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# FORMULATION AND CHARACTERIZATION OF BILAYER TABLETS OF CINNARIZINE AND DOMPERIDONE

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## ABSTRACT

The objective of the present study was to formulate and evaluate bilayer tablets of Cinnarizine and Domperidone to achieve both immediate and sustained drug release from a single dosage form. The immediate-release layer containing Cinnarizine was prepared using suitable superdisintegrants, while the sustained-release layer of Domperidone was developed using hydrophilic polymers. The prepared tablets were evaluated for pre- and post-compression parameters, disintegration time, drug content, and in-vitro drug release studies. All formulations showed acceptable physicochemical properties within pharmacopeial limits. Among the immediate-release batches, formulation IF6 exhibited the fastest disintegration time (63 ± 4 sec) with satisfactory drug content. The optimized sustained-release formulation (F6) provided controlled drug release up to 12 hours. The bilayer tablet demonstrated rapid release of Cinnarizine (98.85% within 1.5 h) and sustained release of Domperidone (98.85% at 12 h), confirming the dual-release objective. The findings indicate that bilayer tablets of Cinnarizine and Domperidone can serve as a promising dosage form, offering both immediate symptomatic relief and prolonged therapeutic effect, thereby improving patient compliance and treatment effectiveness in motion sickness.

**Keywords:** Bilayer tablets; Cinnarizine; Domperidone; Immediate release; Sustained release; Motion sickness; Patient compliance; *In-vitro* drug release.

## INTRODUCTION

Motion sickness and vestibular disorders are often associated with nausea, vomiting, and dizziness, which significantly impair quality of life. Combination drug therapy is frequently employed to improve therapeutic efficacy and patient compliance. Bilayer tablets represent a novel dosage form that can deliver two drugs with different release profiles in a single unit, offering advantages such as reduced dosing frequency, minimized side effects, and improved bioavailability (Gokhale *et al.*, 2013; Arora *et al.*, 2013).

Cinnarizine is a piperazine derivative widely used as an antihistamine and calcium channel blocker for the management of motion sickness, vertigo, and vestibular disorders. However, it suffers from low aqueous solubility and variable bioavailability, which limits its therapeutic effectiveness (Jagdale *et al.*, 2010; Shrikant *et al.*, 2011).

Domperidone, a dopamine $D_2$ receptor antagonist, is an effective antiemetic that acts by blocking peripheral dopamine receptors in the gastrointestinal tract, thereby enhancing gastric motility and controlling nausea and vomiting (Gupta *et al.*, 2012).

It undergoes extensive first-pass metabolism and has a short biological half-life, requiring frequent administration (Satoskar *et al.*, 2015).

The rationale behind formulating a bilayer tablet containing Cinnarizine and Domperidone is to combine the therapeutic benefits of both drugs in a single dosage unit. Cinnarizine can provide symptomatic relief from vertigo and motion sickness, while Domperidone effectively controls nausea and vomiting associated with such conditions. Moreover, the bilayer approach enables simultaneous or sequential drug release, reducing dosing frequency and improving patient adherence (Sharma *et al.*, 2014; Hussain *et al.*, 2012).

Recent advancements in bilayer tablet technology have demonstrated its potential in developing fixed-dose combinations, especially for drugs with different pharmacokinetic profiles. Formulation strategies involving polymers, disintegrants, and controlled release matrices play a crucial role in optimizing release kinetics, ensuring stability, and achieving therapeutic efficiency (Hiremath *et al.*, 2008; Vora *et al.*, 2010).

Thus, the present work is focused on the formulation and characterization of bilayer tablets of Cinnarizine and Domperidone, with the objective of enhancing therapeutic efficacy, improving compliance, and providing a more effective treatment option for motion sickness and associated disorders.

## MATERIALS AND METHODS

### Materials

For the formulation development of bilayer tablets of Cinnarizine and Domperidone, the active pharmaceutical ingredients Cinnarizine and Domperidone were obtained as gift samples from Bioplus Life Science, Bangalore. Various excipients and chemicals used in the study included polyvinylpyrrolidone (PVP) from S. D. Fine Chem. Ltd., Mumbai; citric acid from Qualigens Fine Chemicals, Mumbai; hydroxypropyl methylcellulose (HPMC) from Ozone International, Mumbai; and sodium bicarbonate from Chem Pure Pvt. Ltd. Magnesium stearate was procured from Jiangsu Huaxi International, while talc, lactose, sodium starch glycolate, croscarmellose sodium, crospovidone, and microcrystalline cellulose were all obtained from Loba Chemie Pvt. Ltd., Mumbai.

