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Research Article

Response Surface Methodology to Optimize Novel Fast Disintegrating Tablets Using β Cyclodextrin as Diluent

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Abstract. The objective of this work was to apply response surface approach to investigate main and interaction effects of formulation parameters in optimizing novel fast disintegrating tablet formulation using β cyclodextrin as a diluent. The variables studied were diluent (β cyclodextrin, X_1), superdisintegrant (Croscarmellose sodium, X_2), and direct compression aid (Spray dried lactose, X_3). Tablets were prepared by direct compression method on B2 rotary tablet press using flat plain-face punches and characterized for weight variation, thickness, disintegration time (Y_1), and hardness (Y_2). Disintegration time was strongly affected by quadratic terms of β cyclodextrin, croscarmellose sodium, and spray-dried lactose. The positive value of regression coefficient for β cyclodextrin suggested that hardness increased with increased amount of β cyclodextrin. In general, disintegration of tablets has been reported to slow down with increase in hardness. However in the present study, higher concentration of β cyclodextrin was found to improve tablet hardness without increasing the disintegration time. Thus, β cyclodextrin is proposed as a suitable diluent to achieve fast disintegrating tablets with sufficient hardness. Good correlation between the predicted values and experimental data of the optimized formulation validated prognostic ability of response surface methodology in optimizing fast disintegrating tablets using β cyclodextrin as a diluent.

KEY WORDS: β cyclodextrin; central composite design; fast disintegrating tablets; granisetron hydrochloride; response surface.

INTRODUCTION

Many patients find difficult to swallow tablets and gelatin capsules; consequently, they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem of dysphagia, which results in high incidence of non-compliance and ineffective therapy (1,2). Recent developments in the fast disintegrating tablets provide a convenient solution for patients who have difficulties in swallowing tablets and other dosage forms (3). Fast disintegrating tablet dissolves or disintegrates in the saliva and then it is swallowed to the stomach. The time required for this process is estimated between 5 and 10 min (4). During this passage from mouth to stomach, drug may get absorbed through the membrane of the buccal cavity, pharynx, and esophagus. This may result in improved bioavailability and/or faster onset of action (1).

Diluent in direct compression formulation has a dual role it increases bulk of the dosage form and also it promotes binding of the constituent particles of the formulation. Hence, selection of diluent is important in tablets produced by direct compression method (5). Diluent properties can significantly affect disintegration time as well as tablet hardness. Solubility of the diluent in a formulation has shown to affect the rate and mechanism of tablet disintegration. Water-soluble diluents tend to dissolve rather than disintegrate, while water-insoluble diluents produce rapid disintegration. It has also been shown that superdisintegrants have a greater effect on disintegration time in an insoluble system than a soluble or partially soluble system (6). Addition of one or more effective disintegrants combined with suitable amount of a water-insoluble material produced fast disintegrating tablets with good physical resistance (hardness), maintained optimal disintegration even at low compression force (7). Compressibility and nature (ductile or brittle) of the diluent can also affect tablet hardness. Bi *et al.* (8) in their study showed stronger fast disintegrating tablets can be produced when low substituted hydroxypropyl cellulose was compressed with microcrystalline cellulose.

β Cyclodextrin is a cyclic oligosaccharide composed of seven dextrose units joined through one to four bonds. Ghorab *et al.* (9) evaluated β cyclodextrin as a diluent for tablets, either singly or in blends with spray-dried lactose. β Cyclodextrin has good compression characteristic as it has good compressibility index (10). It is considered to be a promising direct compression material because of its favorable compactibility and dilution potential. One may get harder tablets at lower compression force using β cyclo-

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dextrin. It may also render other advantages such as taste masking of the drug and enhancing solubility of poorly soluble compounds.

In the present work, feasibility of preparing and optimizing novel fast disintegrating tablet formulation using β cyclodextrin as a diluent was considered. Response surface methodology was used to optimize fast disintegrating tablet formulation as it provides empirical models (linear as well as quadratic) that describe the effect of processing variables on the response studied. The advantages of using experimental design method included reduction in number of experiments, identification of interaction between factors, detection of the optimal response within the experimental region, and empirical modeling of the data (11).

Experiments were performed using a three-factor, three-level face-centered central composite design. This design is suitable for exploring quadratic response surfaces and it permits development of a polynomial model. Advantages of central composite design are its abilities to estimate second-order and third-order effects, to detect inter-relationships between factors, and to locate response optima. Disadvantages of this model as compared to a three-level factorial design include inability to estimate certain interactive terms (*i.e.*, quadratic by quadratic). This is usually considered as minor in comparison to the advantage of small number of trials required to obtain a model (12).

