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Research Article

A Novel Approach to Optimize and Formulate Fast Disintegrating Tablets for Nausea and Vomiting

Honey Goel,[1] Nishant Vora,[1] and Vikas Rana[1,2]

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Abstract. The aim of this study was to optimize and formulate fast disintegrating tablets (FDTs) for nausea and vomiting using aminoacetic acid, carmellose and sodium alginate with enough mechanical strength. Ondansetron HCl (water soluble) or domperidone (water insoluble) drug were added to FDTs and their disintegration behaviour was evaluated. Plackett Burman Screening Design was used to screen the independent active process variables [concentration of aminoacetic acid (X_1), concentration of carmellose (X_2) and tablet crushing strength (X_3)] which were found to actively influence the dependent variables [disintegration time in the mouth (DT), wetting time (WT), and water absorption ratio (WAR)] for both the drugs. Also, the coefficients of active variables (DT, WT and WAR) of FDTs containing domperidone was found to be significantly different ($P<0.05$) from the coefficients of active factors (X_1, X_2 and X_3) containing ondansetron HCl FDTs. Further, FDTs containing domperidone was prepared according to central composite design for estimating the effect of active factors (X_1, X_2, X_3) in extended spherical domain. The regression analysis of quadratic fit revealed that DT, WT and WAR were 98% correlated with active factors (X_1, X_2 or X_3). The optimized domperidone FDTs were further compared with superdisintegrants (croscarmellose sodium or crospovidone). The data revealed that optimized domperidone FDTs were better than domperidone FDTs containing croscarmellose or crospovidone. Hence, this novel excipients combination can be used for delivery of water insoluble drugs in place of superdisintegrants.

KEY WORDS: aminoacetic acid; carmellose; fast disintegrating tablets; ondansetron HCl and domperidone.

INTRODUCTION

The geriatrics constitutes a major portion of today's population because of increased life expectancy. Various physiological and neurological conditions like dysphagia, motion sickness and hand tremors lead to non compliance of conventional oral dosage forms. Due to swallowing dysfunction, half of the patients do not take medicines as prescribed. The ease of medication and administration of drug at therapeutic dose has become more important for elderly. Pediatrics also may suffer from ingestion disorders due to underdeveloped muscular and nervous system (1–4).

Fast disintegrating dosage forms are the drug delivery systems that disintegrate in the patient's oral cavity within less than a minute without the intake of water (5). Thus, these tablets are easily swallowed and have high patient compliance. Researchers these days are looking for a new, safe and effective disintegrating agents which can disintegrate tablets rapidly even at a tablet crushing strength of greater than 3.5 kg. The water insoluble diluents such as Avicel (PH 102) and dicalcium phosphate were highly preferable excipients for FDTs. But now-a-days these agents are omitted from the studies as they are expected to cause an unacceptable feeling of grittiness in the mouth. Therefore, water soluble diluents such as spray dried lactose and biodegradable polymers (like sodium alginate and carmellose) were selected as model excipients considering its advantage in terms of easy availability, cost effectiveness and relative moisture insensitivity.

Fukami *et al.* (6) observed that the behaviour of disintegration time in the oral cavity (DT) as well as wetting time (WT) were analysed by surface free energy. For a faster wetting, a molecule should have high polar component of surface free energy. However, for faster disintegration dispersion component should have larger value. Therefore, a combination of sodium alginate (which possess good binding as well as swelling properties) with aminoacetic acid and carmellose (CM) which exhibits greater polar component of surface free energy were explored as superdisintegrants.

Ondansetron HCl [($C_{18}H_{19}N_3O.HCl.2H_2O$), MW-365.86] is a potent selective serotonin 5HT-3 receptor antagonist which has a role in prophylaxis of postoperative chemotherapy/radiotherapy induced emesis. The adult dose is 8 mg and its metabolites are excreted in urine with about 10% of unchanged drug and having 67% of bioavailability through oral route (7). Domperidone ($C_{22}H_{24}ClN_5O_2$, MW-425.91) is a potent antidopaminergic drug used orally and intravenously for suppressing nausea and vomiting. At an adult dose of

[1] Pharmaceutics Division, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India 147002.
[2] To whom correspondence should be addressed. (e-mail: vikas_pbi@rediffmail.com)

10 mg, domperidone has a modest activity without extrapyramidal side effects as it crosses blood brain barrier poorly. Domperidone is absorbed orally and its metabolites are completely biotransformed and excreted in urine. Ondansetron HCl is soluble in water (1 g in 3 ml) (8) whereas domperidone is insoluble in water. Therefore, ondansetron HCl and domperidone with different solubility profiles were selected for formulating FDTs containing aminoacetic acid, carmellose and sodium alginate. Thus, FDTs of these drugs will be helpful in rapid drug delivery, even without the intake of water, thereby alleviating nausea and vomiting sensation at an early stage.

The investigation was aimed at formulating FDTs containing antiemetic agents with different solubilities by using sodium alginate lactose granules (SLG)-carmellose (CM)-aminoacetic acid mixture that were capable of resembling DT of FDTs equivalent to those containing croscarmellose sodium or crospovidone.

