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Formulation of fast disintegrating domperidone tablets using *Plantago ovata* mucilage by 3^2 full factorial design

*S. M. Shahidulla[1], Mohib Khan[2] and K. N. Jayaveera[3]

[1]*Department of Pharmaceutics, Dr Samuel George Institute of Pharmaceutical Sciences, Markapur-523316, India*
[2]*Department of Pharmaceutics, Oriental College of Pharmacy, Mumbai-400705, India*
[3]*Jawaharlal Nehru Technological University, Anantapur-515001, India*

ABSTRACT

The present work was carried out to study the disintegrant property of *plantago ovata mucilage*. The objective of the work was to formulate Fast disintegrating tablets of Domperidon with a view to enhance patient compliances and dissolution rate by direct compression method using 3^2 full factorial design. *Plantago ovata* mucilage (2-10% w/w) was used as natural superdisintegrant and microcrystalline cellulose (0-30% w/w) was used as diluent, along with directly compressible mannitol to enhance mouth feel. The tablets were evaluated for hardness, friability, thickness, drug content uniformity, *in vitro* dispersion time, wetting time and water absorption ratio. Based on *in vitro* dispersion time (approximately 10s); the formulation containing 10% w/w *Plantago ovata* mucilage and 30%w/w microcrystalline cellulose was found to be promising and tested for *in vitro* drug release pattern (in 0.1 N HCl), short-term stability (at 40^0/75% RH for 3 month) and drug-excipient interaction. Surface response plots are presented to graphically represent the effect of independent variables (concentrations of *Plantago ovata* mucilage and microcrystalline cellulose) on the *in vitro* dispersion time. The validity of the generated mathematical model was tested by preparing two extra-design check point formulations. The optimized tablet formulation was compared with conventional commercial tablet formulation for drug release profiles. This formulation showed nearly four-fold faster drug release ($t_{50\%}$ 2.85 min) compared to the conventional commercial tablet formulation ($t_{50\%}$ 7.85 min). Short-term stability studies on the formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p < 0.05$).

Key Words: Domperidon, fast disintegrating tablets, *Plantago ovata* mucilage, microcrystalline cellulose, 3^2 full factorial design.

INTRODUCTION

Mucilage is most commonly used as excipients in the manufacturing of different pharmaceutical dosage forms. They have a variety of pharmaceutical properties, which include binding, disintegrating, suspending, emulsifying and sustaining properties at different proportion in different pharmaceutical dosage forms (Baveja *et al*., 1968, Baveja *et al*., 1968, Mithal *et al*., 1964, Mithal *et al*., 1965). Natural mucilages are preferred over semi-synthetic and synthetic materials due to their non-toxic, low cost, free availability, emollient and non-irritating nature (Kulkarni *et al*., 2002, Washi *et al*., 1985). Ispaghula mucilage consists of epidermis of the dried seeds of *Plantago ovata*.

Fast disintegrating tablet system can be defined as a tablet that disintegrates and dissolves rapidly in saliva within few seconds without need of drinking water (Fu *et al*., 2004). In spite of tremendous development in drug delivery technology, oral route remains perfect route for administration of therapeutic reagents because of low cost of therapy, ease of administration, accurate dose, self-medication, pain avoidance, leading to high level of patient compliance. Tablets and capsules are the most popular dosage forms (Chein *et al*., 1992), but main drawback of such dosage forms is dysphasia or difficulty in swallowing. This problem led to development of novel solid dosage forms such as fast disintegrating tablets that disintegrate and dissolve rapidly in saliva without need of water. Fast disintegrating tablets avoid first pass metabolism and enhance bioavailability of active ingredient (Kuchekar *et al*., 2001).

Domperidone is widely used antiemetic drug acting by an inhibition of the dopaminergic receptors. Domperidone does not cross blood brain barrier. Domperidone is also effective in gastroparesis, paediatric gastroesophageal reflux (infant vomiting). Domperidone after oral dosing undergoes extensive gastric and hepatic first pass metabolism resulting in low bioavailability (15%) which therefore, may not minimize the rate of vomiting (Tripathi *et al*., 2008). The aim was to formulate fast disintegrating domperidon tablets using *Plantago ovata* mucilage by 3^2 full factorial design and developing a dosage form with enhanced bioavailability.

