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Effects of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets

Sameer G. Late, Yi-Ying Yu, Ajay K. Banga*

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Mercer University, 3001 Mercer University Drive, Atlanta, GA 30341, United States

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ABSTRACT

Effects of calcium silicate (disintegration-promoting agent) and various lubricants on an optimized β-cyclodextrin-based fast-disintegrating tablet formulation were investigated. Effects of moisture treatment were also evaluated at 75, 85 and 95% relative humidities. A two factor, three levels (3^2) full factorial design was used to optimize concentrations of calcium silicate and lubricant. Magnesium stearate, being commonly used lubricant, was used to optimize lubricant concentration in optimization study. Other lubricants were evaluated at an obtained optimum concentration. Desiccator with saturated salt solutions was used to analyze effects of moisture treatments. Results of multiple linear regression analysis revealed that concentration of calcium silicate had no effect; however concentration of lubricant was found to be important for tablet disintegration and hardness. An optimized value of 1.5% of magnesium stearate gave disintegration time of 23.4 s and hardness of 1.42 kg. At an optimized concentration, glycerol dibehenate and L-leucine significantly affected disintegration time, while talc and stearic acid had no significant effect. Tablet hardness was significantly affected with L-leucine, while other lubricants had no significant effect. Hardness was not affected at 75% moisture treatment. Moisture treatment at 85 and 95% increased hardness of the tablets; however at the same time it negatively affected the disintegration time.

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1. Introduction

Solid dosage forms like tablets and capsules are the most popular and preferred drug delivery systems because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing, good physical and chemical stability (Marshall and Rudnic, 1990; Joshi and Duriez, 2004). Tablet dosage form is mainly composed of the drug and excipients such as a diluent, a binder, a lubricant, a disintegrant, and a glidant. Lubricant is an important excipient to improve the quality and manufacturing efficiency of tableting process (Miller and York, 1988). Lubricants help in reducing the friction between the powder bed and the die wall during compression and ejection by interposing a film of low shear strength between them (Peck et al., 1989). Thus, it facilitates tableting of the formulation and ejection of the formed tablets. Lubricant can be used to improve the fluidity, filling properties and plasticity of the powders. Some lubricants can also act as antiadherent, which prevents sticking of the powder to the punches and die (Medina and Kumar, 2006). Lubricant also has profound influence on disintegration time, hardness and drug dissolution (Zanorwick, 1994; N'Diaye et al., 2003). Therefore, it is important to optimize concentration of lubricant in the formulation.

Fast disintegrating tablets provide a convenient solution for patients who have difficulties in swallowing tablets and other dosage forms (Fu et al., 2004). The key properties of fast disintegrating tablets are fast absorption of water into the core of the tablets and disintegration of associated particles into individual components for fast dissolution (Fu et al., 2005). Highly porous systems or porous excipients may absorb water faster giving faster disintegration of the tablets. This suggests that highly porous systems or incorporation of porous excipients may prove advantageous to fast disintegrating tablets. Calcium silicate has many pores and a large pore volume with characteristic porous structure (Yuasa et al., 1996). It has been used as an industrial liquid absorber (Jain et al., 2005) and also as a disintegration/disaggregation-promoting agent (Rxcipients FM 1000 application bulletin). It has been shown that, in the presence of superdisintegrant or combination of superdisintegrants (crospovidone, croscarmellose sodium, sodium starch glycolate), calcium silicate (Rxcipients FM 1000®) lowers the disintegration time without much effect on tablet hardness (Rxcipients FM 1000 application bulletin 1–3).

Equilibration of tablets under high humidity and drying of those tablets had shown increased tablet hardness than that of initial tablet hardness (Chowhan and Palagyi, 1978; Chowhan,

* Corresponding author. Tel.: +1 678 547 6243; fax: +1 678 547 6423.
E-mail address: banga_ak@mercer.edu (A.K. Banga).

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1979). In our earlier studies, face centered central composite design was employed to optimize and evaluate effects of formulation parameters β-cyclodextrin, croscarmellose sodium and spray dried lactose. As most of fast disintegrating tablet formulation technologies available in the market compromise hardness for the faster disintegration time, the hardness of these tablets is low. Most of these technologies have hardness values in the range of 0.5–2.50 kg. Therefore, the hardness values of 1.25–1.50 kg, obtained for the optimized fast disintegrating tablet formulation of granisetron hydrochloride, were considered as a moderate hardness value (Late and Banga, unpublished data). It would, thus, be prudent to see effect of moisture treatment on tablet hardness in the optimized formulation.

Traditional experimental methods involves significant amount of time and efforts to get meaningful results for a complex system. It is very much desirable to obtain an acceptable formulation using minimum amount of time and material. Factorial design is an efficient method of finding the relative significance of number of variables and their interaction on the response or outcome of the study. The response surface method is a useful and efficient tool to obtain an appropriate model with minimum experiments. Optimization procedure involving factorial designs and analysis of response surfaces is powerful, efficient and also a systematic tool and has been used in developing different oral dosage formulations (Bodea and Leucuta, 1997; Gohel and Amin, 1998; Bhavsar et al., 2006).

