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RESEARCH PAPER

Evaluation of Critical Formulation Factors in the Development of a Rapidly Dispersing Captopril Oral Dosage Form

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ABSTRACT

New methods of manufacture have enabled the creation of novel dosage forms with unique rapid-dispersion properties. This study combines one such technique with a statistical experimental design to develop dosage forms from captopril, an angiotensin-converting enzyme inhibitor used to treat cases of hypertensive emergency. The TheriForm™ process, a novel microfabrication technique, was used to build the dosage forms in a layer-by-layer fashion. Three key formulation factors were chosen for the design of experiments. A modified central composite design (Box-Behnken design) was used to maximize the efficiency of the experiments. A total of 13 distinct formulations were fabricated and tested, using mannitol as the bulk excipient. In addition, three replicates of the center point were tested to assess variability and experimental error. These formulations were tested for speed of dispersion (flash time), active content, hardness, friability, and moisture absorption. Regression analysis was performed to fit data responses to quadratic equations. Excellent dose accuracy (95% to 102% of target) and content uniformity (between 1.03% to 2.84%) were observed from all experimental formulation batches. As expected, the choice of powder additive (maltitol, maltodextrin, polyvinyl pyrrolidone), level of additive (2.5% to 7.5%), and saturation level of the binder liquid (45% to 65%) were all found to be significant factors for the TheriForm process. The regression analysis suggested that a rapidly dispersing dosage form of optimal physical properties would be obtained when a powder mixture of mannitol (97.5%) and maltitol (2.5%) is used at a saturation level of 45%. In conclusion, rapidly dispersing captopril oral dosage forms were successfully fabricated and tested. A wide range of physical properties, flash time, and hardness, were determined experimentally, and the effects of key formulation factors were identified.

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Key Words: Captopril; Rapidly-dispersing tablet; Quick dissolve; Fast dissolve; Experimental design; Hypertensive emergency; Rapid prototyping; TheriForm™ process; Solid freeform fabrication; 3DP; Mannitol; Maltitol; Maltodextrin; Polyvinyl pyrrolidone.

INTRODUCTION

A significant number of pediatric and geriatric patients experience difficulty in swallowing traditional tablets and capsules.[1] This difficulty often results in a high incidence of noncompliance and ineffective treatment. Noncompliance also is a problem encountered in treating psychiatric patients who willfully refuse to take medication by "cheeking" dosage forms and removing them from their oral cavities when unsupervised. Recent developments in dosage form manufacture attempt to address these problems by introducing tablets that do not need to be swallowed. These dosage forms disintegrate in the oral cavity upon contact with saliva, thus obviating the need for swallowing a solid dosage form. Sublingual or oral administration of rapidly dispersing tablets may be useful for cases when access to water is limited. Since these dosage forms can be taken without water, patients who need to limit water intake (e.g., patients with renal failure) also may benefit from these developments. In addition, sublingual administration of rapidly dispersing dosage forms has the following potential advantages: (1) facile access, (2) potential for quick onset of activity, and (3) improved bioavailability through circumvention of hepatic first-pass elimination.[1,2]

An appropriate area of application for this rapid-disperse technology is in the treatment of hypertensive emergency cases. Hypertensive emergency is a condition of highly elevated blood pressure that can lead to organ damage or even death within a short period of time if left untreated. Timely recognition of the hypertensive crisis and prompt treatment to reduce blood pressure are of utmost significance in reducing morbidity and mortality in these patients. The ideal oral agent to treat a hypertensive crisis would be one with a rapid onset of action, few adverse effects, absence of excessive hypotension, and monitoring convenience. The Fifth Report of the Joint National Committee recommends the use of captopril, nifedipine, clonidine, and labetalol as oral treatments for hypertensive emergency.[3] Captopril, an angiontension-converting enzyme inhibitor, has been used to treat hypertension and congestive heart failure.[3,4] When administered, captopril exerts its antihypertensive effect by inhibition of the conversion of angiotensin I to angiotensin II. After oral administration of therapeutic doses of captopril (12.5 mg to 100 mg), absorption occurs, with peak plasma levels at about one to two hr.[3,4] Blood pressure reduction usually reaches a peak 60 to 90 min after oral administration of a captopril tablet.[3,4]

Sublingual administration has been investigated as an alternative drug delivery route to treat hypertensive emergencies by several authors.[5–8] Karachalios et al. has reported on the effective and safe sublingual delivery of captopril.[8] In this study, 35 patients presented with hypertensive emergency, placed one 25-mg tablet under the tongue. Sublingual captopril tablets used in this study had a mean disintegration time of 3.6 ± 1.2 min. This treatment produced significant hypotensive effect within one hr of administration. Haude et al. compared the effects of sublingual administration of captopril and nitroglycerin in patients with severe congestive heart failure. They reported that captopril induced a more pronounced and prolonged improvement than nitroglycerin.[9] Al-Furaih and McElnay reported significantly decreased peripheral resistance and increased exercise tolerance time in patients with heart failure after treatment with sublingually administered captopril.[10,11]

An objective of the current study was to develop captopril formulations that rapidly disperse in the oral cavity so as to facilitate rapid systemic absorption across the sublingual mucosa for treatment of hypertensive crises as well as congestive heart failure. Several techniques are currently available to formulate rapidly dispersing dosage forms. These include lyophilzation.[12,13] soft compaction,[14,15] use of effervescent salts,[16,17] and compaction of sugar fibers.[18,19] In the current study, the TheriForm™ process was used to formulate rapidly dispersing dosage forms. As with other solid freeform fabrication techniques, the TheriForm process uses computer-controlled mechanisms to form three-dimensional objects, typically one layer at a time. Like MIT's three dimensional printing, the TheriForm process uses this basic approach in

