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Determination of the sensitivity of a tablet formulation to variations in excipient levels and processing conditions using optimization techniques

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Summary

In anticipation of scale-up activities, a stressing study was conducted on a directly compressible tablet formulation to assess its sensitivity to changes in selected formulation and processing variables. Mathematical modeling and computer-assisted multiple regression analysis, techniques often used in optimization studies, were employed to evaluate the ability of the formulation to withstand these variations without producing detrimental effects upon manufacturing characteristics and tablet performance. The term 'optimization' does not precisely describe the activities of this study since the goal was to demonstrate the acceptability and ruggedness of the existing formulation rather than pursue the perfectly optimal formulation. Empirical equations were determined using response–surface modeling techniques and minimum and maximum values of all response variables calculated. These minimum and maximum values were used to demonstrate the ruggedness of the formulation to processing variables. The formulation proved to be quite durable within the ranges of the variables tested, showing only minimal changes in the monitored response variables.

Introduction

In the process of developing a drug product for NDA submission, it is necessary to characterize the performance of the formulation during processing and also to carry out studies which will assure that the final dosage form will behave in a predictable manner. Current Good Manufacturing Practices (CGMP) require that "...procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" (Federal Register, 1978). Information generated during this phase of development can aid the formulator in scale-up activities and give him assurance that the product will perform acceptably in the face of reasonable variations in processing and manufacturing. This type of information can be obtained by employing the techniques of optimization. With respect to pharmaceutical formulations, optimization can be defined as the systematic approach to achieving the best combination of product and/or process design characteristics under a given set of restrictions. Response surface modeling is used in opti-

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mization to identify values for processing variables which produce this desired combination of design characteristics.

The general utility of optimization procedures in pharmaceutical product formulation and processing has been discussed by Schwartz (1973a, 1979, 1981). One of the earliest applications of optimization in the pharmaceutical literature was the use of the Lagrangian method by Fonner et al. (1970) in evaluating a tablet formulation. Schwartz et al. (1973b) described the application of optimization techniques to troubleshooting in a production setting. The techniques of optimization have also been applied to characterizing a suspension formulation (Buck et al., 1975), an enteric film coating procedure (Dincer and Ozdurmus, 1977), a capsule formulation (Shek et al., 1980), and a slow-release tablet formulation (Harris et al., 1985). The current study is not an optimization per se, since the goal was to demonstrate the acceptability and ruggedness of an existing formulation rather than to pursue a perfectly optimal formulation. It does, however, employ techniques used in optimization studies – namely response surface modeling and computer-assisted multiple regression analysis.

Using response surface modeling techniques, this study was conducted to determine whether a directly compressible tablet formulation of a drug entering scale-up activities can be expected to withstand variations in excipient levels and conditions of manufacture which may occur from other than gross error. Important tablet and in vitro performance characteristics were evaluated to determine if the product performed acceptably within the range of manufacturing variations tested.

Methods and Materials

Chemicals

Lactose NF hydrous spray process standard, microcrystalline cellulose NF medium powder (Avicel PH 101, FMC Corp.), croscarmellose sodium NF Type A, magnesium stearate NF powder food grade, and a proprietary, active ingredient were used in all formulations tested in this study. The micronized active ingredient comprised approximately 5%, by weight, of the formulation. The formulation under study is shown in Table 1. To prepare dissolution media, KCl and HCl of analytical grade were used.

Processing methods

All ingredients were passed by hand through a no. 20 mesh screen. The powder was blended for 378, 450, or 522 revolutions in an 8 quart twin-shell blender. A separate lubricant mixing step was not used. Tablets were manufactured by direct compression using a 16-station tablet machine (Manesty Betapress) interfaced with a digital oscilloscope (Nicolet Model 4094) to monitor compression and ejection forces. The press was equipped with a full set of round, half-oval, scored, 5/16 inch diameter punches.