β-Cyclodextrin has good compression characteristics as it has good compressibility index (Wade and Weller, 1994). 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-cyclodextrin, which is very essential for fast disintegrating tablet formulations. Also, it may render other advantages such as taste masking of the drug and enhancing solubility of the poorly soluble compounds.

In this work, factorial design was used to optimize the concentrations of disintegration-promoting agent and the lubricant. A two factor, three levels (3^2) full factorial design was used and nine experimental runs were performed. Statistical models with interaction terms were derived to evaluate influence of calcium silicate (Rxcipients FM 1000®) (X_1) and magnesium stearate (X_2) on tablet disintegration (Y_1) and hardness (Y_2). Magnesium stearate is the most commonly used lubricant in solid dosage formulations. Therefore, in this study lubricant optimization was carried out using magnesium stearate. Effects of other hydrophobic lubricants like stearic acid, glycerol dibehenate, glidant and antiadherent like talc and hydrophilic lubricant like L-leucine (Roscheisen and Schmidt, 1995; Daher, 1999) on an optimized fast disintegrating tablet formulation was evaluated at an obtained optimized concentration. The effects of different relative humidities on the crushing strength and disintegration times of the optimized tablet formulation were also studied.

2. Materials and methods

2.1. Experimental design

A two factor, three levels (3^2) full factorial design was used to optimize disintegration-promoting agent and lubricant concentration. This design provided an empirical second order polynomial model. This model was used to predict the effects of formulation variables on the disintegration time and hardness of the fast disintegrating tablet formulation.

The factorial design is a simplified representation in analytical form of a given reality. In this mathematical approach each experimental response Y can be represented by a quadratic equation of the response surface: $Y = B_0 + B_1X_1 + B_2X_2 + B_3X_1X_2 + B_4X_1^2 + B_5X_2^2$, in which Y is the measured response associated with each factor-level combination; X_1, and X_2 are the factors studied; B_0 is an intercept; B_1–B_5 are the regression coefficients. The equation enables the study of the effects of each factor and their interaction over the considered responses.

Table 1
Variables in 3^2 full factorial design

Independent variable, factor	Levels used		
	Low (−1) (%)	Middle (0) (%)	High (1) (%)
X_1: calcium silicate concentration	0	5	10
X_2: magnesium stearate concentration	0	1	2
Dependent variable, response			
Y_1 = disintegration time (s)			
Y_2 = hardness (kg)			

The two factors as well as their levels and the analyzed response are shown in Table 1. The matrix of the factorial design is represented in Table 2. Each row in the matrix identifies an experiment and each experiment provides a result (response). The levels of the factors studied were chosen so that their relative difference was adequate to have a measurable effect on the response, along with the information that the selected levels are within practical use. Statgraphics Plus, Version 5 (Manugistics, Rockville, MD) was used for the response surface modeling and the evaluation of the quality of the fit of the model. The constant and regression coefficients were calculated using the same software. The polynomial equations derived from this optimization technique were used to predict the disintegration time and the hardness values for fast disintegrating tablet formulations of granisetron hydrochloride in the experimental region.

2.2. Materials

Granisetron HCl was purchased from Ultratech India Ltd. (Bombay, India). The following chemicals were obtained and used as received. β-Cyclodextrin (Wacker-Chemie, GmBH, Germany), croscarmellose sodium, Spray dried lactose (FMC Corporation, Newark, DE), L-leucine (Avacado Research Chemicals Ltd., Heysham, Lancashire, UK), talc (Whittaker, South Plainfield, NJ), stearic acid (J.T. Baker, Phillipsburg, NJ), glycerol dibehenate (Gattefosse, Saint-Priest Cedex, France). Mannitol was purchased from Sigma–Aldrich co. (St. Louis, MO). Calcium silicate (Rxcipients FM 1000®) was received as a gift sample from Huber Corporation (Havre de Grace, MD). Magnesium stearate, monobasic potassium phosphate, dibasic sodium phosphate, and sodium

Table 2
Matrix of 3^2 full factorial design

Exp. #	Calcium silicate concentration (X_1)	Magnesium stearate concentration (X_2)
1	−1	0
2	0	0
3	0	1
4	−1	1
5	1	1
6	1	−1
7	0	−1
8	1	0
9	−1	−1

Table 3
Typical granisetron hydrochloride fast disintegrating tablet formulation

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

[a] Tablet weight = 200 mg.

chloride were purchased from Fisher Scientific (Pittsburgh, PA, USA).