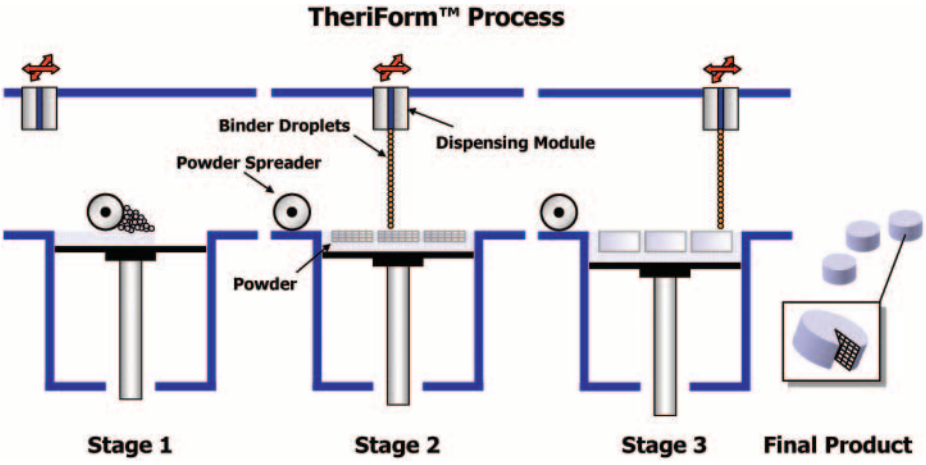

Figure 1. TheriForm process schematics.

conjunction with ink-jet printing technology to dispense small droplets of binder liquid onto a thin layer of powder.[20,21] These droplets facilitate the binding of loose particulates to form solid patterns within the layer, hence the term "binder." After the completion of "printing" these binder droplets onto a layer, another thin layer of powder is applied on top, and the printing process is repeated. Figure 1 illustrates the key components of the TheriForm process and depicts the powder spreading and printing steps of the process.

There are several unique advantages to using the TheriForm process for building pharmaceutical dosage forms.[22–28] The controlled deposition of liquid droplets allows for accurate and precise dosing of actives, even in microgram amounts. This same feature also enables the formation of complex internal geometries of controlled spatial composition and has resulted in the attainment of customized drug release profiles. Finally, this process allows for rapid prototyping of dosage forms because it eliminates the need for any custom tooling for new designs. These benefits already have been exploited in developing the TheriFlash™ dosage forms (TDF),[26,28] with particular emphasis on modulating the extent of "binding" between water-soluble excipient particles. By using this approach, two different formulations may be built with identical material sets (powder and binder liquid) but disparate spatial drop distribution, resulting in different levels of "saturation" in the powder bed. In this context, saturation is defined as the volume ratio of binder deposited to void space available, and its manipulation can result in drastically different properties. The approach is somewhat analogous to using different compaction forces on a conventional tablet press.

Ultimately, a number of factors control the properties of TDFs. These include the original properties of the base excipient and additive materials and the parameters that control the build process. In the current study, the contribution of three key independent formulation variables was evaluated in the context of a single base excipient: choice of additive powder, level of additive powder, and saturation level (ratio of deposited binder volume to available pore volume). A modified central composite design (Box-Behnken design) was used to efficiently evaluate the impact of these variables.

MATERIALS AND METHODS

Experimental Design

Three key independent variables were evaluated by using a Box-Behnken design:

1. Choice of additive powder [maltitol, maltodextrin, and polyvinyl pyrrolidone (PVP)]
2. Level of additive powder (7.5%, 5.0%, and 2.5% w/w)
3. Level of saturation (45%, 55%, and 65% v/v).

Fifteen experimental batches were formulated with three replicates of the center point to assess variability and experimental error (Fig. 2).

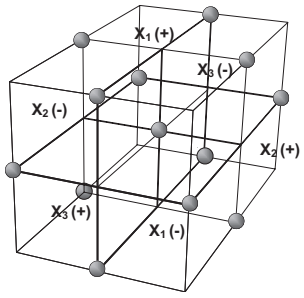

Figure 2. Graphical display of Box-Behnken design.

Table 1. Experimental codes of variables.

Variable	−1	0	1
Choice of additive (X_1)	Maltitol	Maltodextrin	PVP K25
Level of additive (X_2)	7.5%	5.0%	2.5%
Saturation level (X_3)	45% (26 nL/drop 26 layers)	55% (31 nL/drop 21 layers)	65% (37 nL/drop 18 layers)

All formulations used mannitol as the base powder excipient. Experimental codes are shown in Table 1. Hardness, friability, flash time (time required for complete dispersion), and moisture absorption were selected as dependent variables. The flash time was chosen as the target function for the parameter optimization exercise.

Preparation of Powder Mixtures

Mannitol (Mannitol 60; Roquette, Keokuk, IA) was used as the primary ingredient for the powder layers. Binary powder mixtures were prepared by placing a preweighed amount of mannitol into a V-shell blender and adding maltitol (Maltisorb P200; Roquette, Keokuk, IA), maltodextrin (Maltrin M150; Grain Processing Corporation, Muscatine, IA); or PVP (Kollidon 25; BASF, Mount Olive, NJ) before blending for 10 min at 25 rpm.

