

Research Article**FAST DISINTEGRATING COMBINATION TABLETS OF OMEPRAZOLE AND
DOMPERIDONE**

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ABSTRACT

The aim of this study was to prepare fast disintegrating combination tablets of Omeprazole and Domperidone by using pertinent disintegrant. The tablets were prepared using mannitol as diluent and sodium saccharin as sweetening agent along with three different levels of disintegrant. The superdisintegrant used in this study were Kollidon CL, Ac-Di-Sol and SSG. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time (DT) and dissolution study. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. Drug content was estimated by using HPLC method and also assay of sample was compared with standard drugs (Omeprazole and Domperidone). Omeprazole and Domperidone were well resolved and the retention times were around 9.01 and 6.2 respectively. From the results obtained, it can be concluded that the tablet formulation prepared with 4.76% Ac-Di-Sol (internally cross linked form of sodium carboxymethylcellulose) ie. 10 mg showed Disintegration time of 15 seconds in vitro. Also the hardness, friability, dissolution rate and assay of prepared tablets (batch F7) were found to be acceptable according to standard limits.

KEYWORDS Omeprazole, Domperidone, Fast disintegrating tablets (FDT's), Ac-Di-Sol, Direct Compression.

INTRODUCTION:

Many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy.¹

Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally fast disintegrating tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the

tablets and they are thus suitable for geriatric, pediatric and traveling patients.²

FDTs can be prepared by different methods as direct compression, freeze-drying, spray drying, sublimation and wet granulation method.³ The aim of this study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, mannitol used as diluent and sodium saccharin as sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants like Ac-Di-Sol,⁴ Sodium starch glycolate (SSG)⁵ and Kollidon CL⁶ in the formulation of tablets. Two model drugs, with poor aqueous solubility Omeprazole and Domperidone⁷ were selected for the studies. Omeprazole (a proton pump inhibitor) is used in treatment of ulcers and reflux oesophagitis and Domperidone

(prokinetic and antiemetic properties) is used for relief on nausea and vomiting of any cause, uremia and reflux oesophagitis.

MATERIAL AND METHODS

Materials

Omeprazole and Domperidone BP were obtained as gift sample by Torrent Pharmaceutical Ltd., Ahmedabad, India along with their working standard. Sodium starch glycolate (SSG, Avebe, Netherlands), Kollidon CL (Signet Chemical Corp. Mumbai) and Ac-Di-Sol (Croscarmellose Sodium, FMC Europe NV) were obtained as gift sample from Panacea Biotech Ltd., India. Acetonitrile (HPLC grade) were purchased from Qualigens Chemicals, India. All other chemicals used were of suitable analytical grade

Methodology

Omeprazole and Domperidone tablets were prepared with Kollidon CL, Ac-Di-Sol and SSG using 3 different concentrations of the said superdisintegrants. All the formulations contained 40 mg of Omeprazole and 20 mg of Domperidone, Mannitol 0% and 45-70%, preferably 47%- 66% of formulation weight, 3 different superdisintegrants were used in different concentrations ranging from 3% to 66% and 10 mg of sodium saccharine. The mixture was compressed into 210-mg tablets using a Hand operated tableting machine (R&D) using (8 mm punch diameter). Tablets prepared were biconvex. Various batches prepared shown in (TABLE 1).

Evaluation of the prepared tablets

Weight uniformity:

Twenty randomly selected tablets were weighed individually and the average

TABLE 1 It shows the batches prepared using three different concentration of each disintegrant

Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Omeprazole	40	40	40	40	40	40	40	40	40
Domperidone	20	20	20	20	20	20	20	20	20
Mannitol	129.8	99.8	-	129.8	99.8	-	129.8	99.8	-
Kollidon CL	10	40	140	-	-	-	-	-	-
SSG	-	-	-	10	40	140	-	-	-
Ac-Di-Sol	-	-	-	-	-	-	10	40	140
Sodium Saccharine	10	10	10	10	10	10	10	10	10
Mg. Stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total Wt. of Tab.	210	210	210	210	210	210	210	210	210

weight and the standard deviation were calculated.

Hardness

Hardness of the tablets was measured using Monsanto hardness tester.

Friability

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. Twenty tablets were weighed and loss in weight (%) was calculated.