Granisetron [endo-1-methyl –N- (9-methyl-9-aza-bicyclo [3.3.1] non-3-yl)-1 H-indazole-3-carboxamide] is a specific serotonin ($5HT_3$) receptor antagonist (13) used to treat the nausea and vomiting induced by cancer chemotherapy. It is very potent, hydrophilic in nature, and has high first-pass hepatic metabolism (14). Antiemetic drugs with a 5-HT_3-receptor antagonist effect, like granisetron, were initially developed as injectable formulations because patients with nausea and vomiting cannot receive oral preparations. Oral antiemetic drug formulations such as tablets were developed after injectable formulations, as it was easier to give drugs orally than by injection. Fast disintegrating tablets of granisetron hydrochloride can be a better alternative to conventional tablets or injectable formulations for cancer patients as they suffer from nausea and vomiting compounded with difficulty in swallowing. Also, it may give higher bioavailability if drug gets absorbed through buccal or esophageal mucosa. Granisetron is a low-dose compound; hence, effect of diluent will be more prominent in tablet formulation. Therefore, granisetron hydrochloride was selected as drug candidate for the optimization of novel fast disintegrating tablet formulation.

MATERIALS AND METHODS

Experimental Design

The central composite design contains an imbedded factorial or fractional factorial design with center point that is augmented with a group of star points that allow estimation of curvature. In face-centered central composite design, star points are at the center of each face of the factorial space. The second-order regression models were developed based on the regression analysis of the statistically significant variables. Regression models are of the form: $Y = B_o + B_1X_1 + B_2X_2 + B_3X_3 + B_4X_1X_2 + B_5X_2X_3 + B_6X_1X_3 + B_7X_1^2 + B_8X_2^2 + B_9X_3^2$, in which Y is the measured response associated with each factor-level combination; X_1, X_2, and X_3 are the factors studied; B_o is an intercept; B_1–B_9 are the regression coefficients. The polynomial equations from this optimization technique were used to predict disintegration time (Y_1) and hardness (Y_2) values for fast disintegrating tablets. Comparison of predicted values for Y_1 and Y_2 with experimental data was also used to test validity of the response surface models.

Materials

Granisetron HCl was purchased from Ultratech India Ltd. (Mumbai, India). The following chemicals were obtained and used as received. β Cyclodextrin, 2-hydroxypropyl β cyclodextrin and γ cyclodextrin were received as gift samples from Wacker-Chemie (GmBH, Germany). Croscarmellose sodium, lactose monohydrate, spray-dried (NF, USP grade), and mannitol (ACS grade) were purchased from FMC Corporation (Newark, DE, USA) and Sigma-Aldrich co. (St. Louis, MO, USA), respectively. Magnesium stearate, monobasic potassium phosphate, dibasic sodium phosphate, and sodium chloride were purchased from Fisher scientific (Pittsburgh, PA, USA).

Preparation of Tablets

Table I lists a granisetron hydrochloride (1%) fast disintegrating tablet formulation used in this study. Direct compression method was used to prepare tablets because of its ease of manufacture and low cost. Drug and all the excipients except magnesium stearate were passed manually through a #20 mesh screen and mixed in a polyethylene bag for 10 min. Magnesium stearate was added to this blend and mixed properly again for 2–3 min. Blend was compressed using 11 mm flat plain face tooling on B2 rotary tablet press (Globe Pharma, New Brunswick, NJ, USA) at 60 rpm. The targeted tablet weight (die volume) was kept constant at around 200 mg. The independent factors and dependent responses used in the study are listed in Table II. Formulations were prepared according to matrix of the face-centered central composite design; varying levels of the factors, *i.e.*, concentration of diluent (0%, 30%, 60%), concentration of disintegrating agent (0%, 3%, 6%), and concentration of direct compression aid agent (10%, 20%, 30%) as shown in Table II. Compression force was kept constant throughout the study.

Table I. Typical Granisetron Hydrochloride Fast Disintegrating Tablet Formulation

Sr. #	Ingredient	% Tablet weight[a]
1	Granisetron hydrochloride	1
2	β Cyclodextrin	0/30/60
3	Spray dried lactose	10/20/30
4	Croscarmellose sodium	0/3/6
5	Magnesium stearate	1
6	Mannitol	q.s. 100

[a] Tablet weight=200 mg

Table II. Variables in Face-Centered Central Composite Design

Independent variable—factor	Levels used		
	Low (−1)	Middle (0)	High (1)
X_1: β cyclodextrin concentration	0%	30%	60%
X_2: croscarmellose sodium concentration	0%	3%	6%
X_3: spray-dried Lactose concentration	10%	20%	30%
Dependent variable—response			
Y_1=disintegration time (seconds)			
Y_2=hardness (kilograms)			

Disintegration Test

Fast disintegrating tablets disintegrate or dissolve in the mouth by saliva. Amount of saliva in mouth is limited and no simulated tablet disintegration test is found in US Pharmacopeia. Since it was difficult to apply general disintegration test to reflect real conditions, a modified version of simple but novel disintegrating test apparatus developed by Fu *et al.* (15) was used. The device consisted of a cylindrical vessel in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve (Fig. 1). Disintegration test was carried out using 3 ml of simulated saliva fluid (2.38 gm Na_2HPO_4, 0.19 gm KH_2PO_4, and 8.00 gm NaCl per liter of distilled water; pH adjusted to 6.76) so that 2 ml of the media was below and 1 ml above the sieve. The tablet was placed on sieve and the whole assembly was then placed on a shaker. The time at which all particles passed through sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from composite samples for each of the tableting runs and the average value was determined.