***Corresponding Author**:
S. M. Shahidulla, Department of Pharmaceutics
Dr. Samuel George Institute of Pharmaceutical Sciences
Tarlupadu Road, Markapur
Andhra Pradesh, India. Pin: 523316
E-mail: *s.shahidulla@gmail.com*
Contact No.: +91 9963982707

MATERIALS AND METHODS

Domperidon was obtained as gift sample from Man Pharmaceuticals Ltd, Mehsana. The seeds of *Plantago ovata* were purchased from the local market of Ongole, Andhra Pradesh. Directly compressible mannitol (Pearlitol SD200), sodium stearyl fumarate and microcrystalline cellulose (Avicel PH-102) were generous gifts from Strides Arco Labs, Bangalore, Glenmark Ltd., Nashik and Alkem Labs Pvt Ltd, Mumbai, India. All other chemicals used were of analytical reagent grade.

Isolation of mucilage

For the isolation of mucilage (Washi *et al*., 1985; Bhaveja *et al*., 1989) seeds of *Plantago ovata* were used. They were soaked in distilled water for 48 hours and then boiled for 1 hr for complete release of mucilage into water. The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to

Table 1: Factorial design formulations of domperidon prepared by direct compression method.

Ingredients (mg/tablet)	Formulation code											
	DF_0	DF_1	DF_2	DF_3	DF_4	DF_5	DF_6	DF_7	DF_8	DF_9	C_1	C_2
Domperidon	10	10	10	10	10	10	10	10	10	10	10	10
*Plantago ovata*Mucilage	-	2	2	2	6	6	6	10	10	10	4	8
MCC	10	0	15	30	0	15	30	0	15	30	7.5	22.5
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3
Sodium stearyl fumarate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Banana flavour	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol SD-200	72	80	65	50	76	61	46	72	67	42	70.5	51.5
Total	100	100	100	100	100	100	100	100	100	100	100	100

Formulation DF_9 was selected as the best and used in further studies; DF_0 control formulation, C_1 and C_2 are extra design check-point formulations.

Table 2: Evaluation of factorial formulations.

Formulation	Hardness* (kg/cm2)± SD	Thickness (mm)	Friability (%)	*In vitro* dispersion time*(sec) ±SD	Drug content* (%)±SD	Wetting time* (seconds) ±SD	Water absorption ratio (%)
DF_0	2.50±0.10	3.1	0.54	175±1.52	99.1±0.5	192.10±1.0	48.2
DF_1	2.40±0.10	2.63	0.62	45.67±0.57	98.09±0.84	47.49±0.54	61.31
DF_2	2.62±0.105	2.9	0.56	39.14±0.95	96.88±0.72	39.77±0.59	66.02
DF_3	2.46±0.057	2.96	0.68	24.51±0.52	97.77±0.30	25.52±0.61	71.01
DF_4	2.23±0.152	2.86	0.71	39.3±0.97	99.36±0.45	40.19±0.72	66.98
DF_5	2.56±0.057	2.8	0.58	34.33±0.58	99.89±0.29	35.43±1.42	69.15
DF_6	2.36±0.152	2.83	0.45	19.99±0.13	100.10±0.32	21.29±1.08	74.97
DF_7	2.33±0.057	2.73	0.65	34.08±1.05	99.41±0.45	35.77±1.42	71.18
DF_8	2.40±0.10	2.93	0.49	22.44±1.63	100.02±0.43	24.29±0.97	76.27
DF_9	2.26±0.057	3.03	0.55	10.44±0.58	99.33±0.28	12.24±0.43	81.62
C_1	2.30±0.10	2.9	0.48	35.17±0.96	100.10±0.10	37.47±1.31	72.88
C_2	2.36±0.057	3.06	0.52	19.81±0.52	99.73±0.73	22.31±0.79	79.04

*Average of three determinations. Weight variation (97-105 mg) within the IP limits of ±10%

precipitate the mucilage. The separated mucilage was dried (in oven at temperature less than 60°C), powdered, sieved (#60) and stored in a desiccator until further use.

Preparation of fast disintegrating tablets of domperidon

Fast disintegrating tablets of Domperidon were prepared by direct compression method (Shirsand *et al*., 2009) according to the formulae given in table 1. All the ingredients were passed through #60 mesh separately. The drug and MCC were mixed by taking small portion of both each time and blending it to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using 6 mm round flat punches to get tablets of 100 mg weight on a 10-station rotary tablet machine (Clit, Ahmedabad).

Evaluation of fast disintegrating tablets

The prepared Fast disintegrating tablets were evaluated for different parameters like hardness, thickness, friability, weight variation test, drug content, wetting time and water absorption ratio, *In vitro* dispersion time and *In vitro* dissolution test.

Hardness

The crushing strength of tablets was measured by using Monsanto hardness tester (Devendre *et al*., 2012).

Thickness

Tablet thickness was measured by using Screw gauge. Three tablets were randomly taken and measured by placing between two arms of screw gauge.