Wetting time and water absorption ratio:

Procedures similar to those used by Bi Y. et al.⁸ were used to measure tablet wetting time and water absorption ratio (FIG 1). A piece of tissue paper folded twice was placed in a small culture dish (i.d. = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting was measured. The wetted tablet was again weighed. Water absorption ratio, R , was calculated using the formula;

$$R = \frac{100(W_a - W_b)}{W_b}$$

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

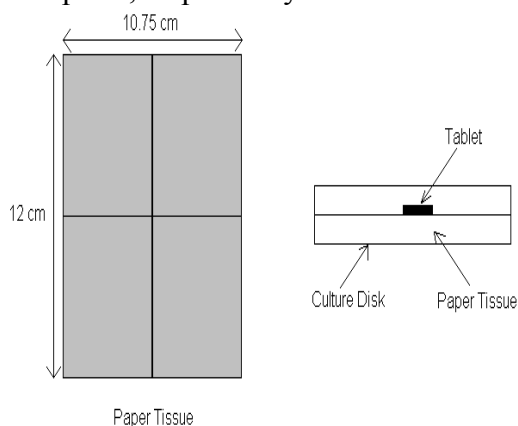


FIG.1. It shows schematization measurement of tablet wetting time and water absorption ratio

Disintegration time (in vitro)

The disintegration time for six tablets was measured, and the average time and standard deviation were calculated for each. Three batches for each disintegrant Kollidon CL, SSG, Ac-Di-Sol with

varying concentration were prepared and analyzed.

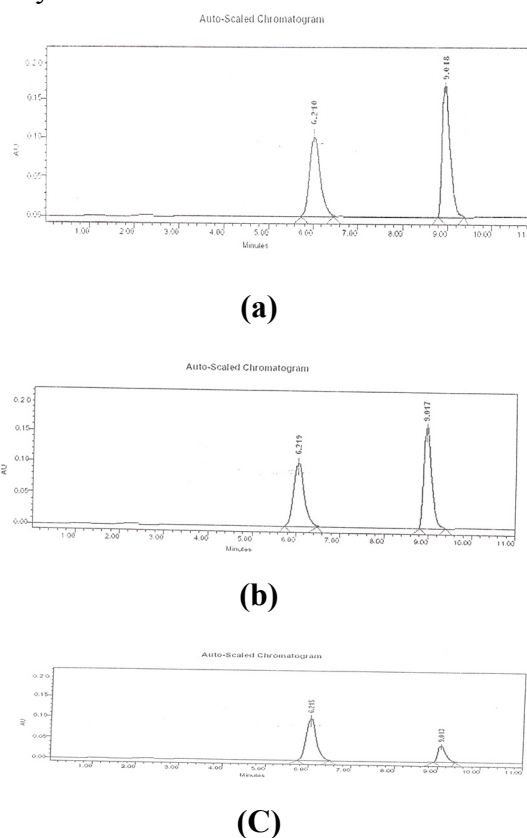


FIG. 2. It shows chromatograph obtained for (a) a sample solution (combination of Omeprazole and Domperidone) (b) dissolution of Omeprazole (c) dissolution of Domperidone.

Analysis of Active constituents

Drug was chromatographed on a reverse-phase C18 column using mixtures of buffer-acetonitrile, and the eluents were monitored using UV detector. The method was validated statistically for its linearity, precision, accuracy and specificity. The mobile phase was a mixture of 0.02 M disodium hydrogen phosphate and acetonitrile (65:35v/v). The pH was adjusted to 7.4 by adding orthophosphoric acid. The flow rate was 1.0 ml/min. The UV detector wavelength was set at 285 nm.

Dissolution studies

For dissolution of the Omeprazole and Domperidone a method was developed

in which two different procedures one for each drug was used. For the dissolution studies, a Modified JP XII dissolution apparatus used for drug Omeprazole and USP type II used for drug Domperidone. One tablet was placed in each basket, Paddles rotated at 100 rpm in 900 ml of the dissolution medium (0.1 N HCl at $37 \pm 0.5^\circ\text{C}$). The samples were withdrawn at suitable time interval. Samples were assayed by HPLC

Development of Analytical Procedures

Dissolution of Omeprazole in 0.1 N HCL.

Dissolution was done to determine the gastro resistance of in 0.1 N HCL. The drug content is to be determined using HPLC.

Experimental condition

Instrument Isocratic HPLC (Waters.); Reagents: Acetonitrile (HPLC grade), Potassium dihydrogen orthophosphate (AR grade), Sodium Hydroxide (GR grade), Hydrochloric acid (GR grade).

Dissolution Parameters

Apparatus: Modified JP XII Dissolution apparatus; Medium: 0.1N HCL (900ml); Speed: 100 rpm; Time: 120 min; Temperature: $37^\circ\text{C} \pm 0.5^\circ\text{C}$.

HPLC Parameters

Column: Waters C18 ODS 5μ ; Mobile phase: Buffer: Acetonitrile (65:35); Flow Rate: 1.5 ml/min; Detection: UV 285 nm; Injection Volume: 20 μ l.