Hardness Test

Hardness was determined by using Monsanto hardness tester (Tab-Machines Ltd., Mumbai, India). Ten tablets were chosen randomly from the composite samples for each of the tableting runs and the average value was determined.

Tablet Properties

Composite samples from the tableting runs were tested for weight variation and thickness to determine any variability associated with the tablet press and method of preparation of tablets. Tablet weight was determined using Mettler Toledo weighing balance (Mettler-Toledo Inc. Columbus, OH, USA). Thickness was determined using Digimatic Caliper (Mitutoyo Corp. Japan). Ten tablets were chosen randomly and the average value was determined.

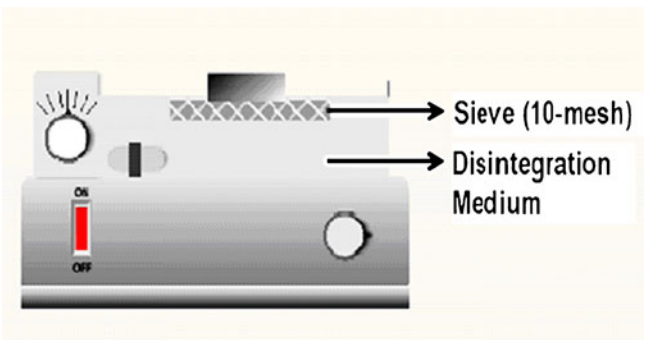

Fig. 1. Device used to determine the disintegration time of fast disintegrating tablets

Comparison of the Optimized Formulation with Marketed Technologies

Tablets of different marketed technologies were obtained from the respective manufacturing companies.

- Orasolve® placebos and Durasolve® placebos—Cima Labs Inc. (Eden Prarie, MN, USA).
- Frosta® placebos—Akina Inc. (West Lafayette, IN, USA).

Fast disintegrating tablets prepared by Durasolve technology consist of nondirect compression sugars, an effervescent agent, a wicking agent, and a lubricant (16). Orasolve consist of a mixture of microparticles and effervescent agent (17). Frosta uses highly plastic granules, which consist of porous and plastic material, a water penetration enhancer, and a binder (3).

These tablets were characterized, as they were received from the manufacturer, for disintegration time, hardness, and tablet properties. Disintegration time, hardness, and tablet properties were determined by same methods as mentioned earlier in respective tests.

Water Uptake Study

For water uptake studies, tablets were placed and simulated saliva fluid (3 ml) was added from side of the plastic weighing boats. Photographs of the tablets were taken by Stereomicroscope (Leica Microsystems Inc., Bannockburn, IL, USA Model-MZ6) at 10-s interval.

RESULTS

Determination of Factors for the Experimental Design

During preliminary trial runs, manufacturing of direct compression tablets were not achieved as compressed tablets were not ejected from the die making tablet press difficult to operate when formulations were composed of 80–95% of β cyclodextrin. When reduction in tablet hardness was tried to solve the problem, intact formation of tablets was not observed. This could be due to high compressibility and/or poor flowability of β cyclodextrin. Shangraw *et al.* (18) in their study found that β

cyclodextrin had a poor flow and it was more compressible. Several other excipients such as dicalcium phosphate, microcrystalline cellulose, mannitol, and starch were tried in conjunction with β cyclodextrin. Several formulation approaches such as addition of lubricant, glidant, reduction in hardness, and change in the speed of tablet press were also tried in this study to prevent the problems faced as described above. The problem was solved when spray-dried lactose was added in the formulation with decrease in β cyclodextrin concentration. Hence, spray-dried lactose was used in the experimental design formulations as a direct compression aid. Mannitol has been used in many marketed fast disintegrating tablet formulations as filler or sweetening agent. Hence, mannitol was used to make composition of tablet formulation to 100%. Mannitol was used as filler as it can serve the purpose of filler as well as a sweetening agent. The concentration of filler (mannitol) was considered as a 'slack factor' (19). The concentration of filler was varied from 12% to 88% in order to keep tablet weight of 200 mg constant. It can be assumed that any changes in the responses were due to the changes in the levels of the variables studied rather than the results of consequential changes in the proportion of the filler, *i.e.*, a 'slack factor' (19).

The independent factors, determined based on preliminary studies and dependent responses used in the study are listed in Table II. The matrix of face-centered central composite design is depicted in Table III. Each row in the matrix identifies an experiment and each experiment provides a result (response). The levels of factors studied were chosen so that their relative difference was adequate to have a measurable effect on the response, along with the information that selected levels were within practical use. The constant and regression coefficients were calculated using commercial software (Statgraphics Plus—5, Manugistics, Rockville, MD, USA) for each response.

