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RESEARCH PAPER

Effect of Formulation Composition on the Properties of Controlled Release Tablets Prepared by Roller Compaction

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ABSTRACT

This study discusses the effect of formulation composition on the physical characteristics and drug release behavior of controlled-release formulations made by roller compaction. The authors used mixture experimental design to study the effect of formulation components using diclofenac sodium as the model drug substance and varying relative amounts of microcrystalline cellulose (Avicel), hydroxypropyl methylcellulose (HPMC), and glyceryl behenate (Compritol). Dissolution studies revealed very little variability in drug release. The t_{70} values for the 13 formulations were found to vary between 260 and 550 min. A reduced cubic model was found to best fit the t_{70} data and gave an adjusted r-square of 0.9406. Each of the linear terms, the interaction terms between Compritol and Avicel and between all three of the tested factors were found to be significant. The longest release times were observed for formulations having higher concentrations of HPMC or Compritol. Tablets with higher concentrations of Avicel showed reduced ability to retard the release of the drug from the tablet matrix. Crushing strength showed systematic dependence on the formulation factors and could be modeled using a reduced quadratic model. The crushing strength values were highest at high concentrations of Avicel, while tablets with a high level of Compritol showed the lowest values. A predicted optimum formulation was derived by a numerical, multiresponse optimization technique. The validity of the model for predicting physical attributes of the product was also verified by experiment. The observed responses from the calculated optimum formulation were in very close agreement with values predicted by the model. The utility of a mixture experimental design for selecting formulation components of a roller compacted product was demonstrated. These simple statistical tools can allow a

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formulator to rationally select levels of various components in a formulation, improve the quality of products, and develop more robust processes.

Key Words: Roller compaction; Controlled release; Sustained release; Diclofenac; Tablets; Glyceryl behenate; Hydroxypropyl methylcellulose; Microcrystalline cellulose.

INTRODUCTION

This report discusses the application of roller compaction for the production of controlled release tablet formulations and evaluates the effect of formulation composition on the attributes of the product obtained. Roller compaction is a dry agglomeration process in which powder densification is achieved by applying mechanical pressure on powders by passing it between two counter-rotating rollers.[1–4] This process results in densified sheets or ribbonlike material, which are then dry sized by milling in a cone mill or impact mill. The resulting granules are often blended with other extragranular excipients and compacted into tablets. Roller compaction is a simple and inexpensive process that does not require wetting and drying steps.[5] The roller compaction process is preferable in instances where the active ingredient is susceptible to moisture of the granulation process and/or heat during the drying process. The characteristics of the product obtained from roller compaction and slugging may be slightly different. As opposed to a slugging process, in roller compaction the product is compressed in an unconfined space between two counter-rotating rollers. In roller compaction, the compacted ribbons are relatively thinner compared to the slugs and therefore require less energy to dry mill into granules. There is virtually no color migration when product is processed by roller compaction. Even though the relatively low manufacturing volumes in the pharmaceutical industry typically dictate the use of batch processes, roller compaction could be more readily adapted for continuous operation for high volume tablet production.

Roller compaction is widely used in many other industries, but it has not found extensive acceptance in the pharmaceutical industry where it has the potential to significantly reduce manufacturing costs and development time. Roller compaction eliminates the need for a drying operation, potentially leading to savings in energy and equipment costs. Furthermore, the process is potentially more easily scalable and may be able to reduce development time. In some situations such as the formulation of controlled release products containing large proportions of rate-modifying hydrophilic polymers, dry granulation by roller compaction may potentially be the most desirable manufacturing process.[6,7]

This study evaluated the use of roller compaction for the production of controlled release formulations and examined the resulting properties of the tablet formulations. Diclofenac sodium was used as the model drug and varying relative amounts of microcrystalline cellulose, hydroxypropyl methylcelullose, and glyceryl behenate were used as the primary excipients. Diclofenac was selected as the model drug because of its acceptable physico-chemical properties, stability, and ultraviolet (UV) detection.[8] Diclofenac is also a good candidate for controlled release because of its short pharmacokinetic half-life. Hydroxypropyl methylcellulose was chosen as the polymer for retarding the release of the drug. Glyceryl behenate was chosen for its ability to decrease the hydration rate of the matrix. Together, these excipients control the release of drug using different mechanisms.