Testing methods

An average value of the crushing strength of 20 randomly selected tablets was determined using a commercially available hardness tester (Herberlein). The disintegration time of 6 randomly selected tablets was determined in a USP disintegration apparatus without discs. The time of the longest disintegrating tablet was used for evaluation. To determine the friability of a formulation, 35 randomly selected tablets were placed in a friabilator (Roche) turning at 25 rpm for 4 min. The weight loss of each trial was recorded and reported on a percentage basis. The average thickness of 20 randomly selected tablets from each trial was determined using a commercially available micrometer (Snap Gauge). The mean weight and relative standard deviation of 20 randomly

TABLE 1

Tablet formulation

Ingredient	Amount/ CT (mg)
Micronized Drug	10
Lactose NF Hydrous Spray Process Standard	150
Microcrystalline Cellulose NF Medium Powder	20
Croscarmellose Sodium NF Type A	6
Magnesium Stearate NF Powder Food Grade	1.5
	187.5

selected tablets were determined using an analytical balance (Sauter RE 1614) interfaced with a microcomputer (Epson HX-20). A USP type 2 (paddles, 50 rpm) dissolution apparatus was used to determine the dissolution rate of 6 randomly selected tablets. The dissolution flasks contained 900 ml of USP buffer (pH = 2 ± 0.05) equilibrated at 37 °C. Samples were withdrawn and the percent dissolved at 15 min determined by UV spectrophotometry. The content uniformity of each formulation was determined using a high-performance liquid chromatographic assay specific for the active ingredient. Ten tablets were individually assayed and the mean and percent relative standard deviation determined. A representative series of ejection force traces was analyzed using the digital oscilloscope. The initial inflection point on the ejection force trace, not necessarily the peak value, was designated as the break-free ejection force. This is the point where the tablet 'breaks free' in the die.

Experimental design

A 5-variable one-half fractional factorial study design (Anderson and McLean, 1974) was selected with the addition of 3 center points for a total of 19 trials. The trials were conducted in a randomized order, as shown in Table 2. The input variable values were coded into scaled units from −1 to +1. Table 3 lists key experimental constants, independent (input) variables and monitored dependent (response) variables.

Likely operating ranges of the independent variables were established, and experimental ranges (boundaries) within these operating ranges were chosen (Table 4). This was done to keep the size of the experimental regions at a practical

TABLE 2

Experimental design

Trial	*LAR*	*MGS*	*MXR*	*CPF*	*RPM*
1	−1	+1	+1	+1	−1
2	−1	−1	−1	+1	−1
3	+1	+1	+1	+1	+1
4	−1	+1	+1	−1	+1
5	−1	−1	−1	−1	+1
6	+1	−1	−1	+1	+1
7	+1	−1	+1	+1	−1
8	−1	+1	−1	+1	+1
9	−1	+1	−1	−1	−1
10	−1	−1	+1	−1	−1
11	+1	−1	+1	−1	+1
12	0	0	0	0	0
13	+1	−1	−1	−1	−1
14	0	0	0	0	0
15	−1	−1	+1	+1	+1
16	+1	+1	−1	+1	−1
17	+1	+1	−1	−1	+1
18	+1	+1	+1	−1	−1
19	0	0	0	0	0

Scaling	Input variables
+1 indicates upper level	*LAR* = Lactose to microcrystalline cellulose ratio
−1 indicates lower level	*MGS* = Magnesium stearate level
0 indicates center point	*MXR* = Number of mixing revolutions
	CPF = Compressional force
	RPM = Tablet press speed

TABLE 3

Experimental constants and variables

Key experimental constants	
Lot size (10,000 CT)	
Processing equipment	
Drug lot no.	
Excipient lot nos.	
Disintegrant (croscarmellose sodium) level	
Independent (input) variables	Abbreviation
Lactose to microcrystalline cellulose (Avicel, FMC) ratio	*LAR*
Level of magnesium stearate	*MGS*
Number of mixing revolutions	*MXR*
Tablet compressional force	*CPF*
Tablet press speed	*RPM*
Dependent (response) variables	
Percent dissolved after 15 min	*SOLT*
Crushing strength (hardness)	*HRDN*
Thickness	*THCK*
Weight variation	*WTVR*
Disintegration time	*DSNT*
Friability	*FRIA*
Content uniformity	*UNIF*
Break-free ejection force	*BFEF*