Data Obtained from the Experimental Design and Fitting the Data to the Model

Tablet weight had some variations (Table III); these variations may be attributed to the differences in bulk density in the formulations. However, all formulations were in agreement with the pharmacopoeial requirements regarding the uniformity of weight. Tablet thickness was relatively constant for all the formulations (Table III). This, uniformity in tablet weight and thickness, suggested that there was a low possibility of any variability associated with the tablet press or the method of preparation of tablets. Table III also summarizes values for the responses: Y_1—disintegration time, Y_2—hardness of the fast disintegrating tablets. This data was analyzed using a statistical package (Statgraphics® Plus, Version 5) and second-order regression models were developed based on the regression of statistically significant variables. Results of multiple regression analysis for each response variable were as follows:

$$Y_1 = 64.37 + 2.93 \times X_1 - 3.39 \times X_2 + 0.98 \times X_3 - 21.70 \times X_1^2 - 26.11 \times X_2^2 + 31.97 \times X_3^2 \quad (1)$$

$$Y_2 = 1.25 + 0.096 \times X_1 \quad (2)$$

The above equations indicate quantitative effect of processing variables (X_1, X_2, and X_3) and their interactions on the responses Y_1 and Y_2. The values of coefficients X_1 to X_3 are associated with effect of these variables on the response. Coefficients with more than one factor (*e.g.*, X_1 X_2) represent an interaction effect while those with higher order terms (Xn^2) denote quadratic relationships. Only statistically significant ($p<0.05$) coefficients were retained in the equations except for coefficients of X_1, X_2, and X_3 in the model for disintegration time of tablets (Y_1). Although coefficients of X_1, X_2, and X_3 were not statistically significant, they were still retained in the equation of Y_1 because ${X_1}^2$, ${X_2}^2$, and ${X_3}^2$ were statistically significant. The confidence with which the regression equations predicted responses for Y_1 and Y_2 were 88.3%, and 83.9%, respectively. Lack-of-fit test (p value greater than 0.05 for both models) indicated that models were fitted adequately to represent the observed data at 95% confidence level. The standard error of estimate for Y_1 and Y_2 was 9.81 and 0.41, respectively.

Table III. Matrix of Face-Centered Central Composite Design and Results for each Experimental Run

Exp #	X_1	X_2	X_3	Y_1: disintegration time (s) (±SD)	Y_2: hardness (kg) (±SD)	Weight (mg) (±SD)	Thickness (mm) (±SD)
1	1	−1	1	50.2 (26.5)	2.2 (0.7)	225.3 (13.7)	2.0 (0.0)
2	1	0	0	48.9 (15.2)	2.7 (0.4)	242.5 (7.4)	2.0 (0.0)
3	0	0	1	101.9 (44.1)	1.8 (0.5)	238.7 (7.7)	2.0 (0.0)
4	0	0	−1	100.1 (56.7)	1.2 (0.4)	228.9 (9.3)	2.1 (0.0)
5	0	0	0	62.7 (22.2)	0.8 (0.2)	221.5 (12.4)	2.0 (0.0)
6	1	−1	−1	54.2 (7.7)	1.0 (0.3)	225.2 (4.7)	2.0 (0.0)
7	0	0	0	53.6 (17.1)	1.1 (0.4)	235.1 (7.4)	2.1 (0.0)
8	−1	−1	1	50.6 (9.9)	0.6 (0.1)	228.7 (5.2)	2.1 (0.0)
9	−1	1	−1	48.8 (14.3)	0.3 (0.0)	231.0 (5.5)	2.1 (0.0)
10	1	1	−1	42.8 (7.4)	1.1 (0.3)	221.6 (5.5)	2.1 (0.0)
11	0	−1	0	54.8 (14.9)	0.9 (0.2)	209.2 (6.2)	2.0 (0.1)
12	−1	1	1	37.5 (4.1)	0.5 (0.2)	203.8 (3.3)	2.0 (0.0)
13	−1	0	0	45.8 (16.0)	0.3 (0.1)	212.4 (8.4)	2.1 (0.0)
14	1	1	1	55.2 (7.4)	1.4 (0.5)	225.9 (5.2)	2.1 (0.0)
15	−1	−1	−1	39.4 (2.5)	0.3 (0.0)	202.3 (4.1)	2.1 (0.0)
16	0	0	0	31.1 (9.1)	0.8 (0.3)	198.1 (4.2)	2.0 (0.0)
17	0	0	0	58.0 (17.8)	1.4 (0.3)	234.4 (5.5)	2.0 (0.0)

From regression equations (1,2), factor X_1 appeared in the regression equations of Y_1 and Y_2. Hence, concentration of β cyclodextrin (X_1) was the main factor having a positive impact on the tablet disintegration and hardness of fast disintegrating formulation. Disintegration time of tablets was significantly affected by the quadratic terms of the variables X_1, X_2, and X_3; however, it was independent of any interaction amongst variables. This suggested that there was a curvature in the response and there were optimal values for these variables. The negative regression coefficient for quadratic terms of variables X_1 and X_2 suggested that disintegration time increased (Y_1) and after maxima, it decreased. The positive regression coefficient for quadratic term of variable X_3 suggested that disintegration time decreased and after minima, it increased. The positive regression coefficient of variable X_1 (concentration of β cyclodextrin) suggested increase in tablet hardness (Y_2) with increased concentration of β cyclodextrin.