Blank Preparation

5ml of 0.1 N NaOH was taken into 50 ml volumetric flask and diluted up to mark with mobile phase.

Standard Preparation

Weighed accurately 20 mg of working standard into a dry 200 ml amber colored volumetric flask, add 70 ml of 0.1 N NaOH and dissolved it. Dilute up to

mark with 0.1 N NaOH and mixed. Then 5 ml of this solution was diluted upto 50 ml with mobile phase and mixed.

Sample Preparation

One tablet in each of six bowls was placed and operated the apparatus for 120 minutes. After 120 minutes filter the solution and the liquid was discarded. The residue was washed with water (approx. 200 ml) and air dried. Transferred the residue quantitatively into six individual dry 200 ml amber colored volumetric flasks. Add 70 ml of 0.1 N NaOH and sonicated for 60 minutes. Then 5 ml of the supernatant was diluted upto 50 ml with mobile phase and mixed.

Procedure

Inject the blank (Dissolution medium) and chromatogram was recorded. Perform six replicate injections of standard and check for the system suitability test criteria. Inject the sample preparation and chromatogram was recorded. Then the response for the analyte peak was measured.

Calculation:

$$\% \text{Gastroresistance} = 100 - \left[\frac{\text{Sample area}}{\text{Avstd area}} \times \frac{\text{Wt of std taken}}{20} \times \% \text{ assay of standard} \right]$$

Dissolution of Domperidone in 0.1N HCL

Dissolution was done to determine the rate of release of Domperidone in Domstal-RD tablets in dissolution test apparatus. The drug content was estimated using HPLC method.

Experimental condition

Instrument: Isocratic HPLC (Waters); Reagents: Acetonitrile (HPLC grade, Qualigens), Potassium dihydrogen orthophosphate (AR grade, Qualigens), Sodium Hydroxide (GR grade, Qualigens), Hydrochloric acid (GR grade, Qualigens)

Dissolution parameters

Apparatus: USP type II, Paddle; Medium: 0.1N HCl (900ml); Speed: 100

rpm; Time: 30 min.; Temperature: 37 °C ± 0.5°C

HPLC parameters

Column: C18 spherisorb; Mobile phase: Buffer: Acetonitrile (65:35); Flow Rate: 1.5 ml/min; Detection: UV 285 nm; Injection Volume: 20 µl

Standard Preparation

Weighed accurately 22.2 mg of Domperidone working standard into a dry 100 ml volumetric flask, add 20 ml of methanol and dissolved it. Dilute upto mark with dissolution medium and mixed. 5 ml of this solution was diluted up to 100 ml with dissolution medium and mixed.

Sample Preparations

One tablet in each of six bowls was placed and operated the apparatus for 30 minutes. After 30 minutes draw samples. Centrifuged it at 3500 rpm for 15 minutes.

Procedure

Inject the blank (Dissolution medium) and chromatogram was recorded. Perform six replicate injections of standard and check for the system suitability test criteria. Inject the sample preparation and chromatogram was recorded. Then the response for the analyte peak was measured.

Calculation

$$\% \text{Drug dissolved} = \frac{\text{Sample Area}}{\text{Av. std. area}} \times \frac{\text{Std. wt. taken}}{22.22} \times \% \text{ assay of std.}$$

Assay

Assay was done to determine the concentration of Omeprazole and Domperidone in tablets.

Experimental condition

Instrument: Isocratic HPLC (Waters); Reagents: Methanol (HPLC grade, Qualigens), Acetonitrile (HPLC grade, Qualigens), Potassium dihydrogen

orthophosphate (AR grade, Qualigens), Sodium Hydroxide (GR grade, Qualigens).

HPLC parameters

Column: C18 spherisorb; Mobile phase: Buffer: Acetonitrile (65:35); Flow Rate: 1.5 ml/min.; Detection: 285 nm; Injection Volume: 20 µl.

Standard Preparation

Weighed accurately about 20 mg of Domperidone Working Standard and transfer it into a 100 ml standard volumetric flask. Weighed accurately about 40 mg of working standard and quantitatively transferred into the same 100 ml volumetric flask. Exactly about 50 ml of methanol was added and sonicated to dissolve. Make up the volume with 0.1 N NaOH and mixed. Then 5 ml of this solution was diluted up to 50 ml with mobile phase and mixed.