TABLE 4

Independent (input) variable ranges

Input variable	Midpoint	Theoretical operating range	Experimental range (−1 to +1)
LAR	7.5:1 (150:30 mg)	5:1 to 10:1 (141.7:28.3 to 154.5:15.5 mg)	6.5:1 to 8.5:1 (147.3:22.7 to 152.1:17.9 mg)
MGS	1.5 mg	0.75–2.25 mg	1.35–1.65 mg
MXR	450 rev	300–600 rev	378–522 rev
CPF	2000	1000–3000	1800–2200
RPM	36 rpm	18–54 rpm	32–40 rpm

level. If the experimental regions were too large, there would have been a decreased likelihood that a standard mathematical model would have described the situation; hence, important details concerning the response surface and the relationships among the variables might have been missed in the analysis.

Data analysis

The data were analyzed using SAS (SAS Institute, Cary, NC), XSTAT (John Wiley and Sons), and a FORTRAN-based in-house regression and optimization package. The collected data are summarized in Table 5.

Results and Discussion

A 5-variable one-half fractional factorial design, with the addition of 3 center points, was employed to provide information on all main effects and two-way interactions with no confounding among terms. This 19-trial, resolution V (Box, 1978) design was also chosen for its expandability (to a central composite design, for example) if a more complicated design was required. The incorporation of replicate center points allows a lack-of-fit test for the model. Standard designs with fewer trials would have resulted in confounding among model terms and increased the risk of

TABLE 5

Data summary

Response variables

Trial no.	*SOLT* (% at 15 min)	*DSNT* (s)	*HRDN* (SCU)	*FRIA* (%)	*THCK* (in.)	*WTVR* (% RSD)	*UNIF* (% RSD)	*BFEF* (lbs.)
1	64.2	110	8.3	0.1353	0.1362	0.6227	1.97	27
2	64.4	107	9.0	0.1492	0.1360	0.7880	1.66	27
3	66.0	110	8.3	0.1782	0.1373	0.4426	0.74	26
4	58.9	90	6.5	0.2235	0.1396	0.8017	1.81	24
5	67.6	80	7.7	0.1815	0.1382	0.4275	0.82	23
6	68.6	105	8.7	0.1800	0.1356	0.4714	1.14	27
7	68.8	85	7.8	0.2084	0.1366	0.5200	1.45	27
8	67.8	70	8.6	0.2100	0.1370	0.5151	0.79	28
9	66.6	95	7.4	0.2248	0.1378	0.4970	0.92	21
10	64.6	80	6.7	0.2688	0.1397	0.5423	0.81	21
11	65.7	80	6.6	0.2602	0.1384	0.4998	3.80	22
12	68.2	100	7.6	0.2531	0.1370	0.6160	1.46	24
13	69.6	70	7.0	0.2244	0.1382	0.4882	0.79	22
14	62.6	105	7.6	0.2203	0.1380	0.4397	0.49	23
15	68.2	115	8.9	0.1735	0.1353	0.3653	1.66	25
16	66.5	120	7.8	0.2192	0.1368	0.4565	2.68	21
17	67.9	80	6.7	0.2512	0.1382	0.3051	0.81	23
18	62.4	85	6.5	0.2749	0.1389	0.4201	0.61	20
19	68.2	105	7.8	0.2221	0.1381	0.4298	0.95	22

SOLT = dissolution time; *DSNT* = disintegration time; *HRDN* = crushing strength (hardness); *FRIA* = friability; *THCK* = Thickness; *WTVR* = weight variation; *UNIF* = content uniformity; *BFEF* = break-free ejection force.

erroneous conclusions. A larger design (e.g. a full factorial) would have required substantially more time and resources, yet would have provided little additional information.