MATERIAL AND METHODS

Materials

The gift samples of CrospovidoneUSP30NF25 and Croscarmellose sodium USP30NF25 (Standard grade, Panacea Biotech Ltd., Lalru, India), Carmellose (CM), domperidone (Nayan Pharmaceuticals Ltd., Patiala, India) and ondansetron HCl (Ind-Swift Labs, Chandigarh, India) were kindly received. Sodium alginate (Loba Chem., Mumbai, India), Aminoacetic acid (Qualigens Fine Chemicals, Mumbai, India) and spray dried lactose (CDH, Mumbai, India) were used as supplied. All other reagents were of analytical grade.

Methods

Formulation Design and Preparation of Ondansetron HCl or Domperidone Fast Disintegrating Tablets

Table I shows the independent and dependent variables used to optimize FDTs of ondansetron HCl or domperidone. Plackett Burman screening design was used to formulate FDTs (Table II) for screening the effect of selected process and formulation variables on dependent variables. Additional FDTs (Table III) were prepared according to central composite design (CCD) using active factors [concentration of aminoacetic acid (X_1), concentration of CM (X_2) and tablet crushing strength (X_3)] that were found to significantly influence the dependent variables during initial screening studies. The DT of FDTs that were prepared using starch-lactose granules, ondansetron HCl or domperidone and croscarmellose sodium or crospovidone was compared with that obtained with CM-Aminoacetic acid-SLG mixture. Multiple linear regression between active variables obtained from CCD and dependent variables was performed and analyzed using Statistica 7.0 (Stat Soft Inc., Tulsa, USA).

All the ondansetron HCl or domperidone FDTs were prepared by the following method:

Preparation of Sodium Alginate-Lactose Granules (SLG). Sodium alginate-lactose granules were prepared by using 2.5% *w/v* sodium alginate solution in distilled water as binder. The wet mass was prepared with 30 g of spray dried lactose using 7 ml of binder solution and passed through 44 mesh sieve. The granules which are retained on 60 mesh sieve were dried at 50 °C for 4 h in a drier (151, Narayan Scientific Works, New Delhi, India). These granules were added to raise the tablet weight to 100 mg.

Preparation of Starch–Lactose Granules. Starch-lactose granules were prepared by using starch paste in distilled water as binder. The starch paste was prepared by swelling 5% *w/v* starch in hot distilled water. The wet mass was prepared with 30 g of spray dried lactose using 9 ml of starch paste and passed through 44 mesh sieve. The granules obtained were dried at 50 °C for 4 h in a drier (151, Narayan Scientific Works, New Delhi, India).

Preparation of Ondansetron HCl or Domperidone Fast Disintegrating Tablets. Granules of sodium alginate-lactose screened with 44/60 mesh sieves were mixed with aminoacetic acid (40%–60% *w/w*), CM (5%–10% *w/w*) and ondansetron HCl (8 mg per tablet) or domperidone (10 mg per tablet) using a V-shaped blender for 5 minutes and were compressed into tablets with a multipunch single station tabletting machine (Cadmach, Ahmedabad, India) at a speed of 10 rpm. The weight and diameter of flat faced tablet was

Table I. The Dependent and Independent Variables Used in Plackett–Burman Screening Design of Eight Experiments and 3^3 Central Composite Design

		Levels				Ondansetron HCl		Domperidone		
Code	Independent variables	Low (−1)	Middle (0)	High (+1)	Dependent variables	Low	High	Low	High	Objective
X_1	Conc. of aminoacetic acid (%*w/w*)	40	50	60						
X_2	Conc. of CM (%*w/w*)	5	7.5	10						
X_3	Tablet crushing strength (kg)	2.0	3.0	4.0						
X_4	Conc. of sodium alginate (%*w/v*)	1	1.5	2.0						
Y_1					DT (seconds)[a]	10±1	46±2	8±1	28±2	Minimum
Y_2					WT(seconds)[b]	12±1	49±1	4±1	26±1	Minimum
Y_3					WAR[b]	1.65±0.01	2.7±0.08	1.54±0.04	3.85±0.03	Maximum

[a] Values are mean±SD, n=12
[b] Values are mean±SD, n=6

Table II. Plackett Burman Screening Design of 8 Experiments for Identifying Active Formulation and Process Variables Influencing Dependent Variables

Exp.no.	X_1 (%w/w)	X_2 (%w/w)	X_3 (kg)	X_4 (%w/v)	X_5	X_6	X_7	Y_1[a] (s)	Y_2[b] (s)	Y_3[b]	Y_4[a] (s)	Y_5[b] (s)	Y_6[b]
1	+1	+1	+1	−1	+1	−1	−1	18±1	12±1	3.42±0.03	27±1	30±1	2.1±0.01
2	−1	+1	+1	+1	−1	+1	−1	24±1	19±1	1.75±0.01	38±1	42±1	2.05±0.01
3	−1	−1	+1	+1	+1	−1	+1	28±2	26±1	1.54±0.04	46±2	49±1	1.65±0.01
4	+1	−1	−1	+1	+1	+1	−1	13±1	8±1	2.95±0.02	18±1	20±1	2.25±0.04
5	−1	+1	−1	−1	+1	+1	+1	17±1	14±1	2.8±0.03	22±1	25±1	2.35±0.05
6	+1	−1	+1	−1	−1	+1	+1	20±1	16±1	2.69±0.02	30±1	34±1	1.9±0.06
7	+1	+1	−1	−1	−1	−1	+1	8±1	4±1	3.85±0.03	10±1	12±1	2.7±0.08
8	−1	−1	−1	+1	−1	−1	−1	26±1	20±1	1.95±0.02	36±1	39±1	1.85±0.06