Sample Preparation

Transferred the whole content of 10 tablets to 50 ml volumetric flask. Add 100 ml methanol and sonicated for 30 minutes. Then about 350 ml of 0.1 N NaOH was added and sonicated for 30 minutes and cooled. Make up the mark with 0.1 N NaOH and mixed. Centrifuged at 3500 rpm for 15 minutes. Then 5 ml of the supernatant was diluted up to 50 ml with mobile phase and mixed.

Procedure

Inject the blank preparation and chromatogram was recorded. Perform six replicate injections of standard and check for the system suitability test criteria. Inject the sample preparation and chromatogram was recorded. Then the response for the analyte peak was measured.

Calculation:

$$\% \text{ Assay} = \frac{\text{Avg. Area of Sample}}{\text{Avg. Area of Std.}} \times \frac{\text{Std. wt. taken}}{20} \times \% \text{ assay of std. (as such)}$$

TABLE 2 It shows the physical parameters of prepared formulation

Formulations	Weight variation (%) ^a	Hardness (Kg/cm ²) ^b	Friability (%) ^a	Wetting time (sec.) ^b	Water absorption ratio (R) ^b
F1	2.4±0.54	2.5±0.13	0.42±0.26	11±0.9	21.11±2.1
F2	3.6±0.27	2.7±0.12	0.51±0.13	20±1.1	32.40±1.9
F3	4.1±0.21	3.1±0.11	0.73±0.33	33±1.7	50.89±1.7
F4	1.1±0.31	3.1±0.18	0.30±0.19	22±1.9	30.26±1.4
F5	3.5±0.11	3.2±0.22	0.48±0.22	39±1.2	49.11±1.0
F6	2.6±0.43	3.6±0.21	0.68±0.21	58±1.7	65.39±1.3
F7	3.2±0.29	2.9±0.30	0.32±0.17	12±0.9	23.22±1.8
F8	2.7±0.17	3.1±0.17	0.53±0.36	22±1.0	34.47±2.4
F9	1.7±0.36	3.4±0.21	0.77±0.34	34±1.1	51.79±2.3

a) n=20, b) n=10

TABLE 3 It shows the Disintegration time (DT) of prepared batches

Batch No.	Disintegrant used per tablet	DT (sec.),(n=3)	Comments
F1	Kollidon CL, 10mg	35±3.1	Soft Mass Left Good Hardness
F2	Kollidon CL, 40mg	25±2.6	Soft Mass Left No Hardness
F3	Kollidon CL,140mg	25±1.0	Soft Mass Left Fragile Tablet
F4	SSG, 10 mg	45±2.2	Hard Mass Left Good Hardness
F5	SSG, 40mg	35±1.6	Soft Mass Left Hardness fair
F6	SSG, 140mg	40±3.0	Soft Mass Left Fragile Tablets
F7	Ac- Di- Sol, 10mg	15±1.0	No mass Left Good Hardness
F8	Ac- Di- Sol, 40 mg	20±2.3	Soft mass Disintegrates on pressing slightly
F9	Ac- Di- Sol, 140mg	15±2.0	Fragile Tablets

$$\% \text{ Assay} = \frac{\text{Avg. Area of Sample}}{\text{Avg. Area of Std.}} \times \frac{\text{Std. wt. taken}}{40}$$

×% assay of std.(as such)

Linearity Study

The calibration curve consisted of a blank sample (blank as specified above), and were prepared individually for each drug. Solutions of concentration range 2, 4, 6, 8, 10, and 12 µg/ml of each drug prepared separately procedure followed is same as for assay standard preparation. The data was analyzed by linear least-square regression and the intercept, slope and correlation coefficient were determined. The variability of slopes and intercepts of the calibration curves were determined by constructing the curves. Six determinations were performed for each concentration. The concentrations of the samples were calculated on bases of potency of working standard. The %R.S.D. of the concentration measured within a run (six replicates) was used to determine the assay, respectively, and was determined as

$$\%R.S.D = \frac{\text{Standard deviation}}{\text{Mean measured concentration}} \times 100$$

RESULTS AND DISCUSSION

Physical properties of the formulation

The prepared tablets were evaluated for physical parameters such as weight variation, hardness and friability (Table 2). Percent weight variation was observed between 1.1 and 4.1; well within the acceptable limit for uncoated tablets as per USP. Since mechanical integrity is of paramount importance in successful formulation of FDTs, hence the hardness of tablets were determined and were found to be in the range of 2-4 kg/cm². Friability was observed between 0.30-0.77%, which was below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. Wetting time and water absorption ratio was determined using the method described by Bi *et al.* (results shown in Table 2). It was observed that formulations F4, F5 and F6 containing sodium starch glycolate had higher water