Analysis of the Data—Disintegration Time of the Tablets

The relationship between the dependent and independent variables was further illustrated using response surface plots. A response surface plot allows visual observation of the significance of regression equations by graphically depicting maxima and minima. Response surface plot in Fig. 2a elicited the effect of concentration of β cyclodextrin (X_1) and concentration of croscarmellose sodium (X_2) and their interaction on disintegration time of the fast disintegrating tablets (Y_1). At low level of croscarmellose sodium (X_2), disintegration time increased from 16.7 to 41.6 s with increased concentration of β cyclodextrin from 0% to 30%. Above 30% of β cyclodextrin, the disintegration time decreased from 41.6 to 23.2 s. At high level of croscarmellose sodium (X_2), disintegration time increased from 10.6 to 34.9 s with increased concentration of β cyclodextrin from 0% to 30%. Above 30% of β cyclodextrin, the disintegration time decreased from 34.9 to 15.7 s. Disintegration time increased with increase in the concentration of β cyclodextrin. It (Y_1) reached maximum at around 30% of β cyclodextrin and it decreased thereafter. Similar kind of observation was observed with crosscarmellose sodium. At high level of β cyclodextrin (X_1), disintegration time increased from 23.2 to 45.6 s with increase in the concentration of croscarmellose sodium from 0% to 3%. Above 3% of croscarmellose sodium, the disintegration time decreased from 45.6 to 15.7 s. Tablet disintegration time increased with the increase in the concentration of croscarmellose sodium but at around 3% of croscarmellose sodium, it started decreasing.

At all concentration of β cyclodextrin, as the concentration croscarmellose sodium increased to 3%, increase in the disintegration time was observed. This suggested the poor disintegrating properties of β cyclodextrin at lower concentrations; hence, tablets need an additional disintegrant like croscarmellose sodium. This seems to support the findings of Saleh (20), who suggested the need of a disintegrating agent because of poor disintegrating property of β cyclodextrin. Further increase in concentration of croscarmellose sodium, increased disintegration of tablets, and decreased disintegration time. This was interesting because superdisintegrants such as croscarmellose sodium typically require only low

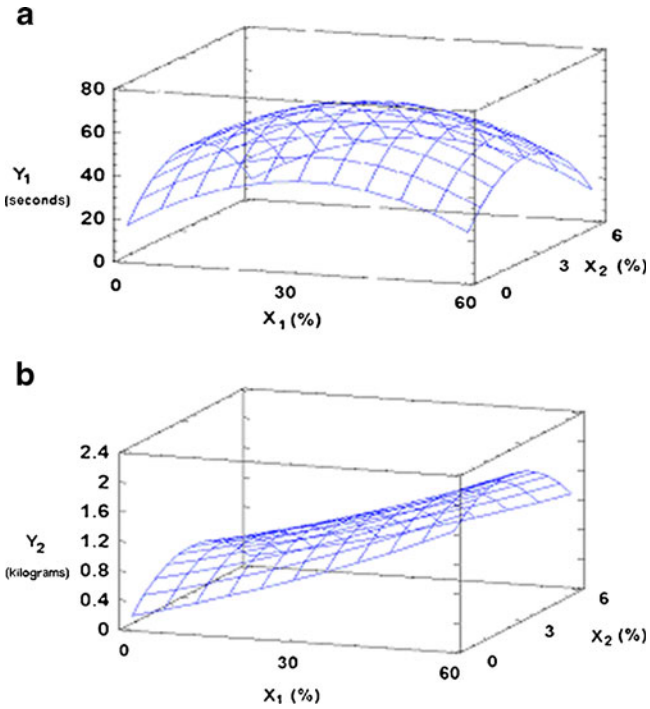

Fig. 2. a Response surface plot eliciting the effect of X_1 (β cyclodextrin concentration) and X_2 (croscarmellose sodium concentration) on Y_1 (disintegration time of fast disintegrating tablets). **b** Response surface plot eliciting the effect of X_1 (β cyclodextrin concentration) and X_2 (croscarmellose sodium) on Y_2 (hardness of fast disintegrating tablets)

concentration for optimum tablet disintegration (21). These agents are very hygroscopic; therefore, they have good 'wicking action', the ability to draw liquid into the matrix. Croscarmellose sodium swells four to eight times its original volume in contact with fluid and its fibrous nature allows intraparticulate and extraparticulate wicking of water (22). Because of this ability, it is effective at lower concentrations (typically 1–3%). Lower concentration of disintegrating agent (1–3%) gave higher disintegration time in this study. Consequently, relatively higher concentration of disintegrating agent (3–6%), disintegration time decreased significantly. This could possibly suggest that results obtained in this work were not just because of poor disintegrating property of β cyclodextrin but there were some other factors contributing to this effect too. The possible reason would be change in the mechanism of tablet disintegration from dissolution mediated to disintegration mediated.