MATERIALS AND METHODS

Materials

The formulations prepared in this study contained a model drug, diclofenac sodium salt (lot 042K1581, Sigma Aldrich, St. Louis, MO); hydrophilic polymer, Methocel K100LV (Dow Chemical Co., Midland, MI); dry binder and release rate modulator, Compritol 888 ATO (glyceryl behenate EP, Gattefosse Corp., Saint-Priest, France, lot 26574); filler/compression aid, microcrystalline cellulose (Avicel PH-101, FMC Corporation, Newark, DE); and lubricant magnesium stearate (Mallinckrodt, St. Louis, MO, lot SP11708).

Methods

Formulation Composition

The formulations and processing conditions were chosen based upon previous experimental data, excipient behavior, and initial feasibility experiments. A

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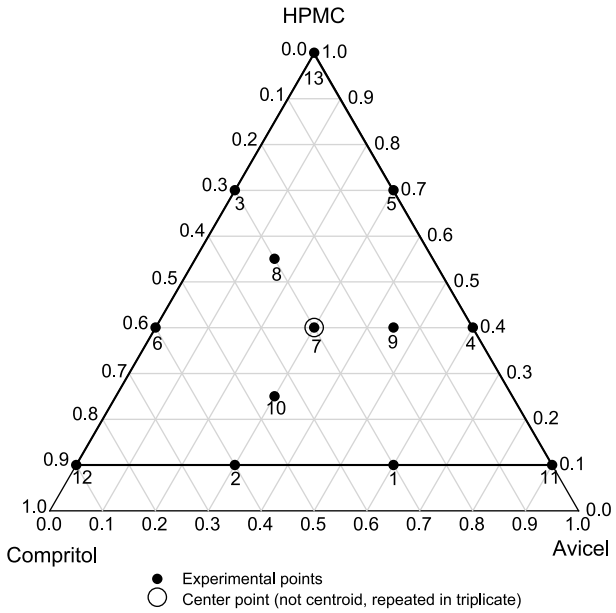

Figure 1. Experimental region and individual formulations studied.

mixture experimental design (Fig. 1) was used to vary the levels of microcrystalline cellulose between 0% and 90%; hydroxypropyl methylcellulose between 10% and 100%, and Compritol between 0% and 90%. The design consisted of a total of 13 distinct experimental points with three replicates of the center-point.

Roller Compaction Process

Powder mixes of 500 g were prepared for these experiments. Each blend contained 100 g of diclofenac sodium salt and 400 g of excipients in various proportions. The formulations were prepared as shown in Fig. 2. Diclofenac sodium salt, Avicel PH-101, Methocel K100 Premium CR, and Compritol were blended together for a period of 5 minutes in a 2-quart V-blender (Patterson–Kelly Co. East Stroudsburg, PA). The blends were then compacted into ribbons on a Fitzpatrick Chilsonator (Model IR220, Fitzpatrick Co., Elmhurst, IL) equipped with concavo–convex roller pair with serrations. Optimum roll speed and feed screw speed were established by observing the point at which compacts with good integrity were obtained. The powders were compacted using the following parameter settings: roll speed of 3 rpm, vertical feed screw speed (VFS) of 125 rpm, horizontal feed screw speed (HFS) of 25 rpm, and a roll pressure of 3000 lb/in. The resulting ribbons were then milled using a Fitzmill Impact Mill (Model L1A, Fitzpatrick Co., Elmhurst, IL) in the ''knives forward'' position with a 0.05-inch sieve and a mill speed of 1000 rpm. The sub-140 mesh size fraction of the milled ribbons was collected using a Ro-tap sieve apparatus (W.S. Tyler, Gastonia, NC). This fraction was reprocessed through the roller compactor using the same parameter settings as used in the first run. The reprocessed ribbon material was then milled and combined with original product in a V-blender for a period of 3 minutes. Each blend was lubricated with 2% w/w magnesium stearate in a V-blender.