Weight variation test

Twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu BL-220H). Tablets were weighed individually and compared with average weight (Banker *et al*., 1987).

Friability test

The friability of tablets was measured in Roche friabilator. 20 tablets were dedusted at 25 rpm for 4 min and weighed again (Lachman *et al*., 1991). Percentage friability was calculated from loss in weight as given in equation below. The weight loss should not be more than 1% (table 2).

$$\%\ Friability = \frac{\text{Initial weight} \_ \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug content determination

In this test, ten tablets were weighed and powdered. The Domperidon content was determined by measuring the absorbance at 283 nm. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations (IP, 1996).

Wetting time and water absorption ratio

For determination of wetting time and water absorption ratio (Chaudari *et al*., 2005), a piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio 'R' was calculated using the equation: R=100×(Wa–Wb)/Wa, where Wa is weight of tablet after water absorption and Wb is weight of tablet before water absorption.

In vitro dispersion time

In vitro dispersion time was determined by placing one tablet in a Petri dish containing 10 ml of water and the

time required for complete dispersion was determined (Nilesh *et al*., 2012; Gohel *et al*., 2004).

***In vitro* dissolution test**

In vitro dissolution studies of the optimized fast disintegrating tablets of domperidon and commercial conventional tablet was performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 0.1 N HCl at 37±0.5ºC as dissolution medium (Bhagwati *et al*., 2005). One tablet was used in each basket. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10 and 12 min) and replaced with the equal volume of fresh medium. The samples were analyzed for drug content by measuring the absorbance at 283 nm. Drug concentration was calculated from the standard calibration curve and states cumulative percent drug dissolved.

Drug-excipient interaction study

IR spectra of Domperidon and its formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to ruled out drug-excipients interactions.

Stability testing

Accelerated stability studies on formulation DF_9 were carried out by storing 15 tablets in an amber coloured rubber stoppered vials at 40°C/75% RH over a period of 3 months. At intervals of one month, the tablets were visually examined for any physical changes, changes in drug Content and *in vitro* dispersion time.

Experimental design

The 3^2 full factorial design was used for the optimization of fast disintegrating tablets of Domperidon (Design Expert 8.0.7.1). The two independent factors, concentration of *Plantago ovata* mucilage (X_1) and concentration of microcrystalline cellulose (X_2), were set to three different levels and experimental trials were performed for all nine possible combinations (Boltan *et al*., 1990). The dependent response, *in-vitro* dispersion time (Y_1) was evaluated.

Validation of the experimental design

To validate the experimental design using a polynomial equation, the dependent response, *in-vitro* dispersion time was selected. The following second order polynomial equation was applied as a tool of mathematical modeling (Singh *et al*., 2008).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 (b_1,b_2,,b_{12},b_{11} and b_{22}) is the estimated coefficient for corresponding factor X_1 (X_1,X_2,X_{12},X_{11},and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) describes the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

RESULTS AND DISCUSSION

Fast disintegrating tablets of Domperidon were prepared by direct compression method using *Plantago ovata* mucilage (POM) as natural superdisintigrant and MCC as diluent along with directly compressible mannitol (Pearlitol SD 200), which was used to enhance the mouth feel. A total of nine formulations, a control formulation (DF_0, without superdisintegrant) and two extra-design check point formulations (C_1 and C_2 to check validity of the developed polynomial equation), were designed.

Powder blends were evaluated for the flow parameters such as angle of repose, tapped density, bulk density and Carr's index. The material was free flowing (angle of repose values were found to be less than 30° and Carr's index was less than 15%).

The tablets were evaluated for weight variation, uniformity of drug content, hardness, friability, *in vitro* dispersion time, *in vitro* dissolution studies, tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specifications (±10%). Drug content was found to be in the range of 95-100%, which is within acceptable limits. Hardness of the tablets was found to be 2.0 to 2.6 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Formulation DF_9 was found to be promising and shown an *in vitro* dispersion time of 10 sec, which facilitates faster dispersion in the mouth.

In order to investigate the factors systematically, a factorial design was employed in the present investigation. Formulation has been done by using 3^2 full factorial design, preparing nine batches of formulations (DF_1 to DF_9). A polynomial equation was derived for *in vitro* dispersion time, by Design Expert 8.0.7.1 software. Formulation DF_9 containing 10% w/w *Plantago ovata* mucilage, 30% w/w MCC was found to be promising with an *in vitro* dispersion time of 10 sec against the 175sec displayed by control formulation (DF_0), which does not contain the superdisintegrant *Plantago ovata* mucilage.