X_1 Concentration of aminoacetic acid, X_2 concentration of CM, X_3 tablet crushing strength, X_4 concentration of sodium alginate, X_{567} dummy variables, (Y_1=DT; Y_2=WT; Y_3=WAR) of FDTs containing domperidone; (Y_4=DT; Y_5=WT; Y_6=WAR) of FDTs containing ondansetron HCl
[a] Values are mean±SD, n=12
[b] Data represent mean±SD, n=6

100±5 mg and 6±0.5 mm, respectively. The batch size was fixed to 300 tablets per batch.

Evaluation of Fast Disintegrating Tablets:

Disintegration Time in the Oral Cavity (DT). The healthy volunteers of either sex (age 18–25) were selected, trained and then DT of each tablet for complete disintegration in the mouth was measured. The time when the tablet placed on the tongue disintegrated without leaving any lumps was taken as end point. After disintegration of tablet in the oral cavity the tablet contents were spit out and the oral cavity was rinsed with water. DT of six tablets per batch (three tablets per trained volunteer or total of two volunteers per batch) was recorded and the average was reported.

Tablet Crushing Strength. Tablet crushing strength was measured using a Monsanto hardness tester and the data reported is the mean of six individual determinations.

WT and WAR. Five circular tissue paper of 10 cm diameter were placed in a Petri dish containing an eosin dye solution in water (10 ml of 0.05% *w/v*) was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for the dye solution to appear on the upper surface of tablet was noted as wetting time.

The water absorption ratio was estimated gravimetrically at 25 °C. A FDT was carefully placed on surface of five circular tissue paper wet with 6 ml of distilled water. The water absorption ratio was calculated using following equation (9):

$$WAR = (W_b - W_a)/W_a \quad (1)$$

Where W_a and W_b are the weights before and after water absorption, respectively.

Weight Variation. A weight variation test was performed according to USP30 NF25 on 20 tablets by taking samples from a batch after production of every 100 tablets and randomly from a total batch of 300 tablets (10).

Table III. 3^3 Central Composite Design Using Active Formulation and Process Variables Influencing DT, WT and WAR of FDTs Containing Domperidone

Exp no.	X_1 (%w/w)	X_2 (%w/w)	X_3 (kg)	Y_1[a] (seconds)	Y_2[b] (seconds)	Y_3[b]
1	−1	−1	−1	26±2	20±1	1.95±0.02
2	1	−1	−1	13±1	8±1	2.95±0.02
3	−1	1	−1	17±1	14±1	2.8±0.03
4	1	1	−1	8±1	4±1	3.85±0.03
5	−1	−1	1	28±2	26±1	1.54±0.04
6	1	-1	1	20±3	16±1	2.69±0.02
7	−1	1	1	24±1	19±1	1.75±0.01
8	1	1	1	18±1	12±1	3.42±0.03
9	−1.682	0	0	26±2	24±3	1.75±0.02
10	1.682	0	0	16±2	9±1	3.45±0.04
11	0	−1.682	0	28±2	23±2	2.27±0.02
12	0	1.682	0	15±2	10±2	2.95±0.02
13	0	0	−1.682	12±2	9±2	2.85±0.04
14	0	0	1.682	24±3	20±3	1.75±0.01
15	0	0	0	19±3	15±2	2.5±0.02
16	0	0	0	19±2	15±3	2.5±0.04
17	0	0	0	20±1	16±2	2.5±0.03
18	0	0	0	20±2	16±1	2.5±0.02

X_1 Concentration of aminoacetic acid, X_2 concentration of CM, X_3 tablet crushing strength; (Y_1=DT; Y_2=WT; Y_3=WAR) of domperidone FDTs
[a] Results are mean±SD, n=12
[b] Values are mean±SD, n=6

Friability. Twenty tablets were randomly selected and friability was measured using a Roche friabilator rotated at 25 rpm for 4 min as per USP30 NF25 (10).

Content Uniformity. Ondansetron HCl as well as domperidone contents were estimated in all the FDTs batches as per the method discussed in USP30 NF25 (10).

In Vitro Release Studies. Domperidone release from different FDTs was evaluated by using the USP30 NF25 pharmacopoeia dissolution apparatus II—paddle (Tab-Machines, Mumbai, India) at 37±0.5 °C using 500 ml of simulated saliva pH 6.8 as a dissolution medium with stirring speed of 50 rpm. Aliquots (5 ml) withdrawn at various time intervals were immediately filtered through Whatmann filter paper, diluted suitably and analyzed for domperidone spectroflourimetrically (SL-174, Elico® spectroflourimeter, India) at 284 nm for excitation and 329 nm for emission. The fluorescence values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2=0.9997). The *in vitro* dissolution test was performed in triplicate for each batch.

