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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF DOMPERIDONE

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Abstract

In the present study, the fast dissolving tablet of Domperidone was formulated for its release. Domperidone acts as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant. The gastroprokinetic properties of Domperidone are related to its peripheral dopamine receptor blocking properties. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. . It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which regulates nausea and vomiting. .

Keywords: Domperidone, fast dissolving tablet, dopamine, gastric emptying

Introduction

Domperidone is antiemetic Drug (Prokinetic Drug). Its chemical name is 1, 3-dihydro-5-chloro-1-(1-(3-(2, 3-dihydro2-oxo-1H-benzimidazol-1-yl) propyl)-4 peridinyl)-2H-benzimidazol-2-one. Its molecular formula is $C_{22}H_{24}ClN_5O_2$ and molecular weight is 425.92. Its melting point is 240-245 $^{\circ}$C and colour and appearance is white. Domperidone is freely soluble in 1.0 M lactic acid, soluble in 1.0 M citric acid, slightly soluble in ethanol and practically insoluble in water, soluble in 0.1N HCl. It is stored in airtight container, protect from sun light.

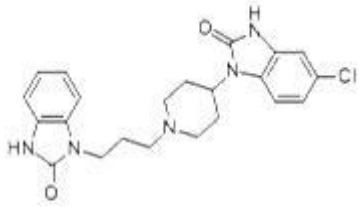

Figure 1: Structure of Domperidone

Domperidone acts as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant. The gastroprokinetic properties of Domperidone are related to its peripheral dopamine receptor blocking properties. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. The antiemetic properties of Domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which regulates nausea and vomiting. The use of domperidone are in Hypokalaemia, Hypomagnesaemia, Congestive heart failure, and adverse effects Angioneurotic, Oedema, Allergic reaction, Dry mouth, Headache, Insomnia, Dizziness, Diarrhoea, Regurgitation, Appetite disorder, Nausea

Heartburn, Constipation, Muscle spasms, asthenias.

Table 1: Pharmacokinetic parameters of Domperidone

Parameters	Values
Dissociation constant	1.75 nM
Half life	7-9 hours
Volume of distribution	440 L
Protein binding	91-93%
Dose	10 mg
Urinary excretion	1%- 2%
Clearance	0.16 ml/min
Peak plasma concentration(C_{max})	10-30 minutes

MATERIALS AND METHODS

Domperidone was received from Vivan Life Sciences Mumbai. Crosspovidone, Croscarmellose sodium were purchase from Vardha Biotech Mumbai. Micro-crystalline cellulose, Camphor, Sodium Saccharin, vanillin, Hydrochloric acid (HCl), Sodium chloride, Mannitol, Dibasic calcium phosphate,Magnesium stearate were purchase from CDH Pvt. Ltd. Mumbai. Pepsin was purchase from Vivan Life Sciences Mumbai. Many solvents Silica gel GF254, Ammonium acetate buffer, Methanol, Trimethanolamine were purchase from R.K. Enterprises, Meerut.

Experimental Methods:

Preparation of Fast Dissolving Tablet of Domperidone

Direct compression method

The tablets were formulated employing direct compression method using single punch tablet punching machine. Tablets were compressed directly from mixtures of the drug and excipients without preliminary treatment like granulation

Table 2: Formulation chart for preliminary trial batches (all quantities in mg)

Fomulation Code Excipients	M_1	M_2	M_3	M_4	M_5	M_6
Domperidone	10	10	10	10	10	10
CP	4	6		-	5	
CCS	-	-	4	6	-	5
Camphor	-	-	-	-	1	1
Sodium Saccharin	2	2	2	2	2	2
Vanillin	2	2	2	2	2	2
Dibasic calcium phosphate	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Mannitol	120	120	120	120	120	120
MCC	58	56	58	56	56	56
Total	200	200	200	200	200	200

Table 3: Formulations based on 3^2 full factorial designs (All quantities in mg)

Ingredients	Formulation Code								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Domperidone	10	10	10	10	10	10	10	10	10
Crospovidone	2	4	6	2	4	6	2	4	6
Camphor	0.5	0.5	0.5	1	1	1	1.5	1.5	1.5
Sodium Saccharin	2	2	2	2	2	2	2	2	2
Vanillin	2	2	2	2	2	2	2	2	2
Dibasic calcium phosphate	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Mannitol	120	120	120	120	120	120	120	120	120
MCC	59.5	57.5	55.5	59	57	55	58.5	56.5	54.5
Total	200	200	200	200	200	200	200	200	200

Evaluation Parameters:

Pre compression parameters

Bulk density (D_b)

It is the ratio of total mass to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It was expressed in gm/cc and given by

$$D_b = \frac{M}{V_0}$$

Where, **M** = Mass of powder

V_0 = Bulk volume of the powder.

