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Fabrication and In-Vitro Evaluation of Fast Dissolving Tablets of Domperidone

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ABSTRACT

Systematic studies were conducted using different concentration of super disintegrant i.e. Croscarmellose sodium and Crospovidone. All prepared systems were evaluated for the different properties. Before preparation of tablets, preformulation studies like micromeritic properties to assess flowability, compressibility properties and solubility studies were conducted. And all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, wetting time, content uniformity, and all the formulations were found to be within the permissible range. Formulation-5 has shown better dissolution profile and has shown maximum % drug release within 10 minutes. Among all formulations (F1-F5), it was observed that formulation-5 has shown better dissolution profile with sufficient wetting capability. So Formulation-5 was found to be the best formulation among others.

INTRODUCTION

The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance [1, 2, 3,4 and,5]. Many patients have difficulty of swallowing tablets and hard gelatin capsules and consequently do not take medications as it is prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy [6, 7, & 8]. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[9, 10]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[11, 12]. FDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms[13,14]. As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism [15].

Advantages of fast dissolving tablets are ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and psychiatric patients. Convenience of administration and accurate dosing as compared to liquids. No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

Good mouth feel property of MDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients. Rapid dissolution and absorption of drug, which may produce rapid onset of action. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, and in such cases bioavailability of drugs in increased. Ability to provide advantages of liquid medication in the form of solid preparation. Pregastric absorption can result in improved bioavailability and as a result of reduced dosage improved clinical performance through a reduction of unwanted effects.

The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic [16, 17,& 18].

Domperidone is specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms.

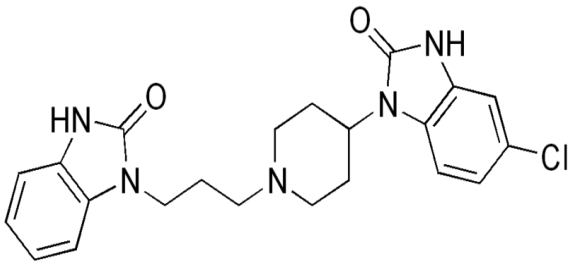

Fig: 1 Structure of Domperidone

Domperidone is a D2 dopamine receptor antagonist that blocks the agonistic action of fescue alkaloids at the cellular level. Unlike other D2 antagonist drugs, domperidone does not readily cross the blood-brain barrier. Distribution studies with radiolabeled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of the drug cross the placenta in rats. In humans, domperidone is 91-93% bound to plasma proteins. Domperidone in humans undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation1. Urinary and fecal excretions of domperidone in humans amount 31 and 66% of the oral dose, respectively. The proportion of the drug excreted unchanged in humans is small (10% of fecal excretion and approximately 1% of urinary excretion). The average terminal plasma half-life of domperidone administered orally to horses is approximately 6 hours with very low systemic bioavailability.[19-20]

MATERIALS AND METHODS

MATERIALS:

Domperidone was obtained as gift sample from Torrent Pharmaceuticals, Bangalore. Cros carmellose sodium, Crospovidone, Lactose monohydrate talc, magnesium state, mannitol and Aspartame were obtained from SD Fine –Chem Pvt, Mumbai. All other ingredients used were of analytical grade.

METHODS:

All the ingredients (except Mg.Stearate) were weighed accurately and sifted through # 44 mesh separately. The ingredients after sifting through sieve no. 44 were thoroughly mixed by

geometrical order and mixed for 10 min. and finally, Glidant (Magnesium Stearate) was added to the above blend and mixed it for 2min. Above lubricated blend was compressed by using 6mm round punches.

Calibration curve of Domperidone

Standard solutions in the range of 2 to 10 mcg/ml were prepared and absorption values were recorded at 284 nm against the reference. From this data, the standard curve of Domperidone was obtained by plotting absorbance on Y-axis against concentration on X-axis.