Similarity and Dissimilarity Factors. A model independent approach was used to estimate dissimilarity factor (f_1) and a similarity factor (f_2) to compare dissolution profile of optimized calculated FDTs with FDTs containing superdisintegrants (11).

The FDA and SUPAC-IR guidelines defines difference factor (f_1) as the calculated percent (%) difference between the reference and test curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \left\{ \left[\sum_{t=1}^{n} (R_t - T_t) \right] \Big/ \left[\sum_{t=1}^{n} R_t \right] \right\} X100 \qquad (2)$$

The similarity factor (f_2) is given by the following equation:

$$f_2 = 50X \log \left\{ \left[1 + 1/n \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} X100 \right\} \qquad (3)$$

Where n is the number of pull points, R_t is the reference batch profile at time point t and T_t is the test batch profile at the same time t. For an *in vitro* dissolution curves to be considered similar f_1 values should be in the range of 0–15 while values of f_2 should lie within 50–100.

RESULTS AND DISCUSSION

Screening of Active Process and Formulation Variables

Plackett–Burman design was employed to formulate FDTs for screening the process and formulation variables that produced a significant (at 95% level of confidence) effect on DT, WT or WAR (12). Table II shows the results obtained with significant test analysis revealed that all these dependent variables were significantly influenced by concentration of aminoacetic acid (X_1), concentration of CM (X_2) and tablet crushing strength (X_3) for FDTs prepared either using ondansetron HCl or using domperidone (Table II). This indicates that the influence of active process and formulation variables on all the dependent variables of both the drugs remained unaltered even though the selected drugs have different solubilities. The coefficients ($b_{1...}b_7$) associated with the effect of various formulation and process variables on DT, WT and WAR of both ondansetron HCl FDTs or domperidone FDTs are shown in Fig. 1. The bars below *x*-axis in Fig. 1 indicates negative effect and bars above x-axis showed

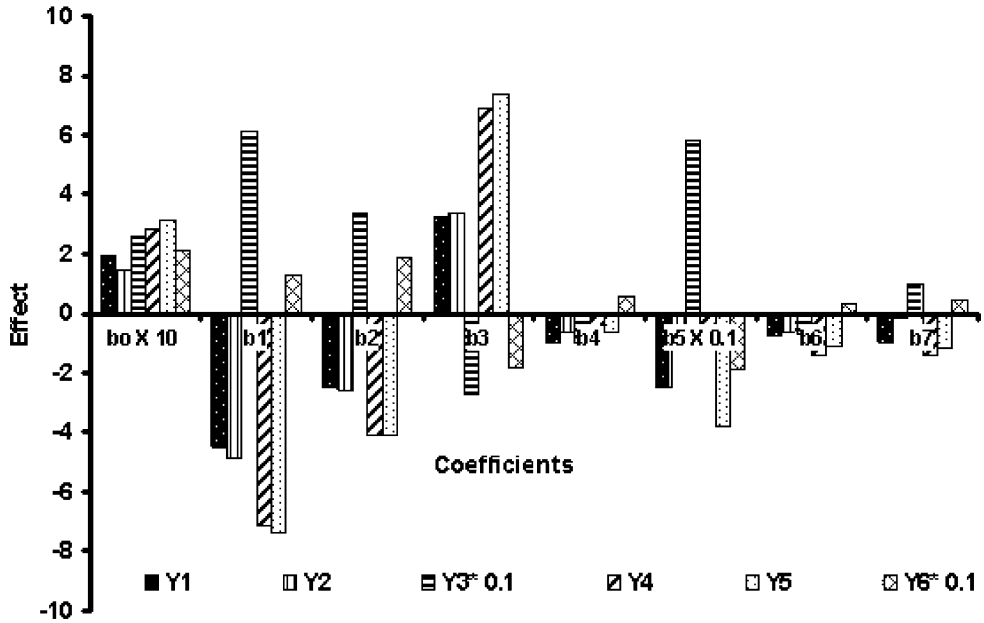

Fig. 1. The coefficients associated with effect of various formulation and process variables on DT, WT, WAR of domperidone and ondansetron HCl

Table IV. Quadratic Model and the Coefficients of Domperidone FDTs for DT in Oral Cavity, WT and WAR

