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Research Article

DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS USING DOMPERIDONE: PEG 6000 SOLID DISPERSIONS

SHAILENDRA BHATT [1]*, PRITI TRIVEDI[2]

[1]CVM Institute for Degree Course in Pharmacy, New Vallabh Vidya Nagar, Anand, [2]K.B. Institute for Pharmaceutical Education and Research, Gandhi Nagar, Gujarat. Email: shailu.bhatt@gmail.com

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ABSTRACT

Domperidone is water insoluble anti emetic drug, with problems of variable bioavailability and bio- in equivalence related to its poor water solubility. The purpose of present investigation to increase the dissolution rate of domperidone by developing domperidone tablet, allowing fast, reproducible and complete drug dissolution using solid dispersions of domperidone. Tablets were prepared by conventional wet granulation and direct compression method. Crosscarmellose sodium (Ac-Di-Sol) and Crosspovidone were used as superdisintegrant to achieve rapid disintegration of tablet. Tablet developed in this study disintegrated 58 seconds (wet granulation) and 49 (direct compression) seconds, and released 80 % and 83% drug in 5 min. whereas marketed tablet released 58% drug in 30 min. This study indicated that fast dissolving tablet can be prepared by conventional methods utilizing the existing infrastructure of tablet manufacturing.

Keywords: Domperidone, Fast dissolving tablet, Scanning electron microscopy, Solid dispersion.

INTRODUCTION

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Aqueous solubility is one of the key determinants of new chemical entities as successful drugs; drugs with poor water solubility typically have lower bioavailability. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions.[1]

Drug amorphization by spray-drying was experimented as a method of increasing the drug dissolution rate, but the amorphous form was instable and rapidly deactivated into the crystalline form.[2]

Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers.[3]

Solid dispersion technique can be applied to increase the dissolution rate by the formation of solid dispersion (SD) with polymeric carrier, such as polyvinyl glycol (PEG) derivatives,[4] polyvinyl pyrrolidone (PVP),[5] and hydroxylpropylmethylellulose.[6] PEG 6000 has been used as carrier for increasing the dissolution rate of several poorly water soluble drugs, such as prednisone,[7] rofecoxib,[8] and paracetamol.[9]

Domperidone exhibits poor aqueous solubility that produces erratic and delayed absorption when administered orally. Rapid absorption of drug requires rapid dissolution, which in turn depends on higher aqueous solubility.

The present study aims to formulate such a tablet that disintegrates rapidly and provides rapid dissolution of drug.

MATERIALS AND METHODS

Domperidone (Madley Pharmaceutical Ltd. Daman, India.), Crospovidone and Crosscarmellose sodium (Ac-Di-Sol) (Panacea Biotech, Ltd., Larlu, India). Polyethylene glycol (PEG) 6000, Starch, Saccharine-Na, D-Mannitol, Lactose monohydrate (S.D. Fine chemicals, Mumbai.), and other chemicals and reagent used in the study were obtained commercially and used as received.

Methods

Preparation of solid dispersion

Solid dispersions of domperidone: PEG 6000 in different weight ratio (1:1, 1:5, and 1:9) was prepared and charecterized as per the previously published method[10]

Preparation of tablets by wet granulation method

Raw materials were passed through a No. 44 screen. Domperidone (as such or in solid dispersion), microcrystalline cellulose, lactose and intra-granular fraction of crosscarmellose sodium (Ac-Di-Sol) were mixed and converted in to a wet mass with starch paste. Wet mass then passed through sieve No. 18 and resulting granules were dried in hot air oven at 40 ^{0} C for 2 h. following sieving through No. 22 sieve, granules were mixed with extra granular fraction of crosscarmellose sodium and magnesium stearate and compressed at constant force in to tablets using concave punches (9 mm diameter) in a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad,India.)