In vitro dissolution studies on the promising formulation (DF_9), the control (DF_0) and conventional commercial tablet formulation (CCF) were carried out in 0.1 N HCl and the various dissolution parameter values,

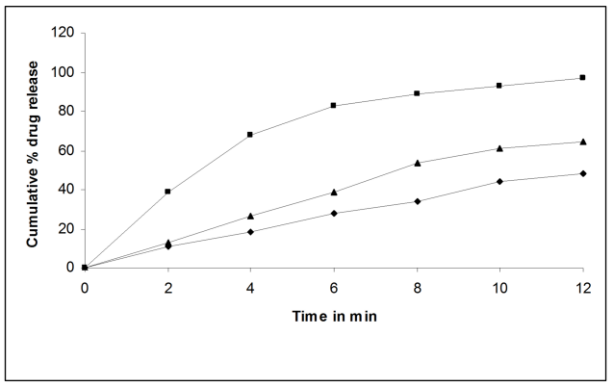

Figure 1: *In vitro* cumulative percent drug release *versus* time profile of promising domperidon formulations.
Plot showing cumulative percent drug release in 0.1 N HCl from control formulations (-♦-); promising DF9 formulation (-▪-); conventional commercial tablet formulation CCF (-▲-).

Table 3: *In vitro* dissolution parameters in 0.1 N HCl.

Formulation code	D_5 (%)	D_{10} (%)	DE_{10min} (%)	$t_{25\%}$ (min)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
DF_0	22.5	43.00	42.35	5.5	>12	>12
DF_9	74.5	93.00	64.02	1.3	2.85	>12
CCF	33.00	61.00	31.35	3.8	7.85	>12

DF_0 is control formulation, DF_9 is promising fast disintegrating tablet formulation, CCF is conventional commercial tablet formulation, D_5 is percent drug released in 5 min, D_{10} is percent drug release in 10 min, DE_{10}min is dissolution efficiency at 10 min, $t_{25\%}$ is time for 25% drug dissolution, $t_{50\%}$ is time for 50% drug dissolution, $t_{90\%}$ is time for 90% drug dissolution.

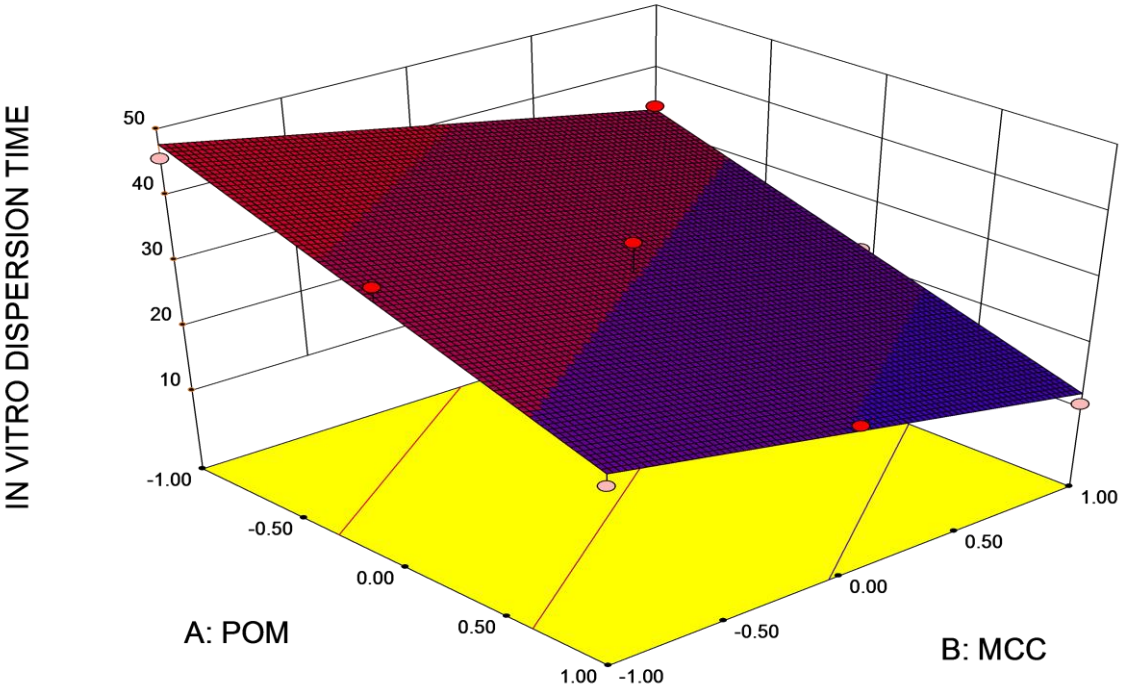

Figure 2: Response surface plot of factorial variables on *in vitro* dispersion time.