Preparation of Captopril Binder Solution

Two key functional characteristics are typically considered in preparing the binder solutions to be used in TheriForm experiments: chemical stability of the active compound and suitability of the liquid for dispensing through a binder delivery technology. Thus, captopril (Sigma Chemical Co., St. Louis, MO) was dissolved in McIlvaine buffer (0.1 M citric acid/0.2 M phosphate buffer, pH 4) at a concentration of 100 mg/mL. Ethylenediaminetetraacetic acid (EDTA) and ascorbic acid (Spectrum Laboratory Products Inc., New Brunswick, NJ) were then added to reduce oxidation of captopril.[29] The viscosity and surface tension of the binder solutions, 7.5 cps and 36.4 mN/m, were deemed suitable for use with the drop-on-demand dispensing technique. These rheological properties were attained by adding PVP K25 and Tween 20 (Fisher Scientific, Fairlawn, NJ) to the above mentioned captopril solution. The final formulation of captopril binder solution was 100 mg/mL of captopril in pH 4 citric acid/phosphate buffer with 0.005 M of EDTA, 0.005 M of ascorbic acid, 12% w/v of PVP K25, and 0.05% w/v of Tween 20. This composition was held constant for all experiments.

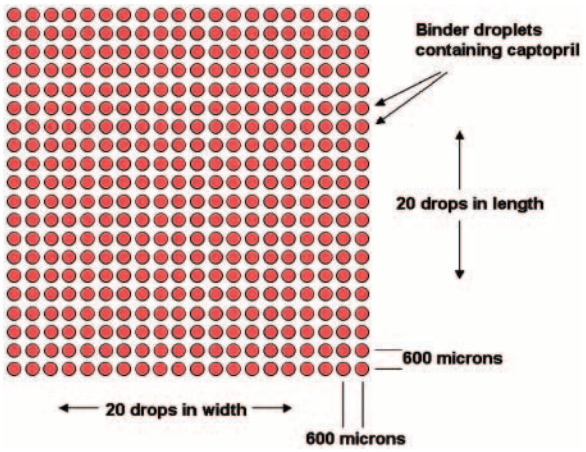

Figure 3. Binder liquid droplet deposition pattern used to fabricate monolithic captopril TheriFlash dosage forms. This pattern is repeated layer by layer to fabricate the three-dimensional structure.

Fabrication of Captopril TDFs

Captopril TDFs were fabricated by using the TheriForm process. After spreading powder mixtures into layers of 250 microns, the captopril binder droplets were deposited onto each powder layer in a pattern illustrated in Fig. 3. Droplets were arranged in a simple square lattice within a layer, 600 microns

apart from each other. After repeating this process of powder spreading and droplet deposition to completion, these dosage forms were allowed to dry in ambient air.

For this set of experiments, the saturation variable was manipulated by changing the droplet volume in the context of fixed droplet spacing. In order to fabricate each of the designs with the same total dose of captopril, the number of layers in the dosage form was adjusted in response to the change in saturation level.

Measurement of Physical Properties

Weight and dimensions were measured for 10 randomly selected TDFs of each batch. Density was calculated based on weight and dimensions. Hardness also was measured for the 10 TDFs (VK 200, VanderKamp) and was normalized by the mean cross-sectional area of the specimens. A Van Kel Friabilator (Model 4J 200) was used for friability measurements. The percent weight loss of 20 TDFs before and after 100 tumbling cycles was reported as friability per the (USP) standard method.

Dispersion time (flash time) was measured on 10 TDFs per batch by an in-house flash time measurement set-up. In this method, each TDF was placed on a glass slide, and 500 microliters of distilled water at ambient temperature were pipetted onto the top surface of the dosage form. Eppendorf Reference pipette and FisherBrand® Redi-Tip™ 101–1000 microliter tips (Fisher Scientific, Fairlawn, NJ) were used to dispense water from approximately 1 cm above the TDF for testing. The time for the dosage form to spontaneously collapse was measured by using a stopwatch and is reported as the "flash time."

Moisture absorption was determined as a weight differential of five unpackaged dosage forms before and after a 6-hr exposure to 25°C and 60% relative humidity by using an environmental chamber. Mean values of all measurements were used for data analysis.

A scanning electron microscope (JSM-5600LV; JEOL) was used to examine the microstructure of the TDFs. Specimens were observed under low vacuum level (30 Pa absolute) without surface coating at varying magnifications.

Measurement of Captopril Content

A previously developed high-performance liquid chromatography (HPLC) method was modified and used to quantify the amount of captopril in binder solutions, as well as dosage forms. An alphabond C-18 column (3.9 × 150 mm) was used with a mobile phase that consisted of 0.05% phosphoric acid and acetonitrile (75:25) at a flow rate of 1 mL min^{-1}. Captopril was detected at 218 nm, and its retention time was 5.8 min.[30] Content uniformity tests were performed on five batches. In these tests, 10 dosage forms were randomly sampled from batches and were individually dissolved in a 100-mL volumetric flask before injection. For assay tests, five TDFs were randomly taken from the remaining batches and were consolidated in a 500-mL volumetric flask before injection.

Statistical Analysis

The significance of independent variables was examined using an analysis of variance (ANOVA) table. A quadratic model (Eq. 1) was written for each dependent variable for regression:

$$Y_1 = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_1X_3 + A_6X_2X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 \quad (1)$$

where Y_1 is the dependent variable, A_1 is the regression parameter estimate, X_1 is the main effect of an independent variable, X_1X_2 is the interaction of two independent variables, and X_1^2 is the quadratic term of an independent variable.