Preparation of tablets by direct compression method

The direct compression technique was used for the tablet preparation. All the raw material were passed through a screen (40 mesh) prior to mixing. Powdered 1:5 solid dispersion, containing amount equivelent to 10 mg of domperidone, was mixed with the other excipients and compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Table 1: Composition of Domperidone Fast dissolving tablet by wet granulation method

Ingredients	Batch						
mg	F1	F2	F3	F4	F5 (1:1)	F6 (1:5)	F7 (1:9)
Domperidone	10	10	10	10	-	-	-
SD	-	-	-	-	20	60	100
Crosscarmellose sodium	0	10	15	20	15	15	15
Starch	10	10	10	10	10	10	10
Micro crystalline cellulose	100	100	100	100	100	100	100
Lactose	126.5	116.5	111.5	106.5	101.5	61.5	21.5
Na-Saccharin	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mag.Stearate	1	1	1	1	1	1	1

Table 2: Composition of Domperidone Fast dissolving tablet by direct compression method

Ingredients	Formulation P1/P2/P3 (mg)
Drug –polymer solid dispersion (1:5)	60
Crosspovidone	5/10/15
D-Mannitol	50
Lactose monohydrate	130/125/120
Na-Saccharin	2.5
Mag.sterate	2.5

Evaluation of tablet properties

The hardness of the tablets was measured using a Pfizer hardness tester (Sheetal Scientific Industries, Mumbai, India). The limits for crushing strength of the tablets was kept in range of 3-4 kp.

The friability of the tablets was measured using a Roche Friabilator (Electrolab, Ahmedabad, India). Twenty pre-weighed tablets were rotaeted for 4 min at 25 rpm. The tablets were then weighed again, and the percentage of weight loss was calculated. The limit of the percent friability was kept below 1%.

The disintegration time was noted using a modified disintegration method. According to this method, a petri dish of 10-cm diameter was filled with 10 ml of distilled water, the tablet was carefully placed at the center of the petri dish, and the time necessary for the complete disintegration of tablet in to fine particles was noted as disintegration time.

Drug content

Randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 10 mg domperidone was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 284 nm.

In- Vitro Drug Release

Dissolution studies of domperidone from tablets were performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8 at $37^0 \pm 0.5^0$C and 50 rpm. Aliquots (5 ml) was removed from the dissolution medium at specific time intervals and was replenished immidiatly with same volume of fresh medium, the amount of released domperidone was detrmined by UV analysis at 284 nm. It was found that PEG 6000 did not interfere with the assay at this wave length. The result presented are mean values of three deteeminations.

Stability study

Representative samples (F6, and P3) were placed in a controlled cabinate at 40^0 C ± 2^0 C and 75% ± 5% RH for 3 months. The content of domperidone was analyzed monthly by UV spectroscopy. The data were analyzed by one way analysis of variance (ANOVA). A value of $P< 0.05$ was considered as significant.

RESULT AND DISCUSSION

Evaluation of tablet properties

The friability, hardness, disintegration time, wetting time, drug content and weight of formulated tablets are described in Table 3. All the parameters are within the acceptable range. Good uniformity in drug content was found amongst different batches. In wet granulation method, tablets prepared using starch disintegrated with in 25 second and release 9 % and 44 % drug in 5 minutes and 30 minutes respectively (Fig. 1). Incorporation of crosscarmellose sodium (6%) as superdisitegrating agent decreased the disintegration time (12 seconds).on the contrary, increase in the crosscarmellose-Na concentration (8 %) increased the disintegration time of tablets with out producing any appreciable change in drug release.