An empirical mathematical model was fitted for each response variable. Eqn. 1 shows the model for the response variable *SOLT* (percent dissolved in 15 min). These regression models include an intercept and terms representing the effect of each input variable, two-way interactions, and the random experimental error.

$$SOLT = \beta_0 + \beta_1(LAR) + \beta_2(MGS) + \beta_3(MXR) + \beta_4(CPF) + \beta_5(RPM) + \beta_{12}(LAR \times MGS) + \beta_{13}(LAR \times MXR) + \beta_{14}(LAR \times CPF) + \beta_{15}(LAR \times RPM) + \beta_{23}(MGS \times MXR) + \beta_{24}(MGS \times CPF) + \beta_{25}(MGS \times RPM) + \beta_{34}(MXR \times CPF) + \beta_{35}(MXR \times RPM) + \beta_{45}(CPF \times RPM) + \varepsilon \quad \text{(Eqn. 1)}$$

This model (designated type I) assumes that higher order effects are negligible. Table 6A contains pertinent regression information as well as minimum and maximum values of the response variables predicted by the model within the design region considered in this study. Appendix 1 contains the estimated regression models for each response as well as *P*-values for tests of model and lack-of-fit significance; r^2-values are also included. A low model (regression) *P*-value indicates that one or more model terms are important for explaining response variability (that is, one or more model coefficients are non-zero). A low lack-of-fit *P*-value indicates that the proposed model is inadequate for describing the data. r^2 measures the proportion of response variability which is associated with the model terms.

As can be seen in Table 6A, the r^2-value for all of the response variables is quite good (84.36–99.78%). However, the lack-of-fit *P*-values

TABLE 6

Regression summary and predicted response variable ranges

Variable	*P*-values		r^2	Predicted values	
	Regression	Lack-of-fit (LOF)		Max.	Min.
A. Model type I					
SOLT	0.5521	0.9235	84.36	69.6%	58.9%
HRDN	0.0016	0.8991	99.78	9.4 SCU	6.3 SCU
THCK	0.0749	0.6345	96.99	0.1397 inch	0.1353 inch
WTVR	0.2640	0.8407	92.13	0.7993%	0.2434%
DSNT	0.2332	0.0276	92.89	–	–
FRIA	0.2170	0.2031	93.29	–	–
UNIF	0.2640	0.2885	92.13	–	–
BFEF	0.1089	0.2529	96.05	–	–
B. Model type II					
DSNT	0.0190	0.3340	98.82	124 *s*	*52 s*
FRIA	0.0150	0.9760	97.50	0.3112%	0.1484%
UNIF	0.0530	0.7270	93.40	3.67%	0.21%
BFEF	0.0290	0.5290	95.63	29 lbs.	18 lbs.

for *DSNT, FRIA, UNIF,* and *BFEF* are quite low, indicating that this type of model is inadequate to describe the situation for these variables. On the other hand, model type I is a good predictor for the variables *SOLT, HRDN, THCK,* and *WTVR*. (A *P*-value for lack-of-fit less than 0.3 was considered to be important enough to warrant the search for an alternate model.)

In those cases where model type I proved to be inadequate, alternate model terms were evaluated. A stepwise regression procedure (*P*-value to enter and stay = 0.15) was used to assess all main effects, two-way interactions, and a quadratic term for usefulness in the model (Kish and Carter, 1984; Neter and Wasserman, 1974). For each of the remaining response variables, it is apparent from the analysis that adding a quadratic term such as $(LAR)^2$ results in a better fit. The lack of fit *P*-value is increased significantly. In order to simplify the models and increase the power for testing model terms, the two or three least significant two-way interactions were eliminated from each model. No model term with $P < 0.4$ was eliminated.