Particle Size Analysis of Formulation

Particle size analysis was performed by a sieving procedure using sieves of the following opening sizes: 250 μm, 212 μm, 150 μm, 106 μm, 90 μm, 75 μm, and a pan to collect fines below 75 μm. Approximately 5 grams of blend was used for each analysis. An ATM Sonic Sifter (Milwaukee, WI) was used in sift/pulse mode with a sift amplitude of 5 and a shaking time of 5 minutes. The geometric mean particle size for each formulation was calculated based on the percent material retained on each sieve.

Flow Analysis of Formulation

Flow analysis of the final formulation (after magnesium stearate addition) was performed using the Erweka Granulate Tester (Model GT, Erweka GmbH, Heusenstamm, Germany). Granulation (25 grams) was passed through a 15-mm aperture and the resulting mass flow rate of the formulation was determined.

Tablet Production and Testing

Tablets (400 mg) were prepared using a Korsch single-punch tablet press (model EK-0, Korsch America Inc., Somerset, NJ) and a 14/32-inch Standard B Round Concave punch. Tablets were prepared using an upper punch force of 25 kN and tested for hardness, friability, and dissolution. The crushing strength of 10 tablets from each run was obtained using a hardness tester (model HT-300, Key International, Englishtown, NJ).

Dissolution Testing

Drug release from the tablets was studied in a United States Pharmacopoeia (USP) dissolution testing station type 2 (Vankel Industries, Edison, NJ). De-ionized (DI) water at 37°C was used as the dissolution medium and the paddle speed was maintained at 50 rpm. The amount of drug released was monitored by UV spectrophotometric detection at 276 nm.

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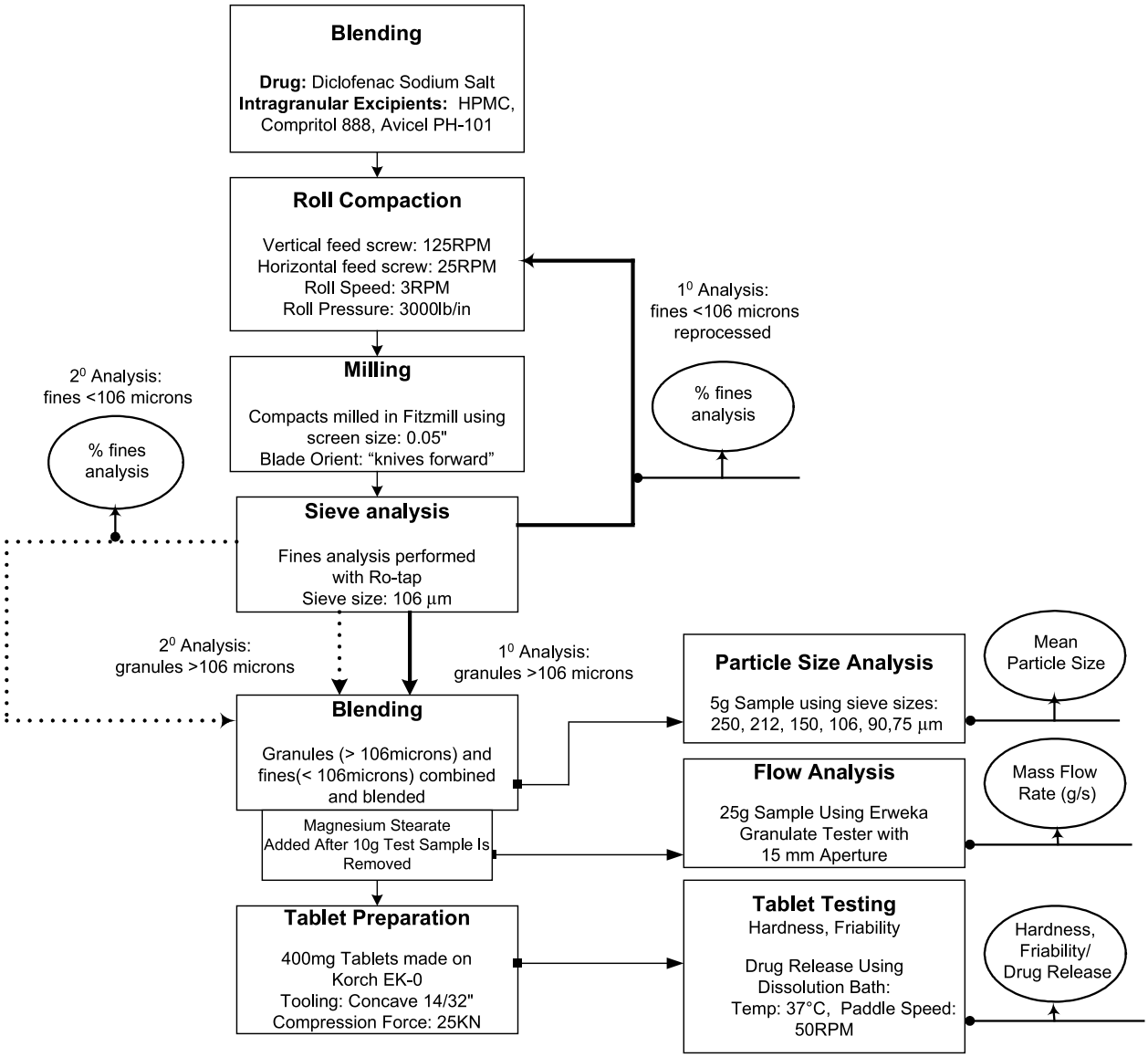