Crosscarmellose-Na is made from sodium carboxymethylcellulose by a cross linking reaction (estrification), which greatly reduce water solubility of sodium carboxymethylcellulose while permitting material to absorb water and swell many times its weight with out losing individual fiber integrity.[11] When Crosscarmellose-Na is added to a tablet formulation at higher concentration, absorption of water may cause an increase in viscosity of liquid with in tablet and may delay further penetration of water. As water absorption is an important step in disintegration process, increase in Crosscarmellose-Na concentration showed a delayed tendency in tablet disintegration. Tablets prepared with starch and Crosscarmellose-Na (6 %) exhibited shortest disintegration time but having poor release rate (Fig. 1) and almost equal to the tablets prepared without Crosscarmellose-Na. Prolong dissolution time could be correlated with poor aqueous solubility of poorly water soluble drugs. In the present study, PEG 6000 was used to prepare solid dispersion of domperidone. Tablets prepared with solid dispersion of drug and PEG 6000 (1:1), disintegrated in 38 seconds and released more than 50 % drug in 5 minutes (Fig. 2). When the ratio of PEG 6000 and drug in solid dispersion was increased, disintegration time of tablets also increased although release of drug was found to be faster (Fig. 2). Drug release from tablets prepared with solid dispersion of drug and PEG 6000 in ratio of (1:5) and (1:9) were found to be 80% and 82% respectively in 5 minutes (Fig. 2). Drug release from formulation F5, F6 and F7 found to be significant ($P< 0.05$). This shows that when the ratio of PEG 6000 and drug in solid dispersion increases, the rate of drug release increases significantly. It was found that the disintegration time was increased with increasing in the concentration of PEG 6000 and for the formulation F6 and F7 it was found to be 58 and 108 seconds respectively. Previous studies indicated that PEG 4000 [12] and PEG 6000 [13] prolong the disintegration time of tablet. When compare amongst various formulations, tablets containing drug: PEG 6000 (1:5) and 6 % crosscarmellose sodium were found to be optimum in relation to rapid disintegration and dissolution.

Physic- chemical state of solid dispersion, studied using DSC, FT-IR and SEM, indicated the absence of formation of solid solution and complexes, instead transformation of crystalline drug to amorphous state was noted. The amorphization together with improved wetting of drug and solubilization of drug by the carrier could be responsible for improvement in solubilization and consequent dissolution of drug.

Domperidone tablets were also prepared by direct compression method using different concentration of crosspovidone as superdisintegrant (2-6 %). Tablets prepared with 2% crosspovidone disintegrated in 60 seconds and release 81% drug in 5 min. while with 6 % of crosspovidone tablet disintegrated in 49 seconds and drug release was found to be 83% (Fig. 3). Considering disintegration time of tablets and drug release, tablets were optimally prepared using solid dispersion of drug in the ratio of drug/PEG 600 at 1:5 and with 6 % crosspovidone.

Optimized formulation (F6, P3), on compare with a commercial marketed tablet of domperidone, exhibited rapid drug dissolution (Fig. 2, and 3)

Stability study

Stability study was performed for the formulation F6, and P3 for 3 month as per ICH guidelines, and there was no significant variation observed in the drug content of all the formulations ($P> 0.05$).

Table 3: Technological Characterization of domperidone fast dissolving tablets

Parameters Formulations	Weight (mg)	Friability (%)	Hardness (kg/cm^2)	Disintegration time (sec)	Drug content (%)
F1	249.8±4.23	0.51±0.05	3.0±0.25	25±0.81	99.72±1.12
F2	249.8±3.52	0.58±0.04	3.0±0.12	17±0.12	99.29±1.04
F3	248.1±2.67	0.57±0.06	3.1±0.16	12±0.58	98.32±1.21
F4	249.2±4.42	0.62±0.042	3.0±0.18	22±0.24	99.08±1.34
F5	250.8±3.32	0.63±0.039	3.4±0.13	38±0.17	100.32±1.02
F6	249.1±2.73	0.54±0.051	3.6±0.15	58±0.25	99.87±1.43
F7	249.9±3.17	0.60±0.049	3.8±0.13	108±0.94	101.02±1.14
P1	249.8±4.23	0.61±0.05	3.5±0.12	60.23±2.11	100.08±1.21
P2	249.8±3.52	0.48±0.04	3.4±0.52	54.30±2.08	99.85±1.43
P3	247.1±2.67	0.47±0.06	3.5±0.16	49.13±2.51	101.01±1.35

Data are expressed as mean ± S.D. (n = 3)