$R^2 \rightarrow$ Regression coefficients	DT (s) Y_1				WT (s) Y_2				WAR Y_3			
	98%				98%				98%			
Term	CF	SE	SE X t_{table}=C[a]	Sig	CF	SE	SE X t_{table}=C	Sig	CF	SE	SE X t_{table}=C[a]	Sig
Constant	19.55	0.80	1.68	S	15.55	0.58	1.2	S	2.49	0.073	0.155	S
X_1	−3.86	0.44	0.92	S	−4.70	0.32	0.67	S	0.566	0.04	0.083	S
X_2	−3.06	0.44	0.92	S	−3.13	0.32	0.67	S	0.289	0.04	0.083	S
X_3	3.38	0.44	0.92	S	3.33	0.32	0.67	S	−0.293	0.04	0.083	S
X_1X_2	0.75	0.57	1.2	NS	0.625	0.42	0.88	NS	−0.017	0.052	0.11	NS
X_1X_3	1.0	0.57	1.2	NS	0.625	0.42	0.88	NS	0.096	0.052	0.11	NS
X_2X_3	1.0	0.57	1.2	NS	−0.125	0.42	0.88	NS	−0.101	0.052	0.11	NS
X_1^2	0.32	0.46	0.96	NS	0.140	0.33	0.70	NS	0.0611	0.041	0.086	NS
X_2^2	0.50	0.46	0.96	NS	0.140	0.33	0.70	NS	0.0647	0.041	0.086	NS
X_3^2	−0.75	0.46	0.96	NS	−0.57	0.33	0.70	NS	−0.0459	0.041	0.086	NS
X_1 X_2 X_3	−0.25	0.57	1.20	NS	0.125	0.42	0.88	NS	0.0587	0.051	0.11	NS

S Significant difference (if CF>C), *NS* no significant difference (if CF<C), *CF* coefficients, *SE* standard error, Sig-significance
[a] The t_{table} value for 18 degree of freedom and 95% level of confidence is 2.1

positive influence of coefficients. The negative effect of coefficients signifies an antagonistic effect while a positive effect of a coefficient signifies a synergistic effect. Therefore, the coefficients generated after multiple linear regression revealed that increasing the concentration of aminoacetic acid had antagonistic effect and retarded DT and WT of FDTs prepared either using ondansetron HCl or using domperidone. This seems to be due to excellent wetting nature of aminoacetic acid (6). However, when the concentration of aminoacetic acid was decreased, the WAR decreases. Also, when the concentration of CM was increased, the DT, WT and WAR were increased. This probably is due to the disintegration of tablets containing CM was mainly affected by the wicking nature of CM. Therefore, the increase in concentration of CM increased the wicking property and hence decreased DT as well as WT and WAR. Further, the process variable, tablet crushing strength (X_3) had an opposite influence on dependent variables as compared to aminoacetic acid and CM. The increase in tablet crushing strength, increases DT in the oral cavity as well as WT and decreases WAR. This suggests an overwhelming role of aminoacetic acid and tablet crushing strength in decreasing DT, WT and increasing WAR. Moreover, the coefficients of active variables of DT, WT and WAR of FDTs containing ondansetron HCl are significantly different (at 95% level of confidence) from the coefficients of active variables of DT, WT and WAR of FDTs containing domperidone. Further, the results also indicated that there is higher DT as well as WT and lower WAR of FDTs prepared using ondansetron HCl as compared to FDTs prepared using domperidone (Table II). Moreover, ondansetron HCl had an agonistic effect on DT, WT and an antagonistic effect on WAR. This probably may be due to higher solubility of ondansetron HCl. Adding, a water soluble drug such as ondansetron HCl into aminoacetic acid, CM and sodium alginate FDTs, during disintegration, the water penetrated and dissolved ondansetron HCl. Therefore, the penetrated water was obstructed as the space was clogged with the dissolved ondansetron HCl, resulted in delay of the DT. On the other hand, in case of poorly water soluble drug such as domperidone, the penetration inhibitory effect would not occur and rapid disintegrating property was maintained. Therefore, these results suggests that the fast disintegrating systems containing carmellose, aminoacetic acid and sodium alginate is best suited for poorly water soluble drug such as domperidone rather than water soluble drug like ondansetron HCl. Hence, additional FDTs were formulated using domperidone.

Central Composite Design (CCD)

For estimating the extended effect of active process and formulation variables (X_1, X_2 and X_3) on dependent variables (Y_1, Y_2, and Y_3) in a spherical domain, additional domperidone FDTs were prepared using extrapolated levels of active process and formulation variables (Table III). It is important to note that the concentration of sodium alginate (X_4) was not found to be an active factor. This may probably be due to higher effect of CM and aminoacetic acid on dependent variables as compared to sodium alginate. However, sodium alginate was found to increase hardness and decrease DT as

Table V. Reduced Model Equations for Domperidone FDTs

Treatment	Equations correlating dependent variables with active factors		
	DT in oral cavity (Y_1)	WT (Y_2)	WAR (Y_3)
X_1 *vs* X_2	$Y_1 = 19.55 - 3.86X_1 - 3.06X_2$	$Y_2 = 15.55 - 4.70X_1 - 3.13X_2$	$Y_3 = 2.49 + 0.566X_1 + 0.28X_2$
X_1 *vs* X_3	$Y_1 = 19.55 - 3.86X_1 + 3.38X_3$	$Y_2 = 15.55 - 4.70X_1 + 3.33X_3$	$Y_3 = 2.49 + 0.566X_1 - 0.29X_3$
X_2 *vs* X_3	$Y_1 = 19.55 - 3.06X_2 + 3.38X_3$	$Y_2 = 15.55 - 3.13X_2 + 3.33X_3$	$Y_3 = 2.49 + 0.280X_2 - 0.29X_3$