Analysis of the Data—Hardness of the Tablets

Response surface plot in Fig. 2b elicited the effect of concentration of β cyclodextrin (X_1) and concentration of croscarmellose sodium (X_2) and their interaction on hardness of the fast disintegrating tablets (Y_2). It indicated that β cyclodextrin had a desirable effect on hardness of tablets. Hardness of tablets increased with increase in the concentration of β cyclodextrin concentration. At 6% of croscarmellose sodium (X_2), hardness of the tablets increased from 0.25 to 1.60 kg with increased concentration of β cyclodextrin from 0% to 60%. Shangraw *et al.* (18) in their study

concluded that β cyclodextrin was more compactable than either spray-dried lactose or unmilled dicalcium phosphate, commonly used as direct compression diluents/fillers. Interestingly, they also found that β cyclodextrin has compactabilities approaching to that of microcrystalline cellulose. ElShaboury (23) also found that tablets produced with β cyclodextrin alone and its combinations with spray-dried lactose produced tablets with better hardness. This suggests that better compactibility of β cyclodextrin was a reason for increased tablet hardness with increased concentration of β cyclodextrin. There was increase in tablet hardness as concentration of croscarmellose sodium increased up to 3% and then it decreased thereafter till 6% of croscarmellose sodium. However, these changes were not significant as seen in Eq. 2.

Comparison of Optimized Formulation with Formulations Prepared Using 2-hydroxypropyl β cyclodextrin and γ Cyclodextrin

In this work, hardness of tablets increased with increased concentration of β cyclodextrin. However, disintegration time of tablets increased with increased concentration of β cyclodextrin until around 30% and decreased with further increase in concentration of β cyclodextrin concentration till 60%.

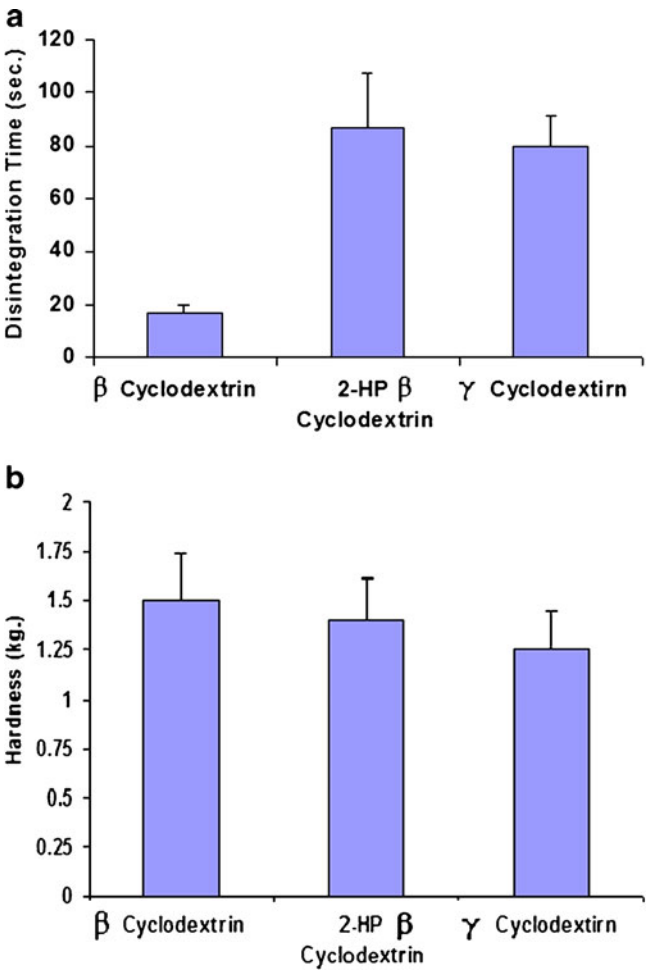

Fig. 3. a Comparison of disintegration time of the optimized fast disintegrating tablets composed of β cyclodextrin, 2-hydroxypropyl β cyclodextrin, and γ cyclodextrin. **b** Comparison of hardness of the optimized fast disintegrating tablets composed of β cyclodextrin, 2-hydroxypropyl β cyclodextrin, and γ cyclodextrin

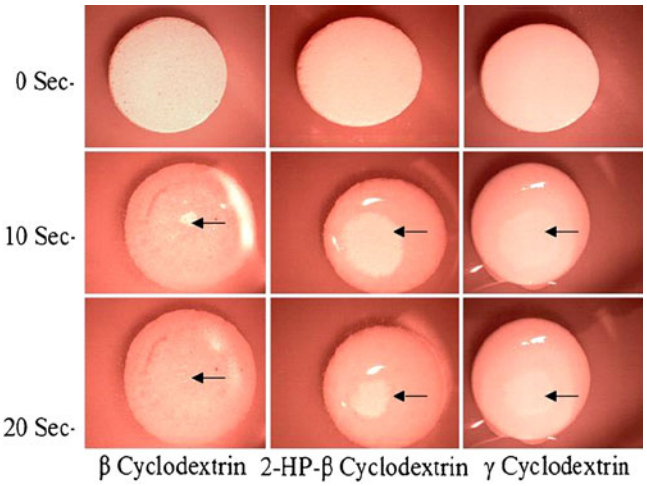

Fig. 4. Stereomicroscopic pictures of water uptake by optimized fast disintegrating tablets composed of β cyclodextrin, 2-hydroxypropyl β cyclodextrin, and γ cyclodextrin