An example is:

$$\begin{aligned} DSNT = {} & \beta_0 + \beta_{11}(LAR)^2 + \beta_1(LAR) + \beta_2(MGS) \\ & + \beta_3(MXR) + \beta_4(CPF) + \beta_5(RPM) \\ & + \beta_{12}(LAR \times MGS) \\ & + \beta_{13}(LAR \times MXR) \\ & + \beta_{14}(LAR \times CPF) \\ & + \beta_{15}(LAR \times RPM) \\ & + \beta_{23}(MGS \times MXR) \\ & + \beta_{24}(MGS \times CPF) \\ & + \beta_{25}(MGS \times RPM) \\ & + \beta_{35}(MXR \times RPM) + \varepsilon \qquad \text{(Eqn. 2)} \end{aligned}$$

This model (type II) also assumes that higher order effects are negligible. Table 6B contains pertinent regression information as well as minimum and maximum values of the response variables predicted by the model within the design region considered in this study. Appendix 2 contains computer regression output about the variables inadequately described by model type I. The insignificant lack-of-fit *P*-values show that inclusion of this extra term provides a good model for these remaining variables.

Since in vitro dissolution data may provide an indication of in vivo bioavailability, *SOLT* (% dissolved at 15 min) was identified as the response variable of primary concern. Its significant lack-of-fit *P*-value (0.9235) and acceptable r^2 value (84.36%) indicate that the hypothesized model is a good one for this variable. The regression *P*-value of 0.5521 demonstrates that the input variables had little effect upon *SOLT* as compared to random experimental error (term ε in the model). The % dissolved in 15 min varied from 62.6% to 68.2% for the three replicated center points as seen in Table 5 (trials 12, 14 and 19). Therefore, in the range of input values tested, the formulation proved to be quite rugged in terms of its dissolution characteristics and can be expected to withstand reasonable variations in excipient levels and processing conditions.

The response variable *HRDN* (tablet crushing strength or hardness) demonstrated an insignificant lack-of-fit *P*-value (0.8991) as well as a significant regression *P*-value (0.0016) and a high r^2 value (99.78%). This indicates that model type I is a good one for this variable, and that, overall, the input variables had a significant effect upon the crushing strength of the tablets. Inspection of the *P*-values for the individual terms reveals that all main effects, as well as several two-way interactions, had a strong impact upon *HRDN*. For example, the variable *MGS* (level of magnesium stearate) gives a regression *P*-value of 0.0090, indicating that it did influence the observed value of *HRDN*. The magnitude of the *MGS* coefficient (−0.1437) indicates that while *MGS* did have an effect upon *HRDN*, it was not as pronounced as the effect of *CPF* (coefficient: 0.7688). Its negative value shows that there is an inverse relationship between *MGS* and *HRDN*. This is not surprising; magnesium stearate is known to have a softening effect upon tablets.

Similar analyses to the above may be made for the remaining terms described by model type I,

namely *THCK* and *WTVR*. The *THCK* regression *P*-value and its r^2-value are significant, indicating that the model is valid and the variability in *THCK* was influenced by the input variables. Not surprisingly, *CPF* was found to have a stronger effect upon *THCK* than any of the other terms in the model. The *P*-value for regression of *WTVR* is only marginally significant, which indicates that the model terms as a whole had an effect upon the variability in *WTVR* which is not much more significant than that which could be explained by random error. The data fit the model, however, as evidenced by the lack-of-fit *P*-value and r^2-value.

Model type II was employed in the analyses of *DSNT, FRIA, UNIF,* and *BFEF*. The *DSNT* lack-of-fit *P*-value (0.3340) is lower than that of the other variables, but is not significant at the 95% level of confidence. This output, along with an r^2-value of 98.82%, indicates that the model describes the variability in *DSNT*. The regression *P*-value (0.0190) shows that the terms of the model did have an effect upon *DSNT*. *CPF* had the strongest impact among the main effects, with a regression coefficient of 10.12 and a *P*-value of 0.0080.

The data of *FRIA, UNIF, BFEF* also fit model type II nicely, as is evidenced by the regression and lack-of-fit *P*-values and r^2-values. *CPF* had the strongest effect upon *FRIA* and *BFEF*, while the interaction term $CPF \times RPM$ had the greatest influence upon *UNIF*.