2.3. Preparation of tablets

Table 3 lists a typical 1% granisetron hydrochloride fast-disintegrating tablet formulation used in this study (Batch size was 10 g). Tablets of 200 ± 50 mg were made by direct compression of mixtures on a B2 rotary tablet press (Globe Pharma, New Brunswick, NJ) with flat plane face punches (punch diameter = 11 mm) at 60 rpm. Drug and all the excipients except the lubricant were passed through a #20 mesh screen. The drug blend was prepared by mixing them manually in a polyethylene bag for 10–12 min. The lubricant was added to this blend and mixed properly again for 2 min. All formulations were prepared according to the matrix of the full factorial design; varying the levels of the factors, i.e. concentration of disintegration-promoting agent (0, 5 and 10%), and concentration of lubricant (0, 1, and 2%), as shown in Table 2.

2.4. Disintegration test

Disintegration or dissolution of fast disintegrating tablets *in vivo* is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in United States Pharmacopeia to simulate in vivo conditions. A modified version of the simple but novel method developed by Fu et al. (2006) was used to determine disintegration time of the tablets. A cylindrical vessel was used in this method 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). To determine disintegration time, 3 ml of simulated saliva fluid ((2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8.00 g NaCl per liter of distilled water, pH adjusted to 6.76 with phosphoric acid), Peh and Wong, 1999) was placed inside the vessel in such way that 2 ml of the media was below the sieve and 1 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

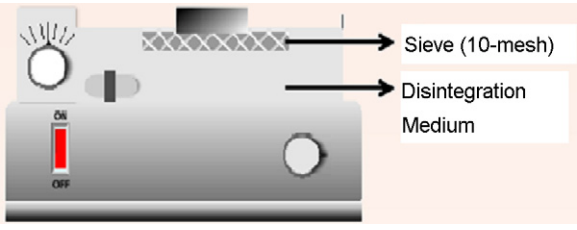

Fig. 1. Device used to determine the disintegration time of fast disintegrating tablets.

2.5. Hardness test

Monsanto hardness tester (Tab-Machines Ltd., India) was used to determine tablet hardness. Ten tablets were chosen randomly from the composite samples for each of the tableting runs and the average value was determined.

2.6. Tablet properties

Composite samples from the tableting runs were also tested for tablet thickness and weight variation to determine any variability associated with the tablet press or the method of preparation. Thickness was determined using digimatic caliper (Mitutoyo Corp., Japan). Ten tablets were chosen randomly from the composite samples for each of the tableting runs and the average value was determined. Uniformity of mass was determined by weighing 10 tablets on an analytical balance (Mettler-Toledo, Inc., Columbus, OH).

2.7. Compression force profile

Tablet press available in the lab was not an instrumented tablet press and it was not possible to quantitate the compression force. Therefore, for compression profile studies tablets with different hardness values with increase in the compression force were prepared to evaluate its effect on disintegration time and friability of the tablets. Tablets were prepared according to the method described as earlier.

2.8. Moisture treatments

Drykeeper desiccator (Bel-Art Products, Inc., Pequannock, NJ) was used for moisture treatment studies. The prepared tablets were placed in a desiccator at three different humidity conditions. Saturated sodium chloride solution, potassium chloride solution, potassium sulfate solution were used to create 75, 85, and 95% relative humidity, respectively. The tablets were sampled at 0, 2, 4, 6, 8 and 24 h and dried for 8 h at room temperature (25 + 1 °C and 35–45%RH). The tablet hardness (10 replications) and disintegration time (6 replications) were then measured.

3. Results and discussion

Direct compression method was used because of its ease of manufacture and lower cost (Medina and Kumar, 2006). In our previous work, the ability of β-cyclodextrin as an effective diluent to formulate fast-disintegrating tablets of granisetron hydrochloride prepared by the direct compression method was demonstrated (Late and Banga, unpublished data). In our previous work, central composite design was used to optimize the fast disintegrating tablet formulation having low disintegration time (17.1 s) with moderate hardness (1.30 kg). Hardness of the tablets was increased with increased concentration of β-cyclodextrin. An optimized formulation was composed of 1% granisetron hydrochloride, 60% β-cyclodextrin, 6% croscarmellose sodium 1% magnesium stearate, 20% of spray-dried lactose and 12% of mannitol. Magnesium stearate concentration at 1% was quite sufficient to prepare tablets, however we did not evaluate if it might affect the compression ability of the formulation. Magnesium stearate decreases the wettability of the matrix and thus, may increase the disintegration time of an optimized formulation. Hence, concentration of lubricant was selected as one of the independent variables for the experimental design. Calcium silicate, a disintegration-promoting agent was selected as another variable as it may decrease the disintegration time of the optimized fast disintegrating tablets.