Table VI. Formulation of Domperidone FDTs Containing Superdisintegrants

	Formulation no.							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Spray dried lactose granules[a] (mg/tablet)	76.5	74	71.5	69	76.5	74	71.5	69
Crospovidone (mg/tablet)	2.5	5	7.5	10	–	–	–	–
Croscarmellose sodium (mg/tablet)	–	–	–	–	2.5	5	7.5	10
Domperidone (mg/tablet)	10	10	10	10	10	10	10	10
Colloidal silica (mg/tablet)	1	1	1	1	1	1	1	1
Total weight (mg/tablet)	100	100	100	100	100	100	100	100
Tablet crushing strength (kg)	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
DT (s)[b]	46±5	30±2	29±1	28±1	43±4	27±2	26±2	26±2

[a] Spray dried lactose granules prepared with starch (5% w/v) as binder.
[b] Values given are mean±SD, n=12

compared to starch. This seems to be due to better binding and swelling characteristics of sodium alginate as compared to starch. Moreover, in a pH of saliva (6.8), the sodium alginate is ionized (ionization of carboxyl groups of sodium alginate) to a considerable extent. This repulsion between negative charges in sodium alginate could synergise the swelling activity of sodium alginate. Therefore, SLG was also added to FDTs prepared as per CCD.

A statistical model incorporating interactive and polynomial terms were used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X2_2^2 + b_{33}X_3^2 + b_{123}X_1X_2X_3 \quad (4)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 18 runs, and b_i is the estimated coefficient for the factor X_i. Further, the values of the coefficients relates to the effects on DT, WT and WAR. Table IV summarizes the coefficients associated with factors X_i. The main effects (X_1, X_2 and X_3) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2, X_1X_3, X_2X_3 and $X_1X_2X_3$) show how the response changes when two or three factors were simultaneously changed. The two degree quadratic terms (X_1^2 , X_2^2 and X_3^2) are included to investigate non linearity. Also, a negative sign signifies antagonistic effect while positive sign indicates a synergistic effect.

The regression statistics of quadratic model revealed that DT, WAR and WT were 98% correlated with active factors X_1, X_2 and X_3. However, the interaction terms and second order quadratic terms had no significant influence on DT, WT and WAR. Therefore, a reduced model was generated omitting interactions and quadratic terms. The reduced equations generated from correlation between dependent variables (DT, WT and WAR) with coefficients of significantly different (P<0.05) active variables of CCD (Table V).

Optimization of FDTs

Croscarmellose sodium and Crospovidone are the well known superdisintegrants used in FDTs. They have excellent disintegrating ability. Croscarmellose sodium swells to a large extent when they come in contact with water to disintegrate tablets. Also, it has a fibrous nature that allows intraparticulate as well as extraparticulate wicking of water even at low concentration levels (13). Crospovidone has excellent wicking nature though it swells only to a small extent. Table VI shows formulations of domperidone FDTs containing crospovidone (F_1–F_4) and croscarmellose sodium (F_5–F_8). The disintegration of FDTs containing croscarmellose sodium or crospovidone in oral cavity revealed that these tablets disintegrated with in 30 s at a hardness of less than 3.0 kg.

Table VII. Optimized Compositions of Domperidone FDTs Capable of Resembling FDTs Containing Croscarmellose Sodium or Crospovidone

Tablets containing s super-disintegrants	Solved values and optimized tablet composition						
			Optimized variables				
Formulation number	DT (seconds) (Y_1)[a] B	Formulation number	X_1 (%w/w)	X_2 (%w/w)	X_3 (kg)	DT (seconds) of optimized tablets containing aminoacetic acid-CM-SLG mixture[a] C	Statistical difference between B and C
F2	30±2	A_1	36.4	3.2	4.5	28±2	NS
F3	29±1	A_2	37.7	3.6	4.3	27±2	NS
F4	28±1	A_3	39.0	4.1	4.2	26±2	NS
F6	27±2	A_4	40.3	4.57	4.1	25±1	NS
F7	26±2	A_5	42.0	4.9	3.9	24±2	NS
F8	26±2	A_6	42.0	4.9	3.9	23±1	NS

NS No significant difference
[a] Values are mean±SD, n=12

Table VIII. Comparison of Optimized Domperidone FDTs (A_1–A_4) with FDTs Containing Crospovidone (F_2–F_4) or Croscarmellose Sodium (F_6–F_8)

Tablet properties	Batch no.										Significant
	F_2	A_1	F_3	A_2	F_4	A_3	F_6	A_4	F_7	A_5	F_8	A_6	*t*-test *F vs A*
Weight variation[a] (%)	1.36±0.4	1.43±0.3	2.34±0.2	2.33±0.6	2.60±0.3	2.38±0.2	2.93±0.4	2.98±0.03	2.04±0.02	2.03±0.07	2.83±0.02	2.8±0.3	NS
Content[a] Uniformity (%)	99.7±0.1	99.9±0.2	99.9±0.1	99.9±0.2	99.8±0.6	99.5±0.6	98.9±0.4	99.6±0.8	99.3±0.3	49.6±0.2	99.3±0.3	99.6±0.1	NS
% Friability[a]	1.34±0.02	0.25±0.02	1.24±0.03	0.17±0.01	1.17±0.01	0.2±0.01	0.9±0.01	0.123±0.01	1.32±0.01	1.01±0.03	1.03±0.03	0.11±0.02	S
Average weight (mg) of 20 tablets[a]	99±1.25	99±0.23	99.3±1.5	98.9±1.6	98.9±1.4	99.3±1.5	98.8±1.4	99.7±1.6	99.2±1.4	99.3±0.01	98.6±0.07	99.3±1.6	NS
Batch size (tablets)	300	300	300	300	300	300	300	300	300	300	300	300	