An advantage of using process optimization techniques in this way is that the empirical models can be used to predict the response values for a given combination of input variables in the design region. An optimization algorithm was employed to search throughout the design region for the largest and smallest response values predicted by the models. These minimum and maximum response value estimates are therefore indicative of the variation in the response that could reasonably be expected to occur due to processing variations in the ranges studied. These predicted extremes are considered to be within acceptable limits. For the formulation studied here, all of the predicted maximum and minimum values are considered acceptable (Table 6A and B). It can therefore be concluded that reasonable variations in processing – such as small changes in lactose to microcrystalline cellulose ratio, magnesium stearate level, mixing time, compression force, and machine speed – still produce a product with satisfactory performance characteristics. It was not the purpose of this study to obtain the ideal, optimized formulation, but rather demonstrate that reasonable variations in processing will not adversely affect product performance. However, if unsatisfactory variations had been predicted in this study, further investigation could easily be done to assess these concerns.

Conclusions

This study confirms that optimization techniques can be a valuable tool for the pharmaceutical formulator. It is shown that computer-assisted regression analysis and mathematical models can be employed to provide accurate representations of the complex relationships between the variables involved in tablet formulation. In this case, tablet dissolution time (*SOLT*) is the response variable of primary concern. It is demonstrated that reasonable alterations in those formulation and processing variables included in this study have an insignificant effect upon this variable. The other response variables are influenced by the input variables, but acceptable minimum and maximum values are predicted by the models.

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Appendix 1

Model term estimates and P-values – model type I

Model term	Coefficient	*SOLT*	*P*-value	*HRDN*	*P*-value	*THCK*	*P*-value	*WTVR*	*P*-value
Intercept	β_0	66.1474	0.0001	7.6579	0.0001	0.1375	0.0001	0.5078	0.0001
LAR	β_1	0.8250	0.3011	−0.2312	0.0023	0.0000	0.9312	−0.0597	0.0703
MGS	β_2	−1.0750	0.2028	−0.1437	0.0090	0.0002	0.1730	−0.0026	0.9118
MXR	β_3	−1.2625	0.1525	−0.2062	0.0032	0.0003	0.1437	0.0166	0.4991
CPF	β_4	0.7000	0.3679	0.7688	0.0001	−0.0011	0.0034	0.0125	0.6045
RPM	β_5	0.2250	0.7563	0.0938	0.0288	0.0000	0.7969	−0.0316	0.2402
LAR × *MGS*	β_{12}	−0.1625	0.8219	0.0437	0.1620	0.0001	0.6714	−0.0418	0.1493
LAR × *MXR*	β_{13}	0.0500	0.9445	0.0813	0.0416	0.0000	0.7969	0.0036	0.8800
LAR × *CPF*	β_{14}	−0.1625	0.8219	−0.0438	0.1620	0.0002	0.2094	0.0097	0.6856
LAR × *RPM*	β_{15}	−0.1125	0.8759	0.0562	0.0981	−0.0001	0.5587	0.0109	0.6493
MGS × *MXR*	β_{23}	−0.9000	0.2671	0.0938	0.0288	0.0000	0.9313	0.0476	0.1156
MGS × *CPF*	β_{24}	0.3875	0.5994	−0.0312	0.2788	0.0002	0.1730	−0.0109	0.6503
MGS × *RPM*	β_{25}	−0.1125	0.8759	−0.0812	0.0416	0.0003	0.0854	0.0402	0.1607
MXR × *CPF*	β_{34}	1.2500	0.1554	0.1062	0.0207	−0.0003	0.1437	−0.0517	0.0972
MXR × *RPM*	β_{35}	−0.3750	0.6106	0.0313	0.2788	−0.0001	0.6713	0.0322	0.2340
CPF × *RPM*	β_{45}	0.6125	0.4230	0.1062	0.0207	0.0000	0.9312	−0.0425	0.1448
		DSNT	*P*-value	*FRIA*	*P*-value	*UNIF*	*P*-value	*BFEF*	*P*-value
Intercept	β_0	94.3158	0.0001	0.2136	0.0001	1.3347	0.0019	23.8421	0.0001
LAR	β_1	−0.7500	0.7859	0.0144	0.1044	0.0988	0.5340	−0.5000	0.2020
MGS	β_2	2.3750	0.4165	0.0044	0.5272	−0.1125	0.4831	−0.2500	0.4752
MXR	β_3	1.7500	0.5383	0.0052	0.4686	0.2025	0.2463	0.0000	1.0000
CPF	β_4	10.1250	0.0279	−0.0285	0.0197	0.1075	0.5011	2.0000	0.0074
RPM	β_5	−1.3750	0.6241	−0.0029	0.6701	0.0425	0.7827	0.7500	0.0923
LAR × *MGS*	β_{12}	4.5000	0.1729	0.0019	0.7838	−0.1800	0.2914	−0.7500	0.0923
LAR × *MXR*	β_{13}	−3.6250	0.2468	0.0007	0.9169	−0.0550	0.7224	0.2500	0.4752
LAR × *CPF*	β_{14}	3.0000	0.3205	0.0004	0.9580	−0.1075	0.5011	−0.2500	0.4752
LAR × *RPM*	β_{15}	3.2500	0.2886	−0.0042	0.5457	0.0775	0.6207	0.2500	0.4752
MGS × *MXR*	β_{23}	2.0000	0.4864	−0.0168	0.0738	−0.2112	0.2309	0.5000	0.2020
MGS × *CPF*	β_{24}	−2.6250	0.3752	−0.0005	0.9418	0.1463	0.3757	−0.2500	0.4752
MGS × *RPM*	β_{25}	−6.1250	0.0938	0.0040	0.5648	−0.2963	0.1263	0.7500	0.0923
MXR × *CPF*	β_{34}	0.5000	0.8558	−0.0130	0.1276	−0.2588	0.1637	0.2500	0.4752
MXR × *RPM*	β_{35}	5.7500	0.1073	−0.0036	0.6069	0.3538	0.0869	−0.5000	0.2020
CPF × *RPM*	β_{45}	−1.3750	0.6241	0.0066	0.3652	−0.4713	0.0443	−0.2500	0.4752