Figure 2. Manufacturing process for diclofenac sodium tablets by roller compaction.

RESULTS AND DISCUSSION

Formulation Composition and the Manufacturing Process

The use of hydrophilic polymers for controlling the release rate of drugs from tablet formulations is well known.[7,9] The most commonly used hydrocolloidal polymer for this application is hydroxypropyl methylcellulose (HPMC). The rate of drug release from tablet matrices containing HPMC can be varied by using polymers with different concentrations, molecular weights, or molecular substitution ratios. Typically, these formulations are prepared by wet granulation and may contain filler materials as well as other excipients useful for tableting. Wet granulation of formulations containing a large proportion of hydrophilic polymers may be more prone to over-granulation because the rate-controlling polymer also functions as a tablet binder.[10] Roller compaction has the advantages of high volume production of granules in a dry process with good control of the granule properties. In this study we used roller compaction to prepare tablets for controlling the release of a highly water-soluble model

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drug, diclofenac sodium. Hydroxypropyl methylcellulose serves the function of a gelling hydrocolloidal polymer for retarding the release of the drug from the matrix. In addition, glyceryl behenate was added as another major formulation component[11] with two expected functions: to reduce the rate of hydration of the matrix, thereby favoring erosion controlled release behavior—this was also expected to reduce variability in the release profiles compared to matrices with HPMC alone; and to improve the bonding during roller compaction, resulting in granules with lower friability. The relatively softer, low-melting glyceryl behenate was expected to function as a plastically deforming binder during roller compaction.

We attempted to systematically study the effect of three primary excipients on the physical attributes of the resulting roller compacted product. The roller compaction variables such as roller speed and feed rate were not studied, as they have been shown to have very little effect on the product attributes.[12] The compaction pressure might be expected to change the granule densities and potentially affect dissolution rate, but the effect of formulation variables was expected to be more significant. The roller compaction speed, feed rate, and pressure were therefore kept constant. The formulation variables were studied by using a mixture design. All formulations contained a minimum of 10% of HPMC K100LV. The levels of glyceryl behenate and microcrystalline cellulose were varied between 0% and 90%. The 13 distinct experimental points within the experimental region are shown in Fig. 1. One of the experimental points that was located approximately in the center of the experimental space was repeated in triplicate to obtain an estimate of the lack of fit during regression analysis.