NS No significant difference, S- significant difference ($P<0.05$)
[a] All values are given as mean±SD, $n=3$

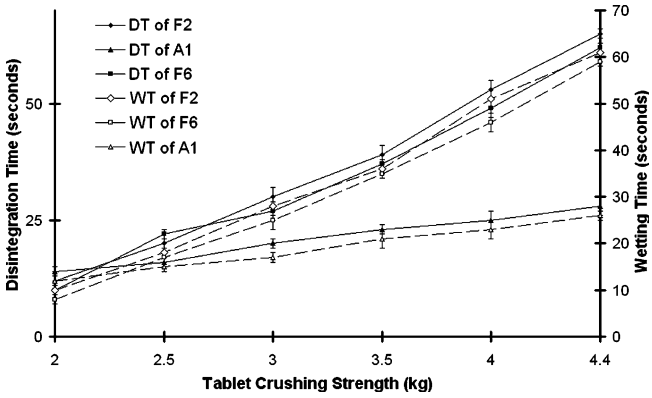

Fig. 2. Relationship between DT and WT with tablet crushing strength of optimized FDTs (A_1) and FDTs containing crospovidone (F_2) and croscarmellose sodium (F_6)

However, if the tablet crushing strength of these tablets rose to more than 3.0 kg, the DT in oral cavity exceeds to more than 60 s. Hence, tablet crushing strength of FDTs prepared using croscarmellose sodium or crospovidone was fixed to 3.0 kg. On this basis FDTs of domperidone were prepared using various concentration of croscarmellose sodium or crospovidone (Table VI). The DT of FDTs containing crospovidone (F_1–F_4) or croscarmellose sodium (F_5–F_8) decreases up to 5% *w*/*v* concentration of both superdisintegrants (Table VI). However, when the concentration of croscarmellose sodium or crospovidone is more than 5% *w*/*v* in domperidone FDTs, no significant difference of DT was obtained (F_2–F_4, F_6–F_8, and Table VI). Therefore, formulation F_2–F_4 and F_6–F_8 were taken for further optimization studies.

The disintegration time is an important characteristic of FDTs. Therefore, DT in oral cavity (Y_1) was selected as dependent variable against which optimized FDTs were fabricated. The reduced model equation generated from correlation between Y_1 and three active variables of CCD (Table IV) were solved for calculating optimum values of X_1(concentration of aminoacetic acid), X_2 (concentration of CM) and X_3 (tablet crushing strength). For this purpose addition or subtraction method was used for obtaining the optimized values of X_1, X_2 and X_3 in terms of Y_1 and constant terms in the equation. The DT in oral cavity of FDTs obtained from various formulations (F_2–F_4, F_6–F_8 Table VII) was then substituted in place of Y_1 to get respective optimized values of X_1, X_2 and X_3. These

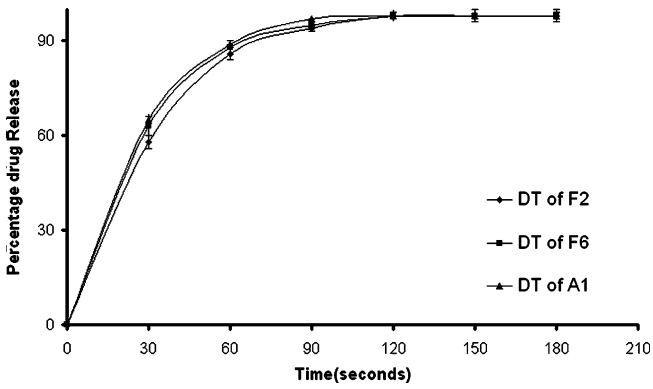

Fig. 3. *In-vitro* dissolution profiles of batches F_2, F_6, A_1

optimized values were used for preparing FDTs containing aminoacetic acid-CM-SLG mixture with domperidone that shall exhibit DT comparable to the DT of FDTs prepared using crospovidone or croscarmellose sodium (Table VII).

It is evident from Table VII that fast disintegrating domperidone tablets prepared by using the optimized values of active variables (A_1–A_6, Table VII) were capable of resembling DT comparable to FDTs containing crospovidone or croscarmellose sodium (F_2–F_4, F_6–F_8, Table VII).

Evaluation of Optimized FDTs

A comparison of optimized FDTs (A) with FDTs containing croscarmellose sodium or crospovidone (F) revealed that the percentage friability of optimized FDTs were statistically different (at 95% level of confidence) to those with FDTs containing croscarmellose sodium or Crospovidone (Table VIII). However, no statistical difference (at 95% level of confidence) was obtained with weight variation, content uniformity and average weight of 20 tablets. This is probably due to good flowability of SLG-CM-aminoacetic acid-domperidone mixture. Interestingly, the optimized FDTs were compressed at higher tablet crushing strength level as compared to FDTs containing croscarmellose sodium or crospovidone to give DT in the oral cavity. Therefore, the best batch A_1 of optimized FDTs was selected for further evaluation as it is compressed at highest crushing strength of 4.5 kg.