To explain these results further, β cyclodextrin from an optimized tablet formulation was replaced by highly soluble cyclodextrins such as 2-hydroxypropyl β cyclodextrin or with γ cyclodextrin to see its effect on disintegration time and hardness of the tablets. Formulations were composed of same excipients at the same concentration. Concentration of either of the cyclodextrins was also kept constant, *i.e.*, 60%. It was found that disintegration time of tablets composed of highly soluble cyclodextrins was significantly different than that of tablets made up of β cyclodextrin (Fig. 3a) with insignificant effect on the tablet hardness (Fig. 3b). Microscopic pictures of water uptake (Fig. 4) by these formulations also revealed that water uptake was faster for tablets composed of β cyclodextrin than that of tablets made up of 2-hydroxypropyl β cyclodextrin and γ cyclodextrin. Tablets prepared with β cyclodextrin also showed some swelling at tablet surface, surface of the tablets, while tablets made up of 2-hydroxypropyl β cyclodextrin and γ cyclodextrin did not show any swelling at their surface. This was attributed to swelling of the disintegrating agent, croscarmellose sodium. Hence, a possible explanation for our results is that at low concentration of β cyclodextrin, below 30%, the disintegration of tablets may be predominantly by dissolution mediated, *i.e.*, disintegration is achieved by dissolution of highly soluble components. Therefore, disintegration time of fast disintegrating tablets was high because of high concentration of soluble components. At high concentration of β cyclodextrin, above 30%, the disintegration of tablets may be predominantly disintegration mediated, *i.e.*, swelling of disintegrating agent due to water uptake and disintegration due to force generated inside the tablet. Therefore, the disintegration time was low because disintegrating agent can act more efficiently because of high concentration of insoluble component, β cyclodextrin.

Validation of the Model and Optimization of the Formulation

Theoretical values of Y_1 for the 17experiments were obtained by substituting values of X_1–X_3 in the response

Table IV. Observed, Predicted, and Residual Values for Response Y_1 and Y_2

	Y_1: disintegration time (s)			Y_2: hardness (kg)		
Exp #	Predicted	Observed	Residual	Predicted	Observed	Residual
1	58.0	50.2	7.8	2.2	2.2	0.0
2	45.6	48.9	−3.3	2.0	2.6	−0.6
3	97.3	101.9	−4.6	1.6	1.8	0.2
4	95.3	100.1	−4.8	1.1	1.2	−0.1
5	64.4	62.7	1.7	1.2	0.8	0.4
6	52.4	54.2	1.8	1.2	0.9	0.3
7	64.4	53.6	10.8	1.2	1.0	0.2
8	49.3	50.6	−1.3	0.6	0.6	0.0
9	43.4	48.8	−5.4	0.2	0.2	0.0
10	46.4	42.8	3.6	1.1	1.0	0.1
11	41.6	54.8	−13.2	0.8	0.8	0.0
12	41.7	37.5	4.2	0.3	0.5	−0.2
13	39.7	45.8	−6.1	0.7	0.3	0.4
14	49.0	55.2	−6.2	1.7	1.4	0.3
15	47.9	39.4	8.5	0.1	0.2	−0.1
16	34.9	31.1	3.8	0.6	0.8	−0.2
17	64.4	58.0	6.4	1.2	1.4	−0.2

surface model for Y_1. The theoretical (predicted) values and the experimental (observed) values were in close agreement as seen in Table IV. Similarly, the values of X_1–X_3 were substituted in the response surface model for Y_2 to obtain the theoretical values of Y_2. The theoretical (predicated) values and the experimental (observed) values were in close agreement (Table IV). The models were validated using three independent measurements at three different levels for each factor, which were not used in the previous experiments (matrix of the design).

Contour plots (not shown) were used to determine the optimum formulation parameters. Models predicted levels of X_1=60%, X_2=6%, and X_3=20%, for the optimal formulation having a maximal hardness value with minimum disintegrating time, within experimental region. An experiment was performed based on these optimal levels. The regression equations predicted responses of Y_1=16.0 s, Y_2=1.3 kg for the optimal formulation. These predicted values were reasonably in good agreement with the observed values of 17.1±2.6 (SD)s, 1.5±0.2 (SD) kg, respectively, for Y_1 and Y_2. Good correlation between the experimental data and predicted values was seen for responses Y_1 and Y_2.