The manufacturing process for the formulations is shown in Fig. 2. Each of the 13 formulations was tested for a variety of response factors such as percentage of fines, mass flow rate, and mean particle size of the resulting granules as well as dissolution, crushing strength, and friability of the tablets produced. The percentage of fines in the granules may provide an indirect measure of the efficiency of the roller compaction process. However, there was no systematic trend in the percentage of fines produced as a function of the formulation components. Similarly, the final tablet friability did not appear to show any systematic dependency on the formulation variables. From the dissolution profiles, the time for release of 70% of the drug (t_{70}) and the release exponent n were derived by fitting the Peppas[13] equation to the first 80% of the dissolution profile. The tablet crushing strength was a

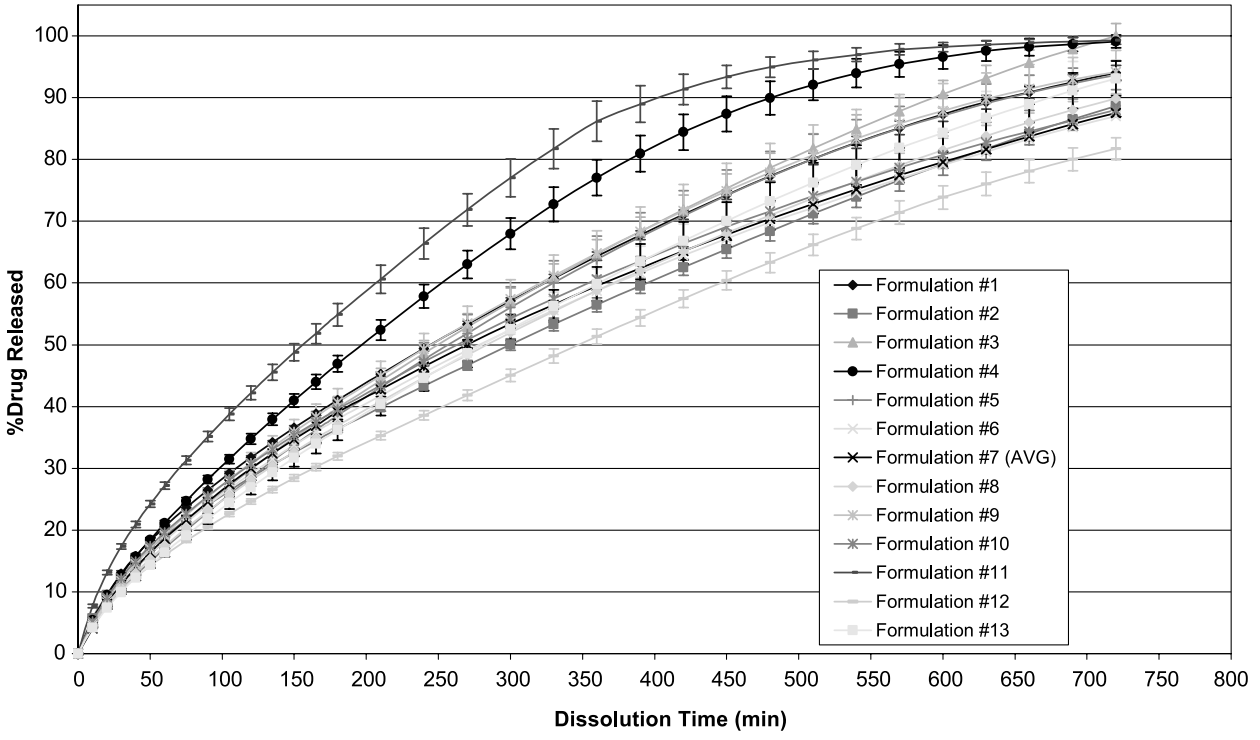

Figure 3. Release profiles of all tablet formulations prepared by roller compaction. (*View this art in color at www.dekker.com.*)

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measured average of 10 tablets compressed at 25 kN in a 14/32" die.