A stepwise regression was performed to fit data responses to Eq. 1 by using an SAS software program (SAS Institute, Cary, NC). The most significant independent variables were selected based on Cp values and on improvement of the regression coefficient (R^2).[31] The regression analysis was performed on both untransformed and transformed dependent variables. A regression model of a transformed dependent variable was selected only if it fits with fewer independent variables and it did not violate the assumption of constant variance.[31] The Lagrangian method was used for the optimization that followed the regression procedure.

RESULTS AND DISCUSSIONS

Captopril Binder Stability

Captopril is stable at an acidic pH such as 1.2. As the solution becomes more alkaline, captopril

Table 2. Experimental formulations and the test results of dose accuracy, content uniformity, hardness, friability, flash time, and moisture absorption of captopril TheriFlash dosage forms.

Formulation	X_1	X_2	X_3	Dose accuracy (% label)	Content uniformity (% RSD)	Hardness[a] (kp) (mean ± std)	Density (g/cc)	Friability (%)	Flash time[b] (sec) (mean ± std)	Moisture Abs[c] (%)
1	Maltodextrin	2.5%	45%	99%	nd	9.13 ± 1.07	0.67	13.23	7.74 ± 1.58	0.48
2	Maltitol	5.0%	45%	102%	nd	7.85 ± 3.19	0.68	12.37	6.09 ± 1.06	0.65
3	Maltodextrin	7.5%	45%	102%	nd	14.43 ± 1.34	0.70	9.13	38.16 ± 4.82	0.81
4	PVP K25	5.0%	45%	99%	1.03%	13.33 ± 1.60	0.68	10.58	12.58 ± 1.72	1.03
5	Maltodextrin	5.0%	55%	97%	1.03%	19.03 ± 0.94	0.71	9	15.23 ± 3.79	0.60
6	PVP K25	2.5%	55%	98%	nd	30.94 ± 2.73	0.67	8.53	17.61 ± 6.95	0.70
7	Maltitol	2.5%	55%	95%	nd	6.9 ± 3.43	0.68	9.05	6.62 ± 1.66	0.22
8	Maltodextrin	5.0%	55%	100%	1.54%	24.29 ± 1.66	0.72	8.81	57.92 ± 11.18	0.46
9	PVP K25	7.5%	55%	97%	nd	30.46 ± 4.81	0.72	7.3	73.30 ± 8.17	1.13
10	Maltitol	7.5%	55%	99%	nd	6.46 ± 2.13	0.69	8.03	14.54 ± 4.96	0.98
11	Maltodextrin	5.0%	55%	99%	2.84%	18.19 ± 2.12	0.68	10.04	51.68 ± 7.94	0.46
12	PVP K25	5.0%	65%	100%	nd	29.45 ± 6.42	0.72	6.89	76.92 ± 15.98	0.95
13	Maltodextrin	2.5%	65%	96%	nd	9.64 ± 6.45	0.71	7.3	53.16 ± 6.15	0.41
14	Maltitol	5.0%	65%	98%	1.34%	5.09 ± 1.23	0.69	5.56	17.40 ± 5.23	0.48
15	Maltodextrin	7.5%	65%	97%	nd	38.87 ± 3.36	0.76	8.45	75.24 ± 11.07	0.75

nd. Not determined.
[a]Mean values after eliminating maximum and minimum values.
[b]Mean values after eliminating maximum and minimum values.
[c]Average % weight gain 6 hr after 25°C/60% humidity chamber.

undergoes a pseudo-first order degradation reaction.[32,33] The instability of captopril in aqueous solution has been attributed to a metal catalyzed oxidative mechanism. The stability of captopril was monitored in the binder solution (100 mg mL^{-1}) at room temperature (25°C) for seven days and beyond. The content of captopril was measured by HPLC analysis. No significant decrease in the amount of captopril was detected over the seven-day period. The addition of ascorbic acid (antioxidant) and EDTA (metal chelating agent) provided sufficient stabilization of captopril in the binder solution. However, an appreciable amount of captopril disulfide, the product of captopril oxidation, was noted on the HPLC test results as the storage duration increased. As a precaution to minimize data scatter due to any potential captopril degradation, freshly prepared solutions were used for all experiments. In addition, maintenance of the captopril binder concentration at the end of the fabrication period was confirmed by the described HPLC method.

Assays and Content Uniformity

Assay tests were performed to measure the dose accuracy of the fabrication process. These results are shown in Table 2. All 15 batches were in the range of 95% to 102% of dose label (25 mg), which was well within the range specified by the USP for most compounds (85% to 115% or 90% to 110%). In addition to the assay test, content uniformity was evaluated for five batches. These results demonstrated excellent content uniformity achieved by the TheriForm process, with the relative standard deviations (RSD) being less than 3% in all cases.

Content uniformity and dose accuracy are critical issues to address in the formulation of rapidly dispersing dosage forms. Since these dosage forms have a general tendency to be less robust than conventional tablets, attritional loss during packaging and handling processes may cause dosage forms to become subpotent. In the current study, the dosage forms were designed as a monolith with uniform distribution of active compound throughout the volume. While this dosage form design is suitable for evaluating formulation factors, an additional feature, such as a placebo shell, can be designed around the active-containing core to prevent attritional loss of the active ingredient during handling. Figure 4 shows schematics of such a dosage form design and how the placebo shell is constructed around the active core during the TheriForm process. Attritional loss of material in these dosage forms is