Tapped density (D_t):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume and expressed in gm/cc as given by

$$D_t = \frac{M}{V_t}$$

Where, **M** = Mass of powder

V_t = Tapped volume of the powder.

Angle of repose:

The frictional forces in a loose powder can be measured by the angle of repose (θ) as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h / r)$$

Where, **θ** = angle of repose

h = height in cms.

r = radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Carr's index (I):

It indicated the ease with which a material could be induced to flow and expressed in percentage as given by

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t = tapped density of the powder.

D_b = bulk density of the powder

Table 4: Results of pre-compression parameters for batches M_1-M_6

Formulation Code	Parameters				
	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
M_1	0.27	0.33	17.66	1.21	27.6
M_2	0.24	0.32	24.98	1.33	25.1
M_3	0.26	0.32	23.92	1.24	25.2
M_4	0.27	0.35	20.93	1.26	26.1
M_5	0.25	0.32	21.88	1.27	27.2
M_6	0.27	0.35	22.86	1.29	27.1

Table 5: Results of pre-compression parameters for batches F_1-F_9

Formulation Code	Parameters				
	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose
F_1	0.28	0.35	20	1.25	28
F_2	0.25	0.32	21.78	1.28	24
F_3	0.27	0.34	20.58	1.26	26
F_4	0.28	0.36	22.22	1.33	27
F_5	0.26	0.33	21.21	1.26	28.17
F_6	0.28	0.36	22.2	1.28	28.30
F_7	0.25	0.34	26.47	1.36	23.96
F_8	0.28	0.35	20	1.25	26.56
F_9	0.28	0.35	21	1.25	28.23

Post compression evaluation parameters

Hardness

The hardness of the tablet was determined using a Monsanto hardness tester and expressed in **Kg/cm^2.**

Friability (F)

The friability of the tablet was determined using Roche Friabilator and expressed in percentage (**%**). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Weight variation

20 tablets were selected randomly from each lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing more than 200 mg is ± 5%.

Thickness

The thickness of the tablets was measured by screw gauge and expressed in **mm.**

Disintegration time

The *In-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining behind in the apparatus was measured in seconds.

***In-vitro* dissolution studies**

In vitro dissolution study was performed using USP type II apparatus (paddle type) at 50 rpm using distilled water and simulated gastric fluid as dissolution media maintained at temperature of 37°± 0.5°C. Aliquots of dissolution media were withdrawn at specific time intervals and replaced with fresh media and filtered. The amount of drug dissolved was determined by U.V. Spectrophotometric analysis of withdrawn sample at 284 nm against reagent blank. The experiments were conducted in triplicate.

Full factorial design

A 3^2 randomized full factorial design was used to optimize the variables in the present study. The two independent formulation variables evaluated included:

Factor A: % of superdisintegrant (crospovidone) (X) (2, 4, 6)

Factor B: % of sublimating agent (camphor) (Y) (0.5, 1, and 1.5)

The D.T (Disintegration time) and percentage friability of tablets were selected as dependent variables.

Table 6: Results of post-compression parameters for batches F_1-F_9

Formulation Code	Parameters			
	%Weight variation	Hardness (kg/cm^2)	Friability (%)	D.T. (sec)
F_1	passes	3	0.75	158.6
F_2	passes	5	0.64	179.3
F_3	passes	7	0.55	193.3
F_4	passes	3	0.71	122.3
F_5	passes	5	0.61	93.6
F_6	passes	4	0.62	81.6
F_7	passes	3	0.72	108.2
F_8	passes	5	0.63	112.1
F_9	passes	7	0.52	130.2

Table 7: *In-vitro* dissolution rate studies of batches F_1-F_5 in 0.1N HCl

S. No.	Time (min)	% drug release				
		F_1	F_2	F_3	F_4	F_5
1.	1	36.60	41.59	41.95	39.40	41.83
2.	2	60.93	65.55	69.08	54.97	58.98
3.	4	85.01	85.37	85.13	81.00	88.66
4.	6	98.87	99.00	99.24	99.00	99.00
5.	8	99.12	99.12	99.00	98.87	99.72
6.	10	98.27	98.63	99.48	98.27	99.48
7.	15	98.14	98.39	99.12	97.66	98.75
8.	20	97.66	98.02	98.39	98.27	98.14
9.	30	97.90	97.66	98.02	98.02	97.54