Dissolution

The release profiles of all 13 formulations in DI water are shown in Fig. 3. The individual release profiles showed very low variability. The Peppas equation was fitted to the first 80% of the dissolution profiles of the 13 formulations:

$$M_t/M_\infty = k\ t^n$$

This equation is a useful means of comparing formulations in vitro. The time taken to release 70% of the drug (t_{70}) and a release exponent (n) were calculated from the fitted equations. The t_{70}s of the 13 formulations varied between 260 and 550 minutes. An empirical polynomial equation was fitted to the t_{70} and n values by least squares regression. The equations that best fit the data are shown in Table 1. A reduced cubic model was found to best fit the t_{70} data and gave an adjusted r-squared of 0.9406. In addition to each of the linear terms, the interaction terms between Compritol and Avicel, and between all three of the tested factors were found to be significant. Ternary graphs showing ''isolines'' with predicted values using the regression equations are shown in Figs. 4–6. Interestingly, the tablets with the longest release times were obtained at higher concentrations of Compritol in the formulation. Tablets with higher concentrations of HPMC were also found to have long t_{70}s. As might be expected, tablets with higher concentrations of Avicel showed reduced ability to retard the release of the drug from the tablet matrix (Fig. 4).

Predicted n values using the regression equation are shown in Fig. 5. The range of values for release exponents varied quite narrowly between about 0.63–0.72. More linear profiles could not be obtained, primarily because of the slight initial burst of drug from these matrices. The release profiles appear quite linear after about 60 minutes of drug release. It is quite possible that film-coating of the tablets might reduce the extent of initial burst release of the drug. In general, it is desirable to have release profiles approaching zero order release or an n value as close as possible to 1. In the experimental space selected, the highest n values were obtained at highest levels of HPMC.

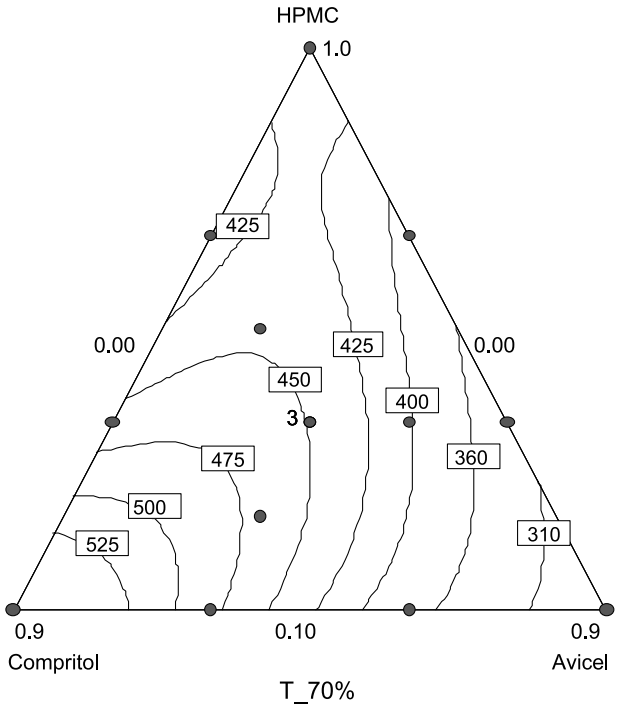

Figure 4. T_70% response as a function of the three independent formulation factors. (*View this art in color at www.dekker.com.*)

Table 1. Regression model coefficients for three responses.

Variables/interaction terms[a]	Log_{10} (crushing strength)	t_{70}	n
Compritol	−0.12	586.73	0.65
Avicel	0.93	269.47	0.65
HPMC	0.77	448.11	0.73
Compritol*Avicel	1.47	–	
Compritol*HPMC	1.57	−361.88	
Avicel*HPMC	–	–	0.19
Compritol*Avicel*HPMC	–	1457.77	−0.54
(Compritol*Avicel)* (Compritol−Avicel)	–	–	−0.29
Model probability>F	<0.0001	<0.0001	<0.0001
Adjusted r-squared	0.9720	0.9406	0.9007
Lack of fit probability>F	0.1082	0.1196	0.3457

[a]In terms of pseudo components.