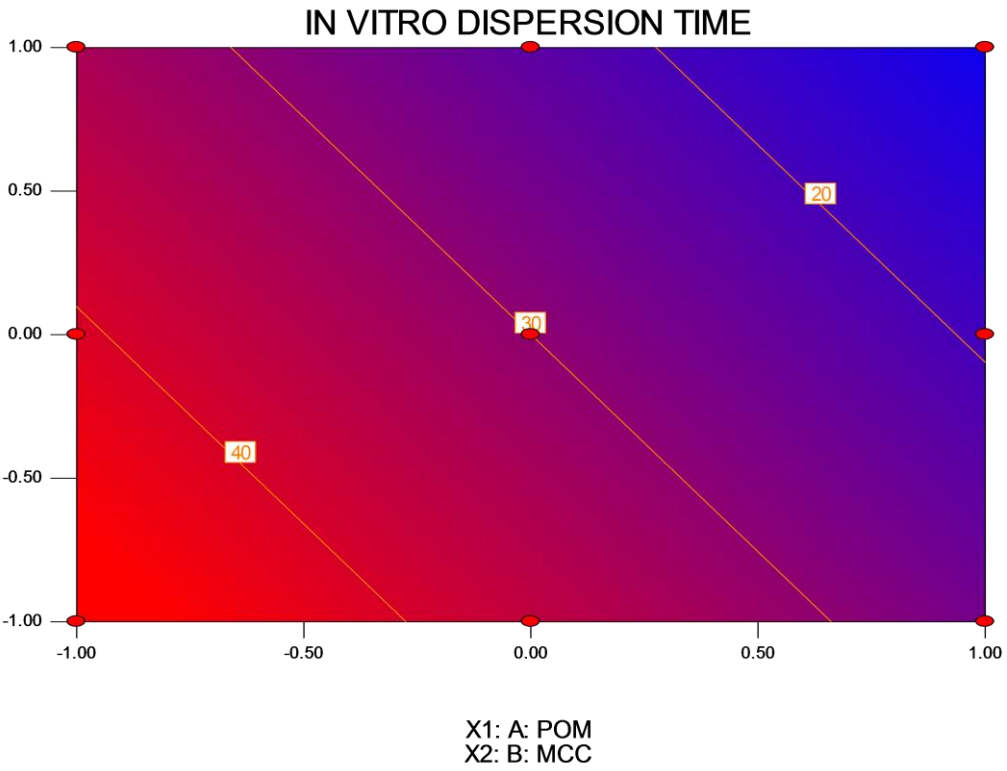

Figure 3: Contour plot of factorial variables on *in vitro* dispersion time.

viz., percent drug dissolved in 5 min (D_5), 10 min (D_{10}), dissolution efficiency at 10 min (DE_{10}min), $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ are shown in table 3 and the dissolution profile shown in figure 1. This data reveals that overall, the formulation DF_9 has shown nearly four-fold faster drug release ($t_{50\%}$ 2.85 min) when compared to CCF ($t_{50\%}$ 7.85min).

IR studies indicated that the drug is compatible with all the excipients. The IR spectrum of DF_9 showed all the characteristic peaks of Domperidon, thus confirming that no interaction of drug with the components of the formulation. Short-term stability studies of the above formulation indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3 months period (P<0.05).

The equation derived for *in vitro* dispersion time of the factorial formulations is, Y_1= 30.00-10.69 X_1-7.06X_2. The negative sign for coefficients of X_1 and X_2 indicates that as the concentration of disintegrants increases, *in vitro* dispersion time decreases. Validity of this equation was verified by designing two extra design check point formulations (C_1 and C_2) and determining the *in vitro* dispersion time. The *in vitro* dispersion time values predicted from the equation for these formulations are 38.87 and 21.13 seconds, where as those observed from experimental results are 35.17 and 19.81 seconds, respectively. The closeness of the predicted and observed values for C_1 and C_2 in the method indicates validity of derived equation for the dependent variable (*in vitro* dispersion time). The computer generated response surface and contour plots for the dependent variable are shown in figure 2 and 3, respectively.

CONCLUSION

A 3^2 full factorial design revealed that the amounts of *Plantago ovata* mucilage (X_1) and microcrystalline cellulose (X_2) significantly affect the dependent variable (Y_1), the *in vitro* dispersion time. It is thus concluded that, by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Direct compression method by using natural superdisintegrants would be an effective approach compared with the use of more expensive excipients in the formulation of fast disintegrating tablets with smaller disintegration time, improved drug dissolution, patient compliance, convenience and acceptability.

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