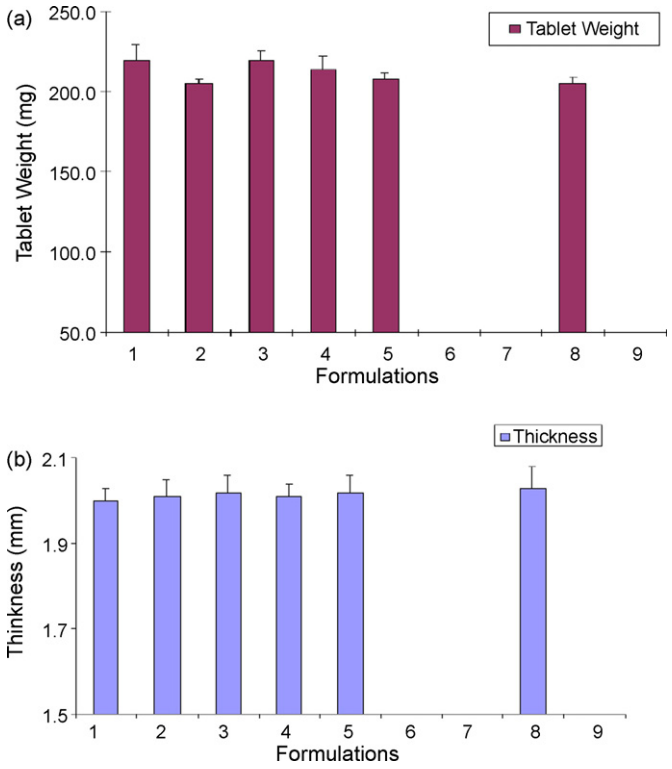

Fig. 2. (a) Tablet weights of formulations 1–9 prepared according to the matrix of the 3^2 full factorial design. (b) Thickness values of formulations 1–9 prepared according to the matrix of the 3^2 full factorial design.

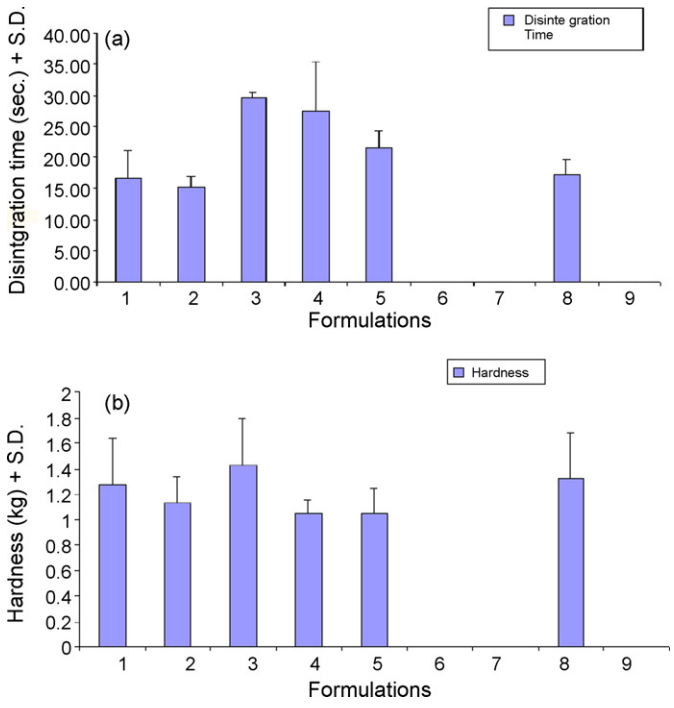

Fig. 3. (a) Disintegration time (±S.D.) of formulations 1–9 prepared according to the matrix of the 3^2 full factorial design. (b) Hardness (±S.D.) of formulations 1–9 prepared according to the matrix of the 3^2 full factorial design.

3.1. Data obtained from the experimental design and model fitting

Average tablet weight of the formulations obtained of all the experimental runs had a range of 205.2–219.3 mg (Fig. 2a) and found to meet the pharmacopoeial requirements regarding the uniformity of weight. Slight variations associated with the tablet weight could be due to differences in the bulk density in the formulations. Tablet thickness had a range of 2.00–2.03 mm and was considered constant for all the formulations (Fig. 2b). Uniformity in tablet weight and thickness suggested that there is a low possibility of any variability associated with the tablet press or the method of preparation of tablets. Lamination or capping was observed with formulations 6, 7 and 9 during the preparation of tablets. Therefore, further analysis with respect to disintegration time, hardness, and tableting properties for those formulations was not carried out. Analysis of the design was not possible without probable values for these formulations. Therefore, for the analysis purpose a value of 0 was assumed for the disintegration time and hardness value of these formulations. Fig. 3 summarizes the values for responses: Y_1, disintegration time of fast disintegrating tablets (Fig. 3a); Y_2, hardness of the fast disintegrating tablets (Fig. 3b). These data were analyzed using a statistical package (Statgraphics® Plus, Version 5) in order to generate mathematical models for each of the responses. Based on the results obtained from this analysis and regression of statistically significant variables, statistical models were generated. The results of analysis for each response variable were as follows:

$$Y_1 = 17.15 + 13.11 \times X_2 \quad (1)$$

$$Y_2 = 1.29 + 0.59 \times X_2 - 0.66 \times X_2^2 \quad (2)$$

The above equations were derived by the best-fit method to describe quantitative effect of process variables (X_1 and X_2) and their interactions on the responses Y_1 and Y_2. The values of the coefficients X_1–X_2 are associated with the effect of these variables on the response. Coefficients with more than one factor represent an interaction effect (e.g. X_1X_2) while those with higher order (e.g. X_2^2) terms denote quadratic relationships. A positive sign signifies a synergistic effect while a negative sign stands for an antagonistic effect. Only statistically significant ($p < 0.05$) coefficients were retained in the equations. The confidence with which the regression equations predicted responses for Y_1 and Y_2 were 98 and 96%, respectively. Lack of fit test (p-value greater than 0.05 for all the models) indicated that models were fitted adequately to represent the observed data at 95% confidence level. The standard error of estimate for Y_1–Y_2 was 2.65 and 0.19, respectively.

Disintegration time and hardness values for all the nine formulations (Fig. 3) varied from 0 to 29.7 s and 0–1.43 kg, respectively. These results indicate that the selected variables have strong influence on disintegration time and hardness of the fast disintegrating tablets. Analysis of variance for the responses (ANOVA) indicated that assumed regression models were significant and valid for each of the responses ($p < 0.05$).

One can conclude, from all the regression Eqs. (1)–(2), that the factor X_2 appears in both the regression equations. Hence, concentration of magnesium stearate (X_2) (lubricant) was the main factor having an antagonistic effect on the disintegration time of an optimized formulation and synergistic effect on the hardness of the optimized formulation. The Eqs. (1)–(2) also indicate that disintegration time and hardness of fast disintegrating tablets were independent of concentration of calcium silicate and any interaction among variables (X_1 and X_2). However, the effect of quadratic terms of the variable X_2 was relevant only on hardness of the tablets (Y_2). This suggests that there is a curvature in the response.

Quality of fit of the model for each response was carried out. Fraction of the response explained by the model was R^2, whereas fraction of the response that can be predicated by the model was Q^2. Goodness of fit of the model was considered statistically excellent with R^2 and Q^2 values approaching to unity. R^2 and Q^2

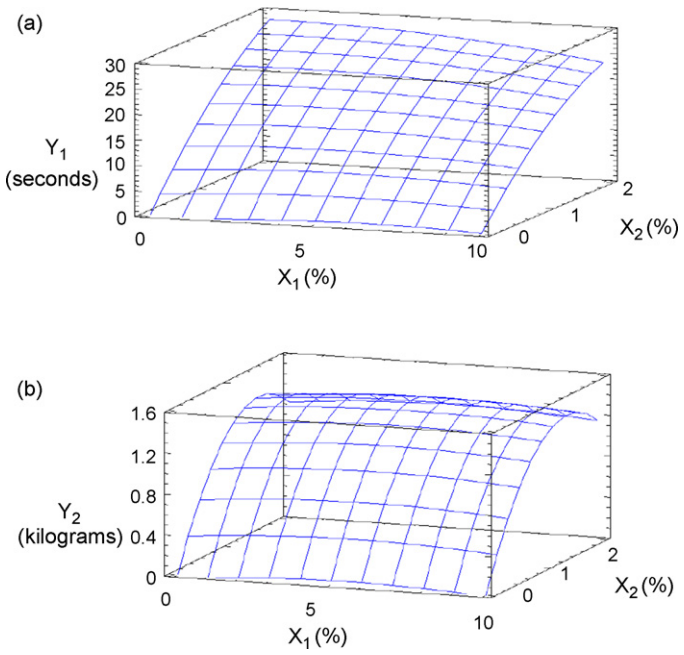

Fig. 4. Response surface plot showing the effect of X_1 (calcium silicate concentration) and X_2 (magnesium stearate concentration) on (a) Y_1 (disintegration time of fast disintegrating tablets) and (b) Y_2 (hardness of the fast disintegrating tablets).

values were close to the unity for response Y_1. Hence, model was found statistically excellent for the response Y_1. For response, Y_2, response variation was nearly 96% with a predictive ability of nearly 69%. Hence, model was considered statistically acceptable for the response Y_2.

3.2. Analysis of the fitted data

A response surface plot allows visual observation of the significance of the regression equations by graphically depicting maxima and minima. The regression Eqs. (1)–(2) is presented in the form of a response surface plots in Fig. 4 showing the influence of independent variables X_1 and X_2 on the responses Y_1 and Y_2. As it can be seen from the plot, concentration of calcium silicate (X_1) had no significant effect on the disintegration time of the optimized fast disintegrating tablet formulation (Fig. 4a). However, disintegration time increased with increased concentration of the lubricant, magnesium stearate (X_2). Disintegration time increased from 0 to 29.7 s with increased concentration of magnesium stearate from 0 to 2% (Fig. 4a). These results are in agreement with the results of Durig and Fassihi (1997) and Aoshima et al. (2005). This delayed disintegration is due to the general agreed observation that magnesium stearate forms a hydrophobic membrane on the surface of the powder particles. Hence, disintegration time will increase with the increased concentration of magnesium stearate.