Table 1: Composition of Domperidone Tablets:

Ingredients (mg)	F1	F2	F3	F4	F5
Domperidone	20	20	20	20	20
Croscarmellose sodium	10	20			10
Crospovidon	---	---	10	20	10
Lactose anhydrous	122	112	122	112	112
Mannitol	40	40	40	40	40
Aspertame	3	3	3	3	3
Magnesium stearate	3	3	3	3	3
Talc	2	2	2	2	2
Total weight(mg)	200	200	200	200	200

Evaluation Test for Tablets[21-26]

Weight variation test:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weight is then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Content Uniformity:

30 tablets were selected randomly. 10 of these assayed individually. The Tablet passes the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Friability:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test and W_2 = Weight of tablets after test

Wetting time:

Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10cm diameter. 10 ml of water at 37°C±0.5°C containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average was reading noted.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation

$$R = W_a - W_b / W_b \times 100$$

Where W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Disintegration time:

The U.S.P. device to test disintegration uses 6 glass tubes that are long open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet was placed in each tube and the basket rack was positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2◦C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test, the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Drug release

The drug release from the Domperidone tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 7.4 pH Phosphate buffer (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV spectrophotometry at λmax=284 nm.

RESULTS AND DISCUSSION

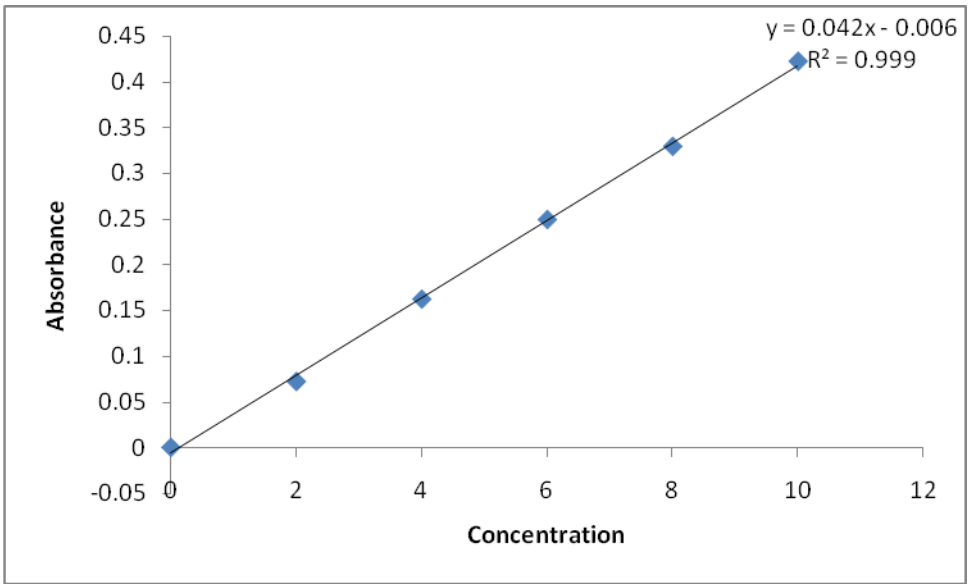

Fig. 2: Calibration curve of Domperidone

Table No: 2. Preformulation studies of blend of all formulation

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of repose(θ)	Carr's Index (%)	*Hausner's* ratio
F1	0.40	0.47	21.5	14.8	1.17
F2	0.41	0.46	20.1	10.86	1.12
F3	0.41	0.47	19.6	12.7	1.14
F4	0.42	0.45	18.8	12.4	1.13
F5	0.43	0.48	17.8	10.4	1.11

Table: No 3 Evaluation studies of tablets

FORMULATION CODE	WEIGHT VARIATION	HARDNESS Kg/Cm^2	THICKNESS (mm)	FRIABILITY (%)	CONTENT UNIFORMITY (%)
F1	Passes	4.5	2.08	0.15%	99.2
F2	Passes	5	1.98	0.12%	99.3
F3	Passes	4.3	1.99	0.13%	98.3
F4	Passes	4.4	2.02	0.14%	98.1
F5	Passes	4.8	2.01	0.12%	99.5

The hardness of the tablets was found to be 4.5, 5, 4.4, 4.8 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 1.98 to 2.08. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%. The drug content was found to be 99.2 to 99.5%, indicating uniform distribution of drug in the tablets.

Disintegration time

The most important parameter that needs to be optimized in the development of fast disintegrating tablets is the disintegration time of tablets. In the present study disintegration time of all batches were found in the range of 15 to 30 sec fulfilling the official requirements (less than1 min) for disintegrating tablets.