Appendix 2

Model term estimates and P-values – model type II

Model term	Coefficient	*DSNT*	*P*-value	*FRIA*	*P*-value	*UNIF*	*P*-value	*BFEF*	*P*-value
Intercept	β_0	103.333	0.0001	0.2318	0.0001	0.9667	0.0086	23.00	0.0001
LAR	β_1	−0.750	0.4478	0.0144	0.0046	0.0988	0.3688	−0.50	0.1019
MGS	β_2	2.375	0.0562	0.0044	0.1917	−0.1125	0.3117	−0.25	0.3632
MXR	β_3	1.750	0.1213	0.0052	0.1404	0.2025	0.0988	0.00	1.0000
CPF	β_4	10.125	0.0003	−0.0285	0.0002	0.1075	0.3316	2.00	0.0005
RPM	β_5	−1.375	0.1980	−0.0029	0.3653	0.0425	0.6886	0.75	0.0301
LARSQ	β_{11}	−10.708	0.0088	−0.0216	0.0330	0.4371	0.1430	1.00	0.1728
LAR × *MGS*	β_{12}	4.500	0.0073	0.0019	0.5536	−0.1800	0.1318	−0.75	0.0301
LAR × *MXR*	β_{13}	−3.625	0.0153					0.25	0.3632
LAR × *CPF*	β_{14}	3.000	0.0282					−0.25	0.3632
LAR × *RPM*	β_{15}	3.250	0.0219	−0.0042	0.2103			0.25	0.3632
MGS × *MXR*	β_{23}	2.000	0.0884	−0.0168	0.0023	−0.2112	0.0884	0.50	0.1019
MGS × *CPF*	β_{24}	−2.625	0.0423			0.1463	0.2035		
MGS × *RPM*	β_{25}	−6.125	0.0024	0.0040	0.2306	−0.2963	0.0314	0.75	0.0301
MXR × *CPF*	β_{34}			−0.0130	0.0069	−0.2588	0.0490		
MXR × *RPM*	β_{35}	5.750	0.0030	−0.0036	0.2798	0.3538	0.0166	−0.50	0.1019
CPF × *RPM*	β_{45}			0.0066	0.0741	−0.4713	0.0053		

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