Production Formula— Predicted	Prepared in Production	—Recommended Change— Predicted	—Prepared in Production— Batch 1	Batch 2
Disintegration time, min.	11.45	13.96	7.08	5.79	5.29
Hardness, kg.	5.97	3.80	7.30	6.60	6.42
Dissolution, % in 30 min.	37.80	35.18	66.26	72.30	72.68
Friability, %	0.91	0.14	1.06	0	0.076
Thickness, mm.	2.44	2.40	2.43	2.43	2.42
Porosity, ml./g.	0.0427	0.0878	0.0443	0.0827	0.0877
Mean pore diameter, μ	0.7135	0.9508	0.6502	0.7336	1.3518
Dissolution, % in 50 min.	57.18	60.00	82.96	89.18	87.48
Mean particle diameter[a], mm.	0.338	—	0.329	—	—
Weight uniformity, *RSD*, %	1.08	2.67	1.40	0.96	1.22
Thickness uniformity, *RSD*, %	0.78	1.18	0.79	0.71	0.58

[a] Samples not available for measurement.

Unlubricated granulation was obtained from the production area and lubricated with the dry "adds" at two levels: (*a*) at the production level and (*b*) with the disintegrant and lubricant levels changed to NDA limits. The responses for the two sets of tablets are shown in Table III. Since the production material responded in the same manner as the experimental material (*i.e.*, dissolution improved with the changes in lubricant and disintegrant), such changes were recommended, although of a lesser magnitude.

As a test, two formulations were prepared in the laboratory. One was prepared with the production formula and one with the recommended changes; the changes involved an increase in disintegrant of 0.4 mg./tablet and a decrease in lubricant level of 0.35 mg./tablet.

By using the appropriate coding in statistical units, the computer was asked to perform the same experiments. The results are shown in Table IV. It is important to note that the predicted change is *qualitatively* correct for each response listed. That is, the predicted change and the experimental change are always in the same direction. This in itself makes the optimization program useful. It *can* point in the direction of an improved formulation.

In addition, many computer predictions in the table are quantitatively matched by experimental results. This, of course, is the ultimate goal of the optimization technique and an ideal situation.

As a final test, since the recommended formula performed satisfactorily in the laboratory, a production sample was necessary. Table V represents predicted and experimental values for the responses for tablets prepared totally in production. These data were obtained using the testing procedures previously mentioned (1). For the improved formulation, the dissolution value obtained by the quality control procedure (increased rotation) is approximately 100%. The results were further substantiated by many subsequent production batches.

CONCLUSIONS

The optimization technique is useful in troubleshooting as well as in the development of a new formulation. Because the statistical design and the computerized calculations result in an understanding of variable interactions, more than one variable can be changed at a time with predictable results. Very small changes in ingredient levels result in significantly improved tablet properties, which are adequately reflected in the computer predictions.

It is unlikely that one would carry out an optimization study if faced with the specific problem presented here. An improved formulation would eventually have been found by trial and error; but, if the optimization information is available, its use allows the investigator to reduce the time necessary to accomplish this objective.

The point to be emphasized is that once the optimization data have been generated (usually during development), it can be of great utility in a troubleshooting situation.

REFERENCES

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