

TABLE 20.2

Central Composite Design for $n = 3$ Factors with No Replicate at the Center Point (0,0,0) with the 5 Coded Levels for Each Factor:

$-\alpha, -1, 0, +1, +\alpha$. For $n = 3$ and $p = 0$: $\alpha = 1.215$

Nr.	x_1	x_2	x_3	Nr.	x_1	x_2	x_3
1	-1	-1	-1	9	$-\alpha$	0	0
2	1	-1	-1	10	α	0	0
3	-1	1	-1	11	0	$-\alpha$	0
4	1	1	-1	12	0	α	0
5	-1	-1	1	13	0	0	$-\alpha$
6	1	-1	1	14	0	0	α
7	-1	1	1	15	0	0	0
8	1	1	1				

Source: Leuenberger, H., *Pharmazeutische Technologie*, Sucker, H., Fuchsm, P., and Speiser, P. (Eds.), Stuttgart, Germany: Thieme, 1978.

the results of technological drug–excipient screening program (Leuenberger, 2013). For the study, caffeine anhydrous was used as a drug model. As bioavailability of the API was not tested, the disintegration time was determined and in addition the dissolution profile was characterized by the time point t (in minutes) of 63% API released ($t = t_{63\%}$) by linearization of the profile using Weibull distribution. The Weibull or RRSB (Rosin, Rammler, Sperling, Bennet) distribution is often used to describe the particle size distribution. However, no correlation could be found between the particle size distribution and the dissolution profile of the ensemble of particles (after the disintegration of tablets into particles). In the case of a central composite design with 5 factors, $x_1 =$ filler, $x_2 =$ compression force, $x_3 =$ disintegrant, $x_4 =$ binder, and $x_5 =$ lubricant, it makes sense to reduce the number of trials by confounding the fifth factor with the unlikely 4–fold interaction, that is, $x_5 = x_1x_2x_3x_4$. Thus, a total of 27 experiments are needed (Table 20.3), corresponding to a central composite design with $\alpha = 1.547$ for $n = 5$ factors and $p = 1$ (confounding). The results of this study (Figures 20.4 through 20.6) were published in 1978 by Leuenberger and Guitard, inspired by a publication of Schwartz et al. (1973).

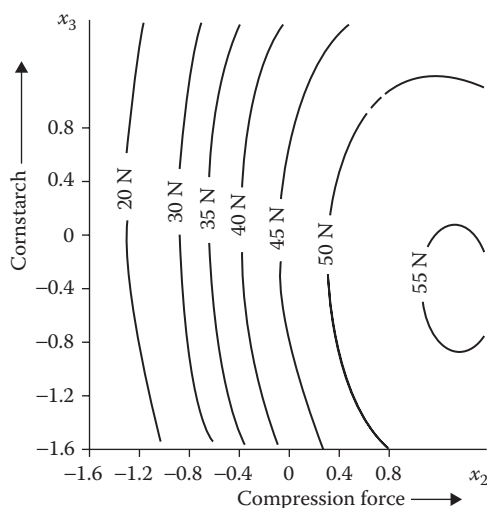


FIGURE 20.4 Contour plot: Tablet hardness [N] as a function of compression force and concentration of corn starch. (From Leuenberger, H., *Pharmazeutische Technologie*, Sucker, H., Fuchs, P., and Speiser, P. (Eds.), Stuttgart, Germany: Thieme, 1978.)