Figure 2 shows the effect of crushing strength on DT in oral cavity and on WT of FDTs prepared using crospovidone (F_2), croscarmellose sodium (F_6) and optimized FDTs (A_1). A comparison of the FDT batches revealed that a nonlinear relationship was obtained between DT in the oral cavity and tablet crushing strength or WT and tablet crushing strength of F_2 and F_6 FDT batches. However, a linear effect was seen in case of DT/WT with tablet crushing strength of A_1 FDTs batch. Further, both DT in oral cavity and WT follows the order $F_2 > F_6 > A_1$ at more than 3.0 kg crushing strength. This indicates that A_1 batch showed most quick wetting as well as disintegration in the oral cavity as compared to F_2 and F_6 batches even if the tablet crushing strength rises to more than 3.0 kg. The % drug release of the F_2, F_6 and A_1 FDT batches was conducted in simulated saliva (pH 6.8). Figure 3 depicts the dissolution profiles of F_2, F_6 and A_1 FDTs batches. The dissolution profiles of all the three FDT batches revealed that 90% of domperidone was released within 60 s. Further, the comparison of dissolution data of F_2 and F_6 batches with A_1 batch was conducted using f_1 and f_2 statistics. An f_1 of 2.443 for F_2 *vs* A_1 or 1.296 for F_6 *vs* A_1 and f_2 of 72.9 for F_2 *vs* A_1 or 83.68 for F_6 *vs* A_1 indicates that the release profile of F_2, F_6 and A_1 batches in simulated saliva were comparable and in good agreement with each other. Therefore, in the light of the above evaluation results, it can be hypothesized that the optimized FDTs prepared using SLG-CM-aminoacetic acid combination were found to be better than FDTs containing croscarmellose sodium or crospovidone with respect to tablet crushing strength, DT and friability.

CONCLUSION

The present investigation revealed overwhelming influence of concentration of aminoacetic acid, concentration of CM and tablet crushing strength in decreasing DT, WT and WAR. Hence, this novel excipient mixture consisting of aminoacetic acid, CM and sodium alginate could be applicable to orally administer water insoluble drugs like domperidone in a condition like nausea and vomiting.

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REFERENCES

1. R. K. Chang, X. Guo, B. A. Burnside, and R. A. Couch. Fast dissolving tablets. *Pharm. Technol.* **24**:52–59 (2000).
2. L. Mallet. Caring for the elderly patient. *J. Am. Pharm. Assoc.* **36**:628 (1996).
3. H. Seager. Drug delivery products and the Zydis fast dissolving dosage. *J. Pharm. Pharmacol.* **50**:375–382 (1998).
4. S. R. Parakh, and A. V. Gothoskar. A review of mouth dissolving technologies. *Pharm. Technol.* **27**:92–100 (2003).
5. S. Schiemeir, and P. C. Schmidt. Fast dispersible ibuprofen tablets. *Eur. J. Pharm. Sci.* **15**:295–305 (2002).
6. J. Fukami, A. Ozawa, Y. Yoshihashi, E. Yonemochi, and K. Terada. Development of fast disintegrating compressed tablets using amino acid as disintegration accelerator: Evaluation of wetting and disintegration of tablet on the basis of surface free energy. *Chem. Pharm. Bull. (Tokyo)*. **53**:1536–1539 (2005).
7. I. I. Salem, J. M. R. Lopez, and A. C. Galan. Ondansetron hydrochloride. In H. G. Brittain (ed.), *Analytical Profiles of Drug Substances and Excipients, vol. 27*, Academic, California, 2001, pp. 301–308.
8. J. E. Hoover. Gastrointestinal and liver drugs. In: Hendrickson R (ed) *Remington:The Science and Practice of Pharmacy*, 21st edn, Lippincott Williams & Wilkins, USA, PA, 2006, p. 1311.
9. J. Fukami, B. Yonemochi, Y. Yoshihashi, and K. S. Terada. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. *Int. J. Pharm.* **310**:101–109 (2006).
10. U. S. Pharmacopoeia. *USP 30-NF25*, USP, Rockville, MD, 2007.
11. V. B. Sutariya, R. C. Mashru, M. G. Sankalia, and J. M. Sankalia. Preparation of rapidly disintegrating tablets of ondansetron hydrochloride by direct compression method. *Ars. Pharm.* **47**:293–311 (2006).
12. G. A. Lewis, D. Mathieu, and R. Phan-Tan-Luu. The scope of experimental design. In G. A. Lewis, D. Mathieu, and R. Phan-Tan-Luu (eds.), *Pharmaceutical Experimental Designs*, Marcel Dekker, NewYork, 1999, p. 50.
13. X. Y. Bi, H. Sunada, Y. Yonezawa, and Danjo. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. *Drug Dev. Ind. Pharm.* **25**:571–581 (1999).