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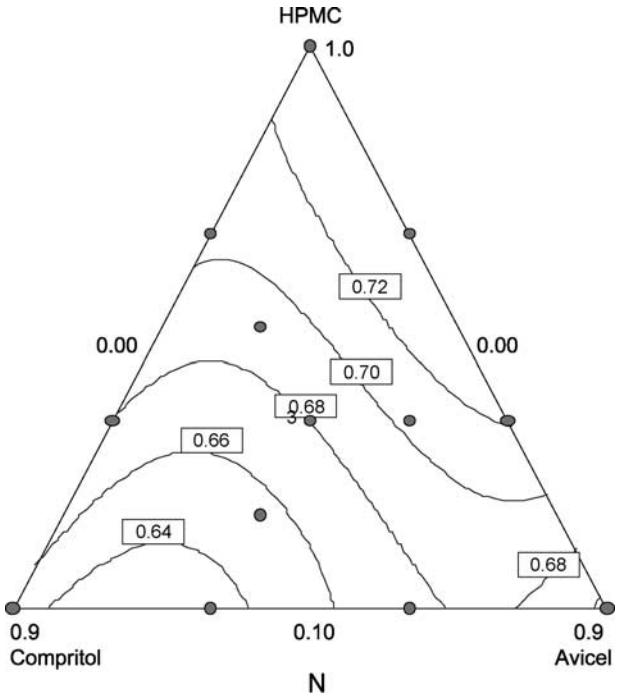

Figure 5. Release exponent (n) as a function of the three independent formulation factors. (*View this art in color at www.dekker.com.*)

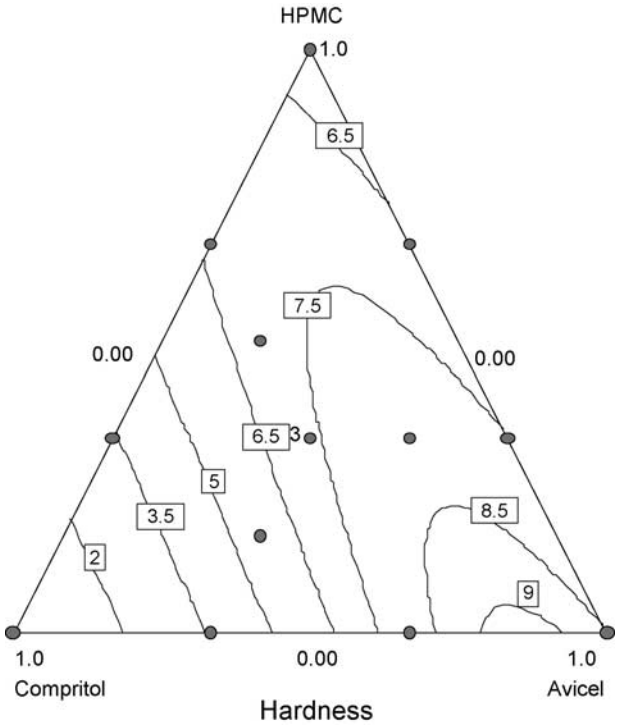

Figure 6. Crushing strength as a function of the three independent formulation factors. (*View this art in color at www.dekker.com.*)

Physical attributes of the tablets such as friability, percentage fines, and crushing strength were also measured. The crushing strength was the only response that showed systematic dependence on the formulation factors and could be modeled using a reduced quadratic model. Significant coefficients were obtained for the linear terms as well the interaction terms between Compritol–Avicel and Compritol–HPMC. A graph of the predicted values of crushing strength at various levels of the formulation factors is shown in Fig. 6. The crushing strength values (at a constant compression force of 25 kN for each formulation) were highest at high concentrations of Avicel. Tablets with a high level of Compritol showed the lowest values of crushing strength.

Optimum Formulation

The three responses, which could be modeled by regression analysis, direct the formulation towards different corners of the experimental region. In order to find an optimum formulation, it is important to define desired values for each of the three responses and mathematically find a formulation within the experimental region that satisfies all the criteria. The software used for regression analysis allows such a simultaneous optimum to be found using a desirability function as defined by Myers and Montgomery.[14] The overall desirability is simply the geometric mean of the desirability values of the three responses. The overall desirability function can take on a value from 0 to 1, with 0 indicating that no formulation satisfies all the criteria. A value of 1 indicates that the formulation exactly satisfies all the criteria. In this example, we arbitrarily defined target values (with ranges) of the three responses for the desired optimum formulation as shown in Table 2. Upon calculating the desirability function at the selected target values across the experimental region, two solutions were found. The solution with an overall desirability value close to 1 was selected as the formulation with which to ascertain the validity of the predictive equations. This formulation with 18.5% Compritol, 38.4% Avicel, and 43.2%

Table 2. Target values and ranges of the desired optimum formulation.