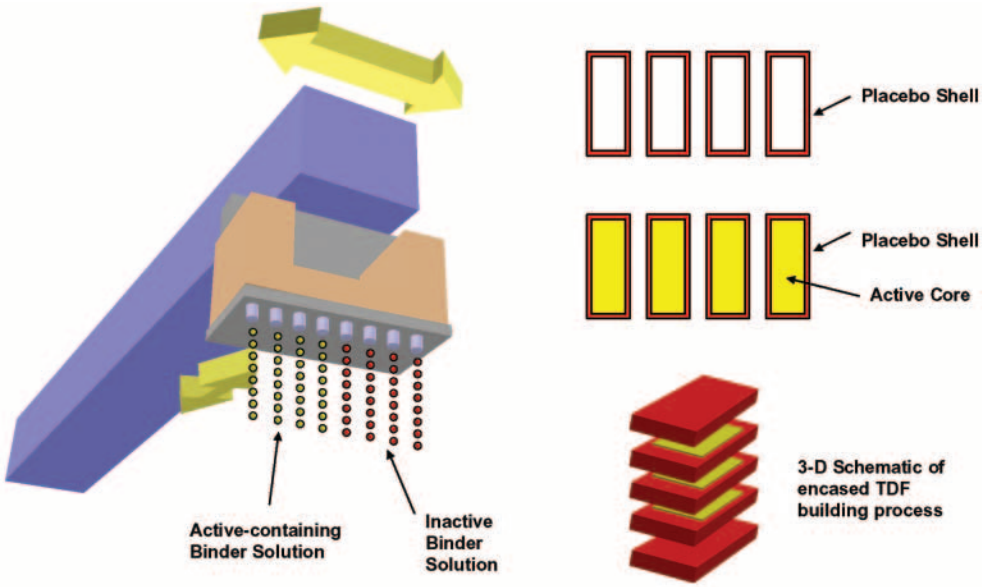

Figure 4. Binder liquid droplet deposition scheme used to build a TheriFlash dosage form (TDF) with core-shell structure. Schematics for the build process also are presented.

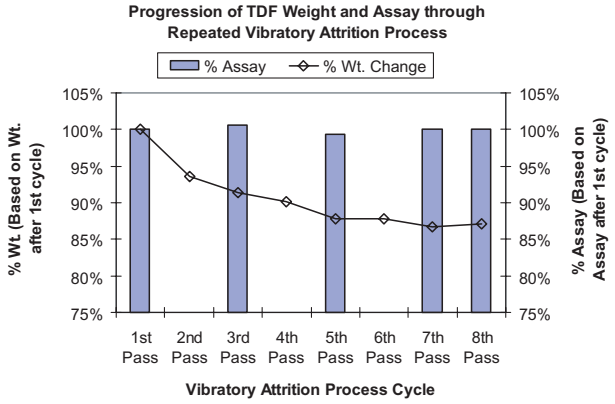

Figure 5. Weight loss and assay results of TheriFlash dosage forms (TDF) that were subjected to repeated vibratory attrition.

attributed mainly to the placebo shell, as illustrated by a study with TDFs containing pseudoephedrine HCl.[34] Figure 5 shows the weight loss and assay results of the TDFs with the core-shell structure after undergoing successive iterations of vibratory sieving cycles. These results confirm the concept that careful design and execution of the TheriForm process can produce rapidly dispersing dosage forms that maintain accurate and precise amounts of the active compound, even following attritional loss due to handling and packaging processes.

Physical Properties

The distinguishing characteristic of a rapidly dispersing tablet is its flash time. Unfortunately, this unique attribute often conflicts with other properties related to mechanical integrity. Such compromises necessitate costly and cumbersome packaging schemes to prevent dosage form breakage and moisture leaks. Hence, it is desirable to strike a good balance between these physical properties. The results of physical property tests (hardness, friability, flash time, density, and moisture absorption) are listed in Table 2. The hardness of captopril TDFs ranged from 5 to 31 kp, and the flash time varied from 6 to 77 sec. The friability and moisture absorption results ranged from 5% to 14% and 0.22% to 1.1%, respectively. Prior to performing the regression analysis on the dependent variables, the hardness and flash time were plotted against independent variables to observe general relationships between responses and factors.

The hardness values of various captopril TDFs are shown in Fig. 6. The hardness of TDFs increased as the saturation level increased from 45% to 65%. As the saturation level is an indicator of the binder liquid content per 3-dimensional tablet structure, increased hardness resulting from a high level of saturation (65%) is consistent with expectations. In this case, the binder droplets "glued" the 3-dimensional tablet