### Methods

#### Preparation of instant layer of Cinnarizine

Fast dissolving (Instant Layer) tablets of Cinnarizine were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine different formulations of Cinnarizine were prepared and each formulation contained one of the three disintegrant in

different concentration (Maggi *et al.*, 1999). Each tablets weighing 350mg, were obtained. Composition of tablets was mentioned in Table 1.

**Evaluation of post compression Parameter**

**Shape and colour of tablets:**

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

**Thickness test**

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan) (Kumar *et al.*, 2012).

**Weight variation test**

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

**Hardness test**

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in $Kg/cm^2$.

**Friability test**

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loose more than 1% of their weight

**Uniformity of drug content:**

The test is mandatory for tablets with 10mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (Simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 252nm for Cinnarizine.

**Method for preparation of Domperidone controlled release tablets**

Direct compression was followed to manufacture the floating tablets of Domperidone. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table No. 2 and all the formulation were used for further evaluations parameters (Jayprakash *et al.*, 2011).

**Evaluation of tablets**

All the tablets were evaluated for following different parameters which includes;

**General Appearance**

Five tablets from different batches were randomly selected and organoleptic properties

such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -) (Karwa and Kasture, 2011).

**Thickness and diameter**

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

**Drug content**

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a $\lambda_{max}$ of 286nm using of 0.1 N HCl as blank.

**Hardness**

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

**Friability**

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

**Uniformity of weight**

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated (Yin *et al.*, 2014).

**Dissolution rate studies**

*In vitro* drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºC and rpm of 75. One Domperidone tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 12 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 12 hours using 10ml pipette. The fresh dissolution medium (37ºC) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 286nm using spectroscopy.

**Formulation development of bilayer tablet**

Optimized formulation IF-8 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet.

**Evaluation of bilayer tablets**

All the tablets were evaluated for following different parameters which includes;

**General Appearance**

Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually (Ohmori and Makino, 2004).

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

**Thickness and diameter**

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

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**Uniformity of weight**

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated (Pandey *et al.*, 2007).

**Drug content**

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of Domperidone was transferred to 10ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10 ml suitably 10 ppm solutions of and determines the Conc. of drug at 252nm for Cinnarizine and 286nm for Domperidone.

**Dissolution rate studies**

*In vitro* drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Cinnarizine and Domperidone bilayer tablets using an automated paddle dissolution system (Labindia) (Peppas and Korsmeyer, 1987; Korsmeyer *et al.*, 1986). A minimum of 6 tablets per batch were tested. The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5ºC. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using UV (Labindia 3000 plus) spectrophotometer.

**RESULTS AND DISCUSSION**

The present work focused on the successful formulation and evaluation of bilayer tablets containing Cinnarizine as an instant-release layer and Domperidone as a sustained-release layer. The tablets were developed to improve patient compliance in the treatment of nausea and vomiting associated with motion sickness by providing rapid relief from symptoms (Cinnarizine) and prolonged therapeutic effect (Domperidone).

All formulations of the immediate-release layer (IF1–IF9) showed satisfactory post-compression parameters (Table 3). Hardness values ranged between 2.9–3.6 kg/cm², which ensured mechanical strength without adversely affecting disintegration. Friability values were within the pharmacopeial limit (<1%), confirming good resistance to abrasion. Drug content uniformity (96.65–99.25%) was also within acceptable range, indicating uniform distribution of drug within the blend.

For Domperidone sustained-release tablets (F1–F8), hardness values (5.5–5.8 kg/cm²) and friability (0.55–0.88%) complied with the pharmacopoeial standards (Table 5). The results demonstrated adequate mechanical integrity and uniformity of dosage units.

The disintegration time of the Cinnarizine immediate-release layer (Table 4) varied from 63 ± 4 to 136 ± 2 seconds, with formulation IF6 showing the fastest disintegration. The

rapid breakdown of IF6 suggested better polymer–superdisintegrant interaction, favoring its selection for incorporation into the bilayer system.

The release pattern of Domperidone sustained-release formulations (Table 6) revealed