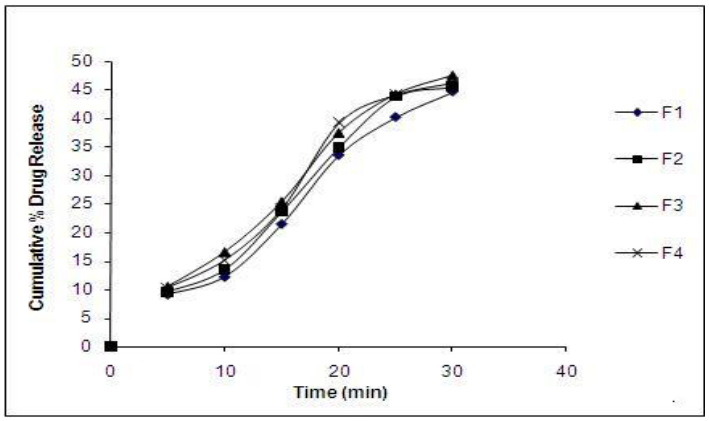

Fig. 1: Cumulative % drug release of formulation F1, F2, F3 and F4

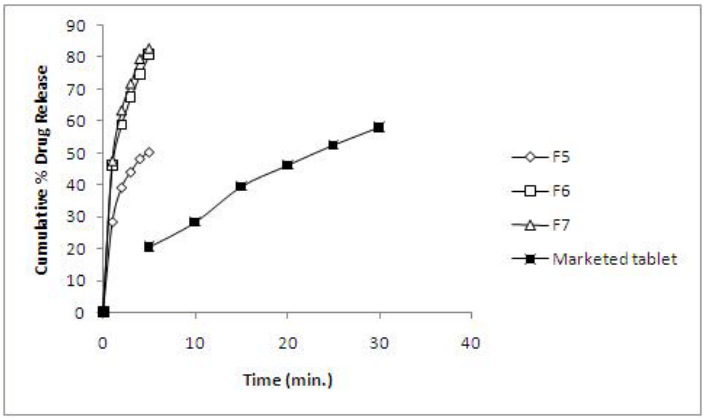

Fig. 2: Cumulative % drug release of formulation F5, F6, F7 and Marketed tablet

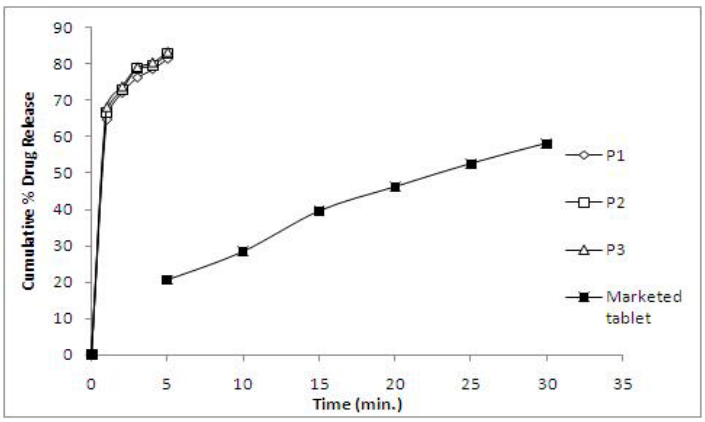

Fig. 3: Cumulative % drug release of formulation P1, P2, P3 and Marketed tablet

CONCLUSION

Fast dissolving tablet of domperidone can be prepared by existing tablet manufacturing technologies such as wet granulation and direct compression method using solid dispersion of drug instead of drug as such. The present study showed the suitability of PEG 6000 as a carrier for the preparation of domperidone solid dispersions. In the present study, use of solid dispersion containing domperidone/PEG 6000 (1:5) in the tablets prepared by wet granulation and direct compression disintegrates in 58 and 47 seconds, and released 80 % and 83% drug in 5 min. It's therefore proposed that the dissolution rate of domperidone can be enhanced to a greater extent, which gives quick relief from emesis.

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