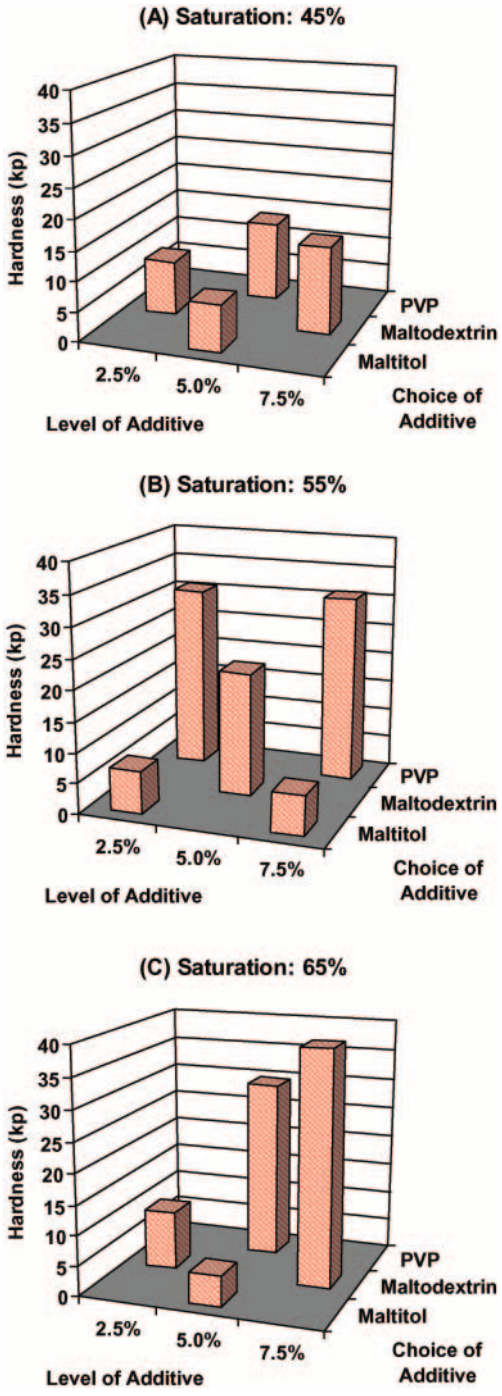

Figure 6. Hardness of captopril TDFs at different saturation levels.

structure more densely and yielded harder TDFs, as shown in Fig. 6 [(A), (B), and (C)]. Hardness values also varied based upon the selection of additive powder, from maltitol to PVP. At the same level of saturation, formulations with PVP resulted in higher hardness than those with either maltitol or maltodextrin [Fig. 6 (B)]. There was no obvious pronounced trend of increase or decrease in hardness when different powder levels (7.5%, 5.0%, and 2.5% w/w) were compared. One exceptional case was observed where hardness of TDFs increased from 10 to 40 kp as maltodextrin content changed from 2.5% to 7.5% w/w [Fig. 6 (C)].

Profiles of flash time of captopril TDFs are shown in Fig. 7. The TDFs constructed with maltitol showed the shortest flash time among the three additive powders [Fig. 7 (A), (B), and (C)]. For each powder, the flash time appeared to decrease as the saturation level decreased (65% to 45%) and powder level changed (7.5% to 2.5%). Maltitol exhibited a more favorable effect on the flash time compared with maltodextrin and PVP. While these flash time results serve as excellent indicators for evaluating relative performance of various dosage forms, care should be taken to avoid direct comparison of flash time results obtained through different measurement techniques. Several parameters, including the volume and temperature of the water used to test the dispersion times, influence the outcome. Use of artificial saliva instead of distilled water as the test medium also has been shown to skew the flashing time results. Furthermore, an identical formulation may yield a different flashing time if subjected to a test method that involves a light compressive load to simulate pressure from the tongue. On a similar note, testing these dosage forms in a disintegration test apparatus may yield significantly faster flashing time since the amount of water and agitation used with the method will far surpass those used in the current study. These observations highlight the need for a standardized test method for this relatively new breed of dosage forms.

Microstructural examinations with a scanning electron microscope revealed consistently porous structures throughout all formulations. No significant difference was noted in the microstructure of the examined formulations. This is not unexpected due to the narrow range of densities (or alternatively, porosities) spanned in the current set of formulations (see Table 2), and the presence of the same bulk powder excipient in high amounts. A representative micrograph is shown in Fig. 8. All of the examined formulations exhibited a loosely bound matrix of mannitol particles with an interconnected network of pores. These pores are of critical importance to the dispersion mechanism since they regulate the intake and subsequent distribution of water in the initial stages of the

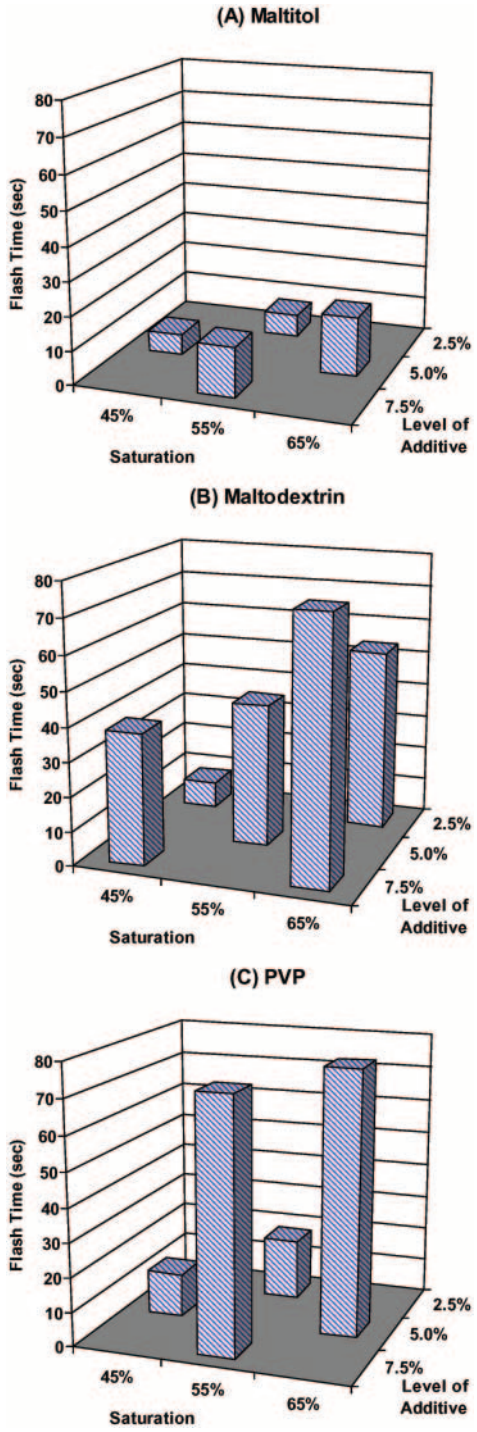

Figure 7. Flash time of captopril TDFs at different powder bed compositions.