Comparison of the Optimized Formulation with Marketed Technologies

The optimized formulation was compared with some of the marketed technology formulations. Results of comparison of optimized formulation with marketed technologies are shown in Table V. These results show that the optimized formulation was comparable to the marketed technology formulations. Tablets of Durasolve technology showed lowest disintegration time amongst all formulations (Table V). However, optimized formulation obtained in this study gave harder tablets with comparable disintegration time. There were differences in tablet thickness and tablet weight amongst the formulations used for comparison. However, it still gave a good idea about the optimized formulation obtained in this study to the marketed technology formulations with respect to hardness and disintegration time.

DISCUSSION

Disintegration is the process of solid form breaking up when it comes into contact with aqueous fluid. In most cases, disintegration is a disaggregation process of constituent particles before dissolution happens. There are two most widely accepted mechanisms for tablet disintegration. Disintegration takes place by annihilation of the interparticle bonding and by the development of separating stress due to swelling of disintegrant by fluid permeating into the tablet (24,25). However, whatever may be the mechanism proposed, water uptake is always the first step (25). Also, in general, disintegration time would increase with the increase in hardness of tablets (26).

The results of tablet hardness in this study seemed contradictory to results obtained with tablet disintegration time. In this work, disintegration time of tablets increased

Table V. Comparison of the Optimized Formulation with some Marketed Technologies

Sr. #	Technology	Disintegration time (s) (±SD)	Hardness (kg) (±SD)	Weight (mg) (±SD)	Thickness (mm) (±SD)
1	Orasolv®	20.6 (4.4)	0.25 (0.0)	300.0 (2.4)	4.1 (0.1)
2	Durasolv®	9.1 (1.5)	0.7 (0.3)	103.8 (1.2)	3.0 (0.0)
3	Frosta®	32.2 (12.9)	1.0 (0.2)	103.6 (2.5)	2.5 (0.0)
4	Optimized formulation	17.1 (2.6)	1.5 (0.3)	216.6 (1.6)	2.1 (0.0)

with increased concentration of β cyclodextrin until around 30%. Disintegration time decreased with further increase in the concentration of β cyclodextrin till 60%, while hardness of the tablets increased with increase in the concentration of β cyclodextrin from 0% to 60%. Dobetti *et al.* (7) reported similar kinds of results in their patent. They found that when they increased the concentration of relatively insoluble components like dibasic calcium phosphate, disintegration time decreased with increase in insoluble components concentration. According to the patent, disintegration of a tablet depends on quantity of the disintegrant and insoluble excipient used. It also depends on the relative weight ratio between water-insoluble and -soluble excipients, if water-soluble excipients are used. Disintegrating agent may act more efficiently when there is increased concentration of insoluble excipients, had been invoked as an explanation for decreased disintegration time. Hence, results obtained in this work, could be explained on the basis of exhibited insolubility by β cyclodextrin in comparison to other excipients of the formulation. β Cyclodextrin has a solubility of one part in 50 ml of water, which is lower than that of spray-dried lactose and mannitol, while croscarmellose sodium is hygroscopic (10). At low level, below 30% of β cyclodextrin concentration, concentration of soluble components was more. These soluble components competed with each other for small amount of water molecules that was present in the disintegration media. These competitions affect the optimum disintegration efficiency of disintegrating agent, croscarmellose sodium, exhibiting higher disintegration time. When β cyclodextrin concentration was at high level, above 30%, concentration of soluble components was lower and therefore less competition. This less competition may allow disintegrating agent to uptake more water molecules and act more efficiently providing lower disintegration time. These results are in agreement with the general theory that soluble excipients compete for the locally available water; thus, inhibiting the action of disintegrating agent (27,28). Water-soluble excipients tend to dissolve rather than disintegrate, while insoluble excipients produce rapid disintegration. Several studies have shown that superdisintegrants like croscarmellose sodium have a greater effect on disintegration time in a system when insoluble excipient concentration is more (6,27,29).

CONCLUSION

Response surface methodology was used to generate a highly significant mathematical model, which can adequately describe or predict the optimization of novel fast disintegrating tablets using β cyclodextrin as a diluent. A composition with 60% β cyclodextrin, 6% croscarmellose sodium, and 20% of spray-dried lactose fulfilled a maximum requisite of an optimum formulation. A statistical experimental design allowed collecting maximum information with minimum number of experiments. The combined use of a face-centered central composite design and mechanistic studies facilitated the identification of factors and/or its interaction effects. It also proved important in understanding the mechanisms involved, which often would have not been detected from a one factor at a time-classical experimental approach. Good correlation between the predicted values and experimental data of the optimized formulation validated prognostic ability of response surface methodology in optimizing fast disintegrating tablets using β cyclodextrin as a diluent.

From the factors examined, β cyclodextrin had the largest effect on the optimization of fast disintegrating tablets. In general, disintegration of tablets has been reported to slow down with increase in hardness. However, in the present study, higher concentration of β cyclodextrin was found to improve the hardness of tablets without increasing the disintegration time. Thus, β cyclodextrin is proposed as a suitable diluent to achieve fast disintegrating tablets with sufficient hardness.

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