Wetting time

Wetting time was used as a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in the presence of little amount of water. Since the dissolution process of a tablet depends upon the

wetting followed by disintegration of the tablet. The wetting time of the formulated tablets was found to be in the range of 19 to 25 sec.

Water absorption ratio

Depicts the relation between the formulation and water absorption ratio was performed to know the water absorption and water uptake properties of super disintegrants. Water

absorption ratio was increased and disintegration time was decreased with an increase in concentration of super disintegrants.

Table: 4 Disintegration time, wetting time and water Absorption ratio

Formulation	Disintegration time (sec)	Wetting time (sec)	Water Absorption Ratio
F1	21	16	22.95
F2	18	15	24.29
F3	22	18	22.5
F4	20	17	21.5
F5	15	12	24.92

Table: 5 Dissolution profiles of prepared formulations:

Time (Min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	20.69	22.58	28.14	30.41	36.14
4	27.74	37.11	40.85	44.82	52.95
6	51.01	61.55	65.66	70.41	67.75
8	74.32	80.63	82.17	87.21	91.43
10	85.76	92.58	91.38	94.72	99.80

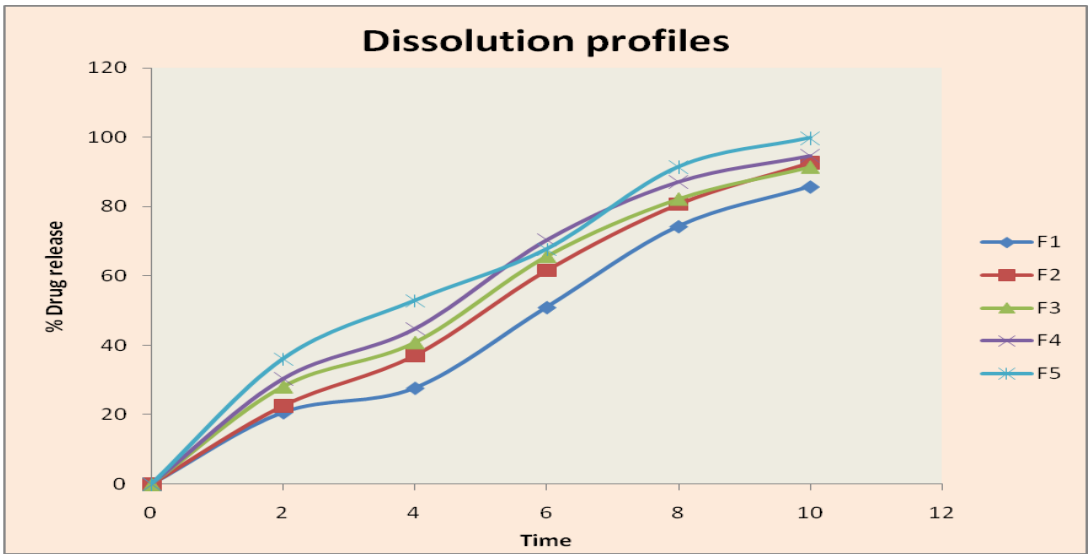

Fig: 3 Dissolution profiles of prepared formulations

Above graph indicates that %Drug release of F5 formulation shows better drug release when compared with other formulations.

CONCLUSION

In this present study, an attempt was made to improve onset of action as well as to enhance bioavailability of drug. Systematic studies were conducted using different concentration of super disintegrant i.e. Croscarmellose sodium and Crospovidone. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies were conducted like micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, wetting time, content uniformity, all the formulations were found within the permissible range.

Then prepared tablets were evaluated for *in-vitro* drug release. Formulation 1 and 3: Drug and super disintegrant (i.e. Croscarmellose sodium and Crospovidone) in the ratio of 1:1 which was prepared by direct compression method have poor wetting property as it contains less concentration of super disintegrant. Formulation 2 and 4: consists Drug and super disintegrants in the ratio of 1:2. Formulation 5: consists Drug and combination of super disintegrants in the ratio of 1:2. Formulation-5 has shown better dissolution profile and also maximum % drug release within 10 minutes. Among all formulations (F1-F5), it was observed that formulation 5 has shown better dissolution profile with sufficient wetting capability. So Formulation 5 was found to be the best formulation among others.

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