TDF dispersion process. Once the dosage form is saturated with water, localized dissolution of the loosely connected network follows, leading to an eventual collapse of the dosage form under its own weight.[26]

Statistical Analysis

The best subsets of independent variables were selected through a stepwise regression procedure by using the SAS program. This procedure attempts to achieve an equation of best subsets of variables by inserting independent variables in turn until the regression equation is satisfactory. During the procedure, correlations of all independent variables with the dependent variables are calculated. The software then selects the first variable to enter the regression, the one most highly correlated with the dependent variable, and regresses the response on the first selected variable. The next step is to calculate the partial correlation coefficients of remaining variables. The order of insertion is determined from the partial correlation coefficients, which are a measure of the importance of variables.[31] The variable with the highest partial correlation coefficient then is chosen to enter into regression.

Each dependent variable was fitted to a quadratic model by using the parameter estimates listed in Table 3. Also listed in Table 3 are the resulting regression coefficients from the calculations. Data transformations on dependent variables were performed to obtain a ''best fit'' by using fewer independent variables and thus avoid a potential over-fit.[31] Logarithmic transformation on flash time provided a simpler regression equation of four independent variables compared with the six independent variables by using untransformed flash time. The lack-of-fit tests and residual plot tests of regression models confirmed the adequacy of the model fitting process.

Estimates of parameters revealed the influence of the independent variables on the dependent variables. The choice of powder additive (X_1) and level of saturation (X_3) had positive effects on hardness and flash time, while the level of additive (X_2) had a negative effect on both (Table 3). The regression result agrees with the observations from Fig. 6 and 7, which suggested that formulations with maltodextrin and PVP, combined with high levels of saturation, yielded dosage forms with greater hardnesses and longer flash times. The negative effect of the additive level (X_2) on hardness was clearly demonstrated from the regression, which was not obvious from cursory examination of Fig. 6. In addition to the main effects, dependency of flash time on a quadratic term (X_1^2) was revealed through this analysis. For parameter estimates of additive level and saturation level (X_2 and X_3), the regression model for friability showed opposite signs to those of hardness and flash time.

In other words, friability increased as the saturation levels decreased or the additive powder level moved toward +1. Friability also depended on the interaction terms (X_1X_3 and X_2X_3) and a quadratic term (X_1^2). Moisture absorption showed dependence on the choice of additive (positive effect) and its level (negative effect). In general, regression results of dependent variables verified the understanding of the overall relationship: a positive correlation between hardness and flash time, and a negative correlation between hardness and friability.

In an effort to identify a formulation with balanced physical properties, the experimental space was calculated, and an attempt was made to capture an optimum value of flash time with appropriate hardness and acceptable friability. The response surface regression procedure of flash time was performed to find a local optimum (either minimum or maximum) without constraints. The stationary point of the response surface was a saddle point, suggesting that the experimental space did not hold a local optimum of flash time.

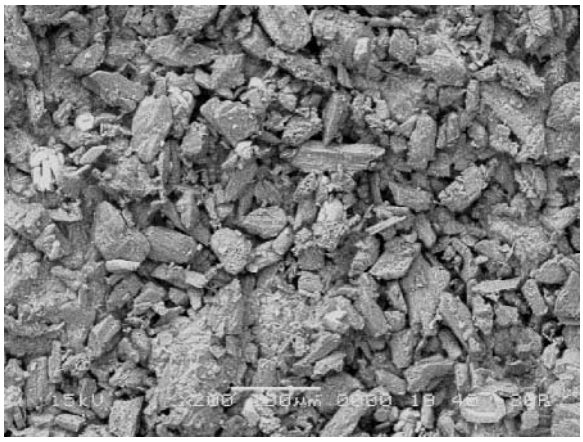

Figure 8. Representative microstructure of a TDF (2.5% maltitol at 55% saturation level) observed with a scanning electron microscope.

Contour plots of flash time, hardness, and friability were plotted for level of additive (X_2) and level of saturation (X_3) for a given choice of powder additive (X_1). Figure 9 presents contour plots of three dependent variables for maltitol formulations, which yielded captopril TDFs with the shortest flash times. As shown in Fig. 9, flash time and hardness decreased and friability increased as X_2 moved toward 1 and X_3, towards –1. These contour plots suggest that captopril TDFs of optimal physical properties may be obtained in the neighborhood of $X_1 = -1$, $X_2 = 1$, and $X_3 = -1$ (2.5% maltitol at 45% saturation).

Furthermore, Microsoft Excel (Solver function) was used to solve for a target function of flash time at fixed powder mixture values as shown in Table 4. Constraints were placed on the minimum allowable hardness (>3 kp) and maximum allowable friability (<10%) for the purpose of this exercise. Flash time was optimized with maltitol ($X_1 = -1$), 2.5% w/w powder level ($X_2 = 1$), and 53% saturation level ($X_3 = -0.19$). The calculations suggested an anticipated flash time of about 5 sec with 10% friability and 3.9 kp hardness at this point. When the flash time was optimized by removing the constraint on friability (i.e., constraint on hardness only, >3 kp), the calculated flash time was about 3 sec with 13% friability and 4.85 kp hardness at $X_1 = -1$, $X_2 = 1$, and $X_3 = -1$ (2.5% maltitol at 45% saturation). This result suggests that small increases in saturation (and compromises on flash time) may provide adequate friability.