Concentration of calcium silicate (X_1) had no effect on the hardness of an optimized fast disintegrating tablet formulation (Fig. 4b). Concentration of magnesium stearate (X_2) had a positive impact on the hardness of an optimized formulation. Hardness of the tablets increased from 0 to 1.43 kg when concentration of magnesium stearate increased from 0 to 1.5% (Fig. 4b). Hardness decreased from 1.43 to 1.13 kg with the increase in the concentration of magnesium stearate from 1.5 to 2.0%. These results were quiet interesting and contradictory to the general notion that the tablet hardness is known to decrease with increase in the magnesium stearate concentration. Several authors (Shah and Mlodozeniec, 1977; Williams and Mcginity, 1989; Aoshima et al., 2005) have demonstrated that because of high extensibility of magnesium stearate, it spreads over the surface of the powder particles. This in turn prevents bonding among powder particles, giving low tensile strength and decrease in tablet hardness with increase in the concentration of magnesium stearate. At this point, it is worth to point out that lamination or capping of tablets was observed when magnesium stearate was absent in the tablet formulation (formulations 6, 7 and 9). This observation suggested the need or presence of lubricant for intact formation of the fast disintegrating tablets.

In general, energy consumption is involved in the powder bed compaction, volume reduction and the associated force–time-cycle. These highly complex processes increase interparticulate attraction forces. These events can be regarded as endothermal processes. Bond formation, on the other hand, is an exothermal event. When the mechanical stress is applied, hardness or tensile strength of the tablets is influenced by different factors such as, the elastic and plastic characteristics of the material, changes in porosity, density and anisotropic force distribution within the compact. In addition, lubrication at appropriate levels can enhance and normalize the relative transmission of forces within the die cavity and greatly improves volume reduction (Durig and Fassihi, 1997). It has been shown that β-cyclodextrin is highly brittle material, which results in brittle fracture during compaction (Tasic et al., 1997). Brittle material causes formation of new surface due to fragmentation, extensive and strong interparticulate bonding and formation of solid bridges during compaction (Hiestand and Smith, 1984). When magnesium stearate was absent in the formulation, the cause of lamination or capping thus can be attributed to the brittle nature of the granules, pronounced anisotropic force distribution within the compact and large residual wall pressure. This lamination and capping may be a direct effect of extensive elastic recovery in both axial and radial directions and the development of large differential stresses within the compacts. The increased hardness with increased levels of magnesium stearate can partially be explained on the basis of improved volume reduction, and consolidation behavior. It may also be assisted by formation of new surfaces and denser compacts by bringing the particle surface areas into closer proximity, and an increased ability to transmit the compression force resulting in more cohesive compacts. It should be noted that with a brittle material in the presence of a lubricant film, bond formation could easily be established due to penetration by point irregularities (Karehill and Nystrom, 1990; Karehill et al., 1993). Above 1.5%, of magnesium stearate, there was decrease in the hardness of the tablets. This can be attributed to negation of the enhanced volume reduction and ability to consolidate by greater particle surface coating and subsequent interference in the bonding, when an excess of lubricant was present.

3.3. Validation of the model and optimization of the formulation parameters

To validate the regression equations or model, a check point of $X_1 = 0\%$ and $X_2 = 1.5\%$ was selected. The predicted and observed values of disintegration time and hardness of the tablets for the check point were in close agreement with the values predicted by the model. Lubricant concentration showing highest hardness and low disintegration time was chosen as an optimum concentration. Optimization was carried out using two-dimensional contour plots of both the responses (not shown). Optimum lubricant concentration was found to be 1.5% from the contour plots of both responses. At an optimum concentration, fast disintegrating tablets showed disintegration time of 23.4 (predicted), 25.0 ± 4.0 (observed) seconds with hardness value of 1.42 (predicted), 1.50 ± 0.25 (observed) kg.