Table 8: *In-vitro* dissolution rate studies of batches F_6-F_9 in 0.1N HCl

S. No.	Time (min)	% drug release			
		F_6	F_7	F_8	F_9
1.	1	44.39	57.89	61.78	71.39
2.	2	61.17	62.02	79.41	94.74
3.	4	92.18	97.17	97.41	99.97
4.	6	99.48	98.51	99.85	99.48
5.	8	99.36	97.41	99.48	99.24
6.	10	99.00	98.63	99.00	99.60
7.	15	99.36	98.14	98.14	98.87
8.	20	97.54	97.66	98.51	98.63
9.	30	97.05	96.81	97.41	97.90

Figure 2: Comparative release profile of batches F_1-F_9in 0.1N HCl

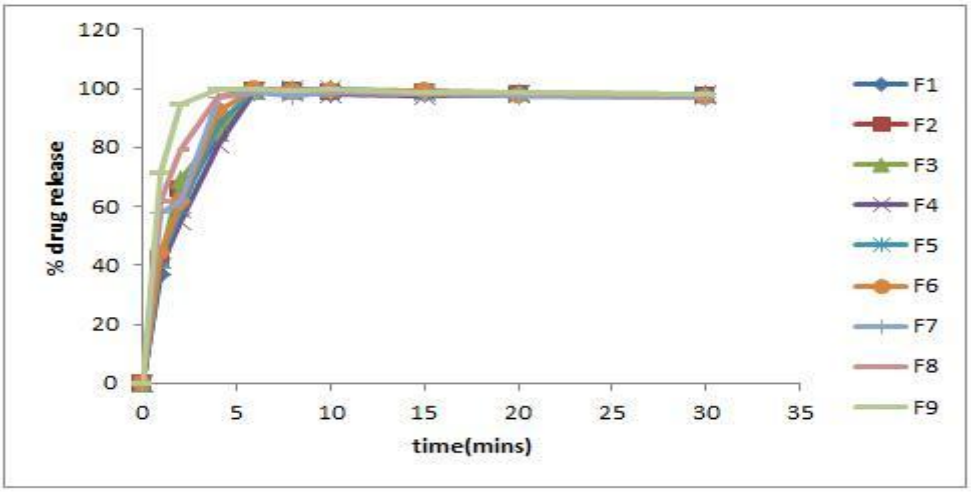

Table 9: 3^2 Full Factorial Design Layouts

Formulation Code	Variable levels in coded form		Friability (%)	D.T. (sec)
	X (%)	Y (%)		
F_1	1.00	1.00	0.75	158.6
F_2	0.00	1.00	0.64	179.3
F_3	1.00	-1.00	0.55	193.3
F_4	-1.00	-1.00	0.71	122.3
F_5	-1.00	0.00	0.61	93.6
F_6	-1.00	1.00	0.62	81.6
F_7	1.00	0.00	0.72	108.2
F_8	0.00	-1.00	0.63	112.1
F_9	0.00	0.00	0.52	130.2

Table 10: Optimized formula obtained and their desirability

Name	Goal	Lower limit	Upper limit
Factor A	In range	2	6
Factor B	In range	0.5	1.5
% friability	Targeted at 0.635	0.52	0.75
D.T.	Targeted at 109.29	81.6	193.6

Table 11: Predicted solution for optimized batch

Values	Camphor	Cospovidone	Friability %	D.T. (min)	Desirability
Coded	0	1	0.635	109.29	0.963
Actual	1	6	0.635	109.29	0.963

Discussion

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In the present study, the fast dissolving tablets were prepared using 3^2 full factorial design containing two factors evaluated at three levels. Initially six trial batches containing different superdisintegrants alone and in combination with sublimating agent were formulated and evaluated. The best batch containing crospovidone and camphor was selected as a source of information for designing factorial batches. Two evaluated independent formulation variables included: - Factor A (% of superdisintegrant 2, 4, 6 %) and Factor B (% of sublimating agent 0.5, 1.5, 1 %).

The experimental trials were performed at all possible combinations. The two response parameters like % friability and disintegration time were determined using design expert version (8.5.0.1) software for the construction of polynomial equation. All the formulated batches were evaluated for pre-compression and post-compression studies.

Calculations for testing the model in portions were performed by ANOVA. A full and reduced model for dissolution and disintegration were obtained which gave summary of regression analysis.

The derived optimized final batch of formulation was subjected to release profile studies in 0.1N HCl and simulated gastric fluid. The actual response values were in accordance with the predicted values which showed validity of the model. The validated formulation was subjected to stability studies which revealed the dosage form as stable with probable enhanced bioavailability pertaining to the inference drawn on *in-vitro* drug release profile.

Conclusion

The present worker suggested that such a formulation design could be applied to drugs of various categories paving the way to future researchers aiming at enhancing the drug release in desired manner and further formulating oral dosage forms presumably with enhanced bioavailability.

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