Response	Goal	Lower limit	Upper limit
Crushing strength	Target = 8.00	7.00	9.00
T_70	Target = 420	410	420
n	Target = 0.70	0.65	0.75

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Table 3. Observed vs. predicted response values of calculated optimum formulation.

Response	Compritol	Avicel	HPMC	Crushing strength	t_{70}	n	Desirability
Predicted	0.185	0.384	0.432	8.02	420.0	0.700	0.993
Observed	–	–	–	8.9	431.0	0.6919	–
Bias (%)	–	–	–	11.25	2.62	1.16	–

HPMC was manufactured and tested for the three responses. The observed values were in very close agreement with the predicted values as shown in Table 3.

CONCLUSIONS

The utility of a mixture experimental design for selecting formulation components of a roller compacted product was demonstrated. The predictive value of the model for some physical attributes of the product was validated by experiment. These simple statistical tools can allow a formulator to rationally select levels of various components in a formulation, improve the quality of products, and develop more robust processes.

REFERENCES

1. Inghelbrecht, S.; Remon, J.P. Roller compaction and tableting of microcrystalline cellulose/drug mixtures. Int. J. Pharm. **1998**, *161*, 215–224.
2. Miller, R.W. Advances in pharmaceutical roller compactor feed system designs. Pharm. Technol. **1994**, *18* (3), 154–162.
3. Murray, M.; Laohavichien, A.; Habib, W.; Sakr, A. Effect of process variables on roller-compacted ibuprofen tablets. Pharm. Ind. **1998**, *60* (3), 257–262.
4. Murray, M.; Sakr, A. Comparison of roller compacted and commercial ibuprofen tablets. Pharm. Res. **1996**, *9* (13), S181 Suppl.
5. Li, L.C.; Peck, G.E. The effect of agglomeration methods on the micromeritic properties of a maltodextrin product, Maltrin 150T. Drug Dev. Ind. Pharm. **1990**, *16* (9), 491–503.
6. Sheskey, P.J.; Cabelka, T.D.; Robb, R.T.; Boyce, B.M. Use of roller compaction in the preparation of controlled-release hydrophilic matrix tablets containing methylcellulose and hydroxypropyl methylcellulose polymers. Pharm. Technol. **1994**, *18* (9), 132–150.
7. Sheskey, P.; Sackett, G.; Maher, L.; Lentz, K.; Tolle, S.; Polli, J. Roll compaction granulation of a controlled-release matrix tablet formulation containing HPMC. Pharm Technol. Tabletting and Granulation Yearbook. **1999**, 6–21.
8. PDR Generics. *Diclofenac Oral,* 4th Ed.; Medical Economics Company: Montvale, NJ, 1998; 866–870.
9. Sheskey, P.J.; Dasbach, T.P. Evaluation of various polymers as dry binders in the preparation of an immediate-release tablet formulation by roller compaction. Pharm Technol. **1995**, *19* (10), 98–112.
10. Sheskey, P.J.; Parsons, C.A.; Boyce, B.; Robb, R.; Caswell, O. Preparation of immediate-release niacinamide tablets by roller compaction using cellulose ether binders. Pharm. Res. **1993**, *10* (10), S148 Suppl.
11. Obaidat, A.A.; Obaidat, R.M. Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate. Eur. J. Pharm. Biopharm. September, **2001**, *52* (2), 231–235.
12. Sheskey, P.J.; Hendren, J. The effects of roll compaction equipment variables, granulation technique, and HPMC polymer level on a controlled-release matrix model drug formulation. Pharm. Technol. **1999**, *23* (3), 90–106.
13. Peppas, N.A. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. **1985**, *60*, 110–115.
14. Myers, R.H.; Montgomery, D.C. *Response Surface Methodology: Process and Product Optimization Using Designed Experiments*; John Wiley & Sons: New York, NY, 1995.

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