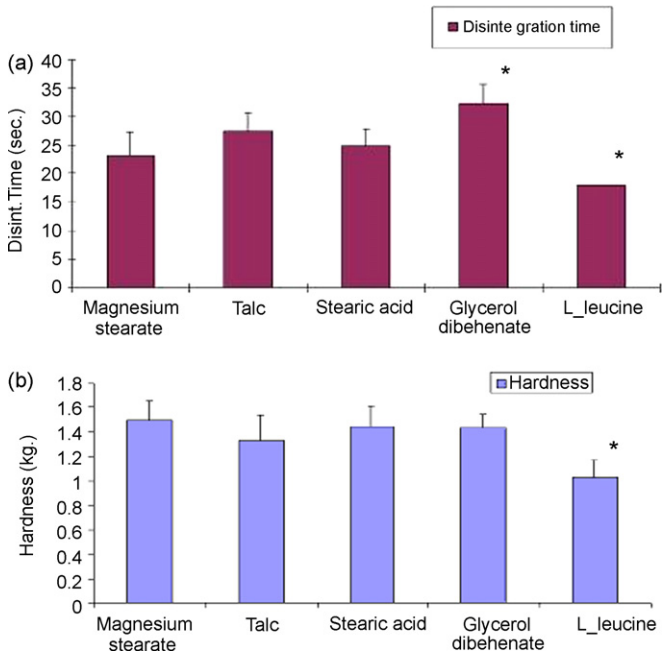

Fig. 5. Comparison of influence of different lubricants on (a) disintegration time and (b) hardness of the optimized fast disintegrating tablet formulations.

3.4. Effect of different lubricants on hardness and disintegration time of an optimized formulation

The optimum concentration (1.5%) of lubricant was used to evaluate effects of different lubricants on the disintegration time and the hardness of the optimized fast disintegrating formulation.

Disintegration time and hardness of the tablets are displayed in Fig. 5. Hydrophobic lubricants, glycerol dibehenate increased disintegration time to 32.4 s. Talc, and stearic acid had no significant effect on the disintegration time of the tablets, however hydrophilic lubricant, L-leucine, showed decrease in disintegration time to 18.0 s. These observed differences could be attributed to differences in the penetration velocity of the disintegrating media through the respective lubricant film. Hydrophobic lubricants like glycerol dibehenate, stearic acid and glidant and antiadherent such as talc did not affect hardness of the tablets as compared to magnesium stearate. Hydrophilic lubricants like L-leucine showed significant reduction in hardness of the tablets to 1.03 kg. Tablet weight and thickness of all the formulations in this study were constant (not shown). Based on this study, magnesium stearate was chosen as a lubricant at 1.5% concentration as it gave optimum hardness value with low disintegration time.

3.5. Compression force profile study

To evaluate the effect of compression force on tablet properties, tablets were prepared at different hardness values increasing the compression force. Compression force was increased from formulation A to formulation E. All other parameters related to preparation of the tablets were kept constant except the compression force. The exact values of the compression force were not able to determine, as the tablet press was not an instrumented press. The formulation composition used in this study consisted of following components, Granisetron hydrochloride (1.0%), β-cyclodextrin (60.0%), spray-dried lactose (20.0%), croscarmellose sodium (6.0%), magnesium stearate (1.5%) and mannitol (11.5%). The tablets were evaluated for tablet weight, thickness, disintegration time, hardness and friability. The results are shown in Table 4.

Table 4
Effect of compression force on the optimized formulation

	Formulation				
	A	B	C	D	E
Tablet weight (mg) (±S.D.)	251.42 (4.49)	248.25 (1.30)	244.68 (1.70)	246.02 (2.96)	232.58 (9.09)
Thickness (mm) (±S.D.)	2.22 (0.04)	2.05 (0.03)	1.91 (0.02)	1.80 (0.03)	1.69 (0/06)
Disintegration time (sec) (±S.D.)	20.84 (7.76)	49.01 (4.19)	95.95 (20.34)	314.14 (26.53)	366.17 (32.00)
Hardness (kg) (±S.D.)	1.25 (0.24)	2.78 (0.28)	3.73 (0.43)	5.83 (0.62)	4.73 (0.62)
% Friability	1.35	0.72	0.36	0.19	0.19

The results in Table 4 show that by increasing compression force disintegration time increased and friability decreased. The results can be explained by the formation of more condensed compacts with increasing the compression force. Hardness also increased with increasing compression force, however at highest compression force there was decrease in tablet hardness. Consolidation or formation of compacts in a die takes place either by plastic deformation mechanism or fragmentation mechanism. This formation of compacts is also dependent on the physicochemical properties of the material and the tableting conditions. Particle characteristics, size, size distribution, ability to bond following deformation, moisture content and elastic recovery during decompression affects the consolidation process. As particle characteristics, size, size distribution moisture content were same for all the formulations in compression force profile study, decrease in the tablet hardness at the highest compression force can be attributed to a decrease of the material's ability to undergo plastic deformation.

3.6. Effect of moisture treatment on disintegration time and hardness of an optimized formulation

Table 5 presents the effects of moisture treatment on the disintegration time and hardness of the final optimized formulation with 1.5% of magnesium stearate. The tablets were placed at three different conditions of relative humidity (RH). Relative humidity of 75, 85 and 95% were selected based on the critical relative humidity of the components present in the formulation. Mannitol and spray dried lactose have a critical relative humidity value of 80% (Wade and Weller, 1994) and 90%, respectively (Wade and Weller, 1994). Tablet hardness increases when tablet gain moisture and subsequently loose it. Hence, 85 and 95% relative humidity were chosen so that tablet can gain moisture. Relative humidity of 75% was used as a control.