Table 3. Parameter estimates, regression coefficients, and Cp values of regression models of dependent variables.

Independent variable	Hardness (kp)	Friability (%)	ln[flash time (sec)]	Moisture absorption (%)
Intercept	17.60	9.42	3.52	0.57
X_1	9.74	ns	0.60	0.18
X_2	−4.20	0.65	−0.51	−0.23
X_3	4.79	−2.13	0.68	ns
X_1X_2	ns	ns	ns	0.20
X_1X_3	ns	0.78	ns	ns
X_2X_3	−5.98	−1.31	ns	ns
X_1^2	ns	−0.88	0.62	ns
X_2^2	ns	ns	ns	ns
X_3^2	ns	ns	ns	ns
R^2	0.75	0.92	0.85	0.87
C_p	3.78	4.16	2.87	3.79

ns: Not significant.

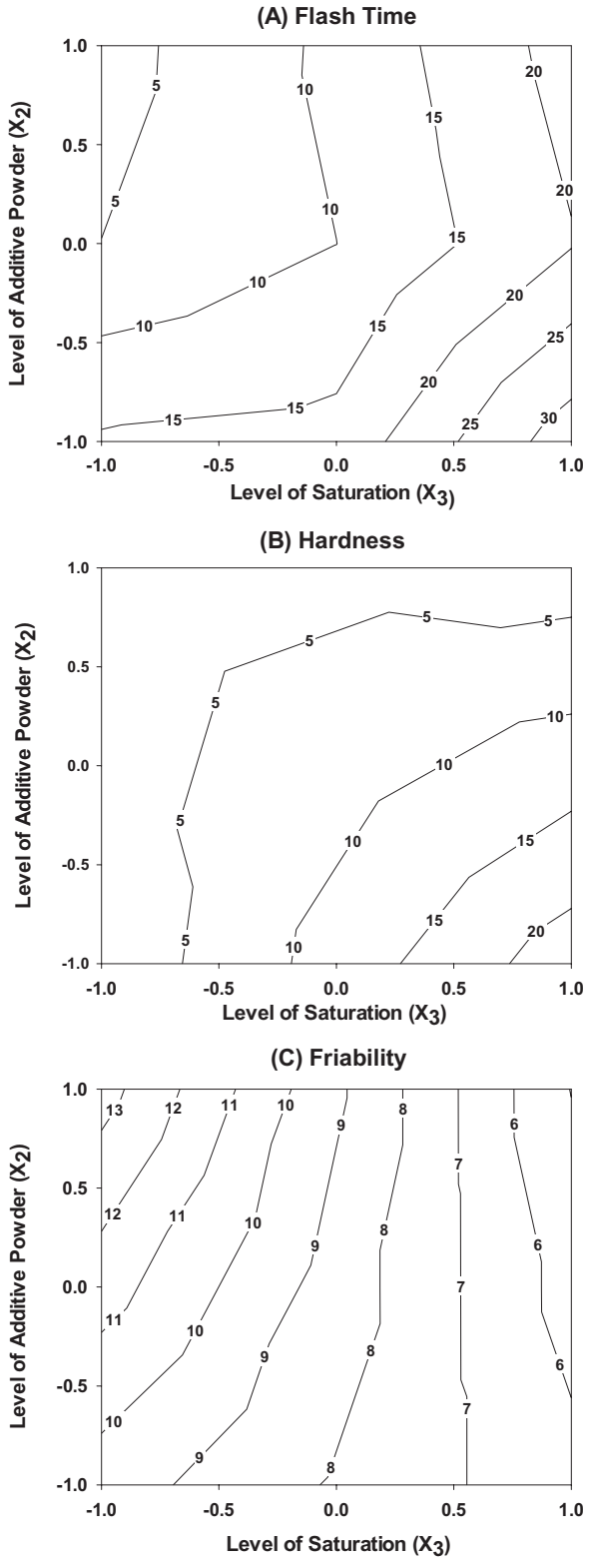

Figure 9. Contour plots of flash time, hardness, and friability by using a powder bed of mannitol/maltitol mixtures.

Table 4. Predicted values of flash time with a constraint of hardness (>3 kp).

X_1X_2:X_3	Flash time (sec)	Hardness (kp)	Friability (%)
−1:1:−0.19[a]	5.26[b]	3.89	10
−1:1:−1	3.03	4.85	13.41
0:1:−1	10.28	14.59	13.51
1:1:−1	10.07	24.33	11.85

[a]Saturation level: 53%.
[b]Obtained with constraints of hardness (>3 kp) and friability (<10%).

CONCLUSION

Rapidly dispersing captopril TDFs were successfully fabricated and tested. The TheriForm process proved to be a viable and useful technique in fabricating various rapidly dispersing formulations in a rapid fashion. Excellent dose accuracy and content uniformity were achieved in all of the formulations investigated in the current study. Wide ranges of physical properties, including flash time, hardness, and friability were obtained, and the effects of variations in the key formulation factors were identified by using a modified central composite design (Box-Behnken design). Stepwise regression analysis provided mathematical models to predict dependent variables (flash time, hardness, and friability). A set of independent variables, which yield minimal flash time with sufficient hardness and appropriate friability, was identified. A set of independent variables also was identified that yields minimal flash time with sufficient hardness and appropriate friability. The formulation knowledge obtained through the regression modeling in the current study formed the basis for rational design of rapidly dispersing formulations using the TheriForm process.

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