absorption ratio and take more time for wetting of tablets (TABLE 2). Wetting was closely related to the inner structure of the tablets and the hydrophilicity of the excipients. SSG shows its disintegrant effect by the mechanism of "swelling". Ac-Di-Sol (cross linked sodium carboxymethyl cellulose) shows its disintegrant action by wicking (due to its fibrous structure) and swelling with minimum gelling.^{9,10} Tablet prepared with Ac-di-sol (as in batch F7) had less wetting time and minimum water absorption ratio for hydrophilic combination of Omeprazole and Domperidone. The disintegration times for formulation F1-F9 was compared (as shown in Table 3), that indicates the formulation (F7) containing Ac-Di-Sol (10 mg) disintegrated the fastest with no mass left and had good hardness.

Dissolution study

The dissolution study of selected batch no. F7 of tablet formulations revealed that 94% of was resistant to acid deterioration in 0.1 N HCl after 2 hrs of dissolution. Domperidone release was 99% from the formulation after 30 min of dissolution (as shown in TABLE 4). Chromatogram for dissolution of Omeprazole and Domperidone shown in FIG. 2.b, c respectively.

Assay

The HPLC conditions for the assay of tablets are same as for the dissolution of the Omeprazole and Domperidone. Six replicates of each concentration were analyzed for standard and ten replicates for each prepared tablets and also for different brands (as shown in Table 5). Chromatogram obtained from sample solution i.e., Combination of Omeprazole and Domperidone shown in FIG. 2.a.

TABLE 4 It shows the Dissolution results of two different brands and prepared final formulations (batch F7)

Number of tablets (n=6)	Dissolution Time (min.)	Mean Concentration found ($\mu\text{g/ml}$)	Mean % Drug dissolved	%RSD
Omeprazole Prepared tablet	120	9.35	93.54	0.35
Omeprazole Brand 1	120	9.45	94.44	0.32
Omeprazole Brand 2	120	9.68	96.85	0.2
Domperidone Prepared tablet	30	11.03	99.36	0.23
Domperidone Brand 1	30	11.05	99.60	0.24
Domperidone Brand 2	30	10.95	98.65	0.36

TABLE 5 Six replicates of each concentration were analyzed for standard and ten samples for assay.

Injections Analyzed	Concentration Standard ($\mu\text{g/ml}$)	Mean (found) Concentration ($\mu\text{g/ml}$)	% RSD
Omeprazole (STD) ^a	10	-	0.06%
Domperidone (STD) ^a	11.1	-	0.14%
Assay Omeprazole prepared tablets ^b	10	9.97	0.32%
Assay Domperidone prepared tablets ^b	11.1	11.06	0.16%
Assay Omeprazole Brand1 ^b	10	9.98	0.30%
Assay Domperidone Brand 1 ^b	11.1	11.08	0.14%
Assay Omeprazole Brand 2 ^b	10	9.96	0.32%
Assay Domperidone Brand 2 ^b	11.1	10.8	0.18%

Validation

From the results obtained, it can be concluded that the tablet formulation (F7) prepared with Ac-Di-Sol (10mg) showed Disintegration time of 15 seconds in vitro. Dissolution data described that the only 6% of omeprazole and 1% of domperidone

was deteriorated and so drug released content were acceptable.

Linearity

The typical calibration curves for Omeprazole and Domperidone were $Y = 14066X$ (correlation coefficient, $r = 0.9987$) and $Y = 6779.8X$ ($r = 0.9992$), respectively, X : concentration in $\mu\text{g/ml}$, Y : Omeprazole/ Domperidone peak area ratio.

The limit of quantization was 1.44 μ g/ml for Omeprazole and 1.47 μ g/ml for Domperidone and limit of detection was 0.43 μ g/ml for Omeprazole and 0.44 μ g/ml for Domperidone, which attest the linearity of the method.

Precision

Mean contents of Omeprazole and Domperidone in the precision analysis ($n = 6$) were 9.35 μ g/ml (R.S.D. = 0.35%) and 11.03 μ g/ml (R.S.D. = 0.23%), respectively. For R.S.D. values, lower than 2.0%, assure the precision of the method.

Accuracy

It was investigated by means of addition of Omeprazole and Domperidone reference standards to a mixture of the tablet excipients. Omeprazole mean recovery ($n = 6$) was 94% and Domperidone mean recovery was 99%, demonstrating the accuracy of the method.

Specificity

Peak purities higher than 99.0% were obtained for Omeprazole and Domperidone in the chromatograms of sample solutions, demonstrating that other compounds did not co-elute with the main peaks. Omeprazole and Domperidone were well resolved and the retention times were around 9.01 and 6.2 respectively.

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