At 75% relative humidity, there was slight increase (statistically insignificant) in the disintegration time of the tablets till 8 h of moisture treatment. After 24 h of moisture treatment, disintegration time increased significantly to 35.2 s. This could be explained on the basis of moisture absorption by the disintegrating agent, croscarmellose sodium. Superdisintegrants like croscarmellose sodium are very hygroscopic and can absorb the moisture. This in turn could affect its disintegrating efficiency; prolonging the disintegration time of the tablets. Moisture treatment at 75% relative humidity also affected (statistically insignificant) hardness of the tablets too. Moisture affects the bonding efficiency of the powder particles and this could lead to reduction in the hardness of the tablets.

At 85% relative humidity, disintegration time of the tablets increased with increase in the duration of moisture treatment. Disintegration time significantly affected after 6 h of moisture treat-

Table 5
Effect of moisture treatment on the optimized formulation

%RH	Time (h)	Disintegration time (s) (±S.D.)[a]	Hardness (kg) (±S.D.)[b]	Weight (mg) (±S.D.)[b]
75	0	26.0 (7.4)	1.40 (0.34)	236.5 (5.3)
	2	27.5 (6.8)	1.33 (0.38)	237.9 (1.2)
	4	25.2 (3.1)	1.33 (0.29)	233.1 (9.9)
	6	25.7 (5.7)	1.25 (0.25)	235.4 (2.2)
	8	26.7 (3.2)	1.33 (0.29)	232.1 (8.2)
	24	35.2 (13.7)*	1.25 (0.25)	236.8 (8.0)
85	0	26.0 (7.4)	1.40 (0.34)	236.5 (5.3)
	2	28.2 (5.3)	1.42 (0.14)	235.5 (7.9)
	4	31.9 (9.1)	1.50 (0.25)	236.6 (0.6)
	6	29.9 (3.6)*	1.50 (0.25)	237.3 (0.8)
	8	33.2 (5.1)*	1.58 (0.14)*	236.8 (6.2)
	24	36.1 (5.5)*	1.58 (0.14)*	239.5 (2.8)
95	0	26.0 (7.4)	1.40 (0.34)	236.5 (5.3)
	2	47.9 (10.3)*	1.25 (0.0)	237.4 (1.3)
	4	44.5 (7.5)*	1.42 (0.14)	228.4 (4.1)
	6	52.6 (13.6)*	1.67 (0.14)*	235.3 (5.4)
	8	55.7 (4.5)*	1.67 (0.14)*	241.0 (2.0)
	24	58.4 (6.9)*	1.67 (0.14)*	233.8 (1.7)

Significantly different at 95% confidence interval (*T*-test).
[a] Mean of 6 replications.
[b] Mean of 10 replications.

ment. Decreased disintegration efficiency of the disintegrating agent could be a possible reason in this situation too. Moisture treatment at 85% relative humidity, however, significantly increased hardness of the tablets to 1.58 kg after 8 h of moisture treatment. This was quiet interesting and can be attributed to recrystallization of mannitol particles. Mannitol has a critical relative humidity of 80%. When relative humidity is higher than the critical relative humidity, mannitol can absorb the moisture from the environment and can form a liquid layer on the particle surfaces because of its dissolution. Liquid bridges between adjacent particles can be formed when the adjacent liquid layers merge together. After drying, solid bonds can be formed between these particles because of formation of solid bridges. These formed bonds can increase the hardness of the tablets as compared to tablet hardness before moisture treatment. Fu et al. (2006) observed similar kind of results in their study.

Moisture treatment at 95% relative humidity showed similar kinds of results. Tablet hardness increased to 1.67 kg; it negatively affected disintegration time too. At 95% relative humidity, mannitol and spray dried lactose both could have formed solid bonds because of absorption of the moisture. This could lead to more increase in the hardness. The order of increase in the disintegration time was found to be 95% > 85% > 75%.

4. Conclusion

The application of full factorial design was useful in evaluating influence of calcium silicate concentration and lubricant (magnesium stearate) concentration on an optimized fast disintegrating formulation of granisetron hydrochloride. Presence of lubricant was critical for the preparation of fast disintegrating tablets. Concentration of the lubricant had an influence on disintegration time and hardness of the optimized fast disintegrating tablet formulation, however calcium silicate concentration had no influence on the disintegration time and tablet hardness. From the statistical design, 1.5% magnesium stearate concentration was selected as an optimum concentration as it gave optimum hardness value with low disintegration time. Moisture treatment increased hardness of the fast disintegrating tablets; however it delayed the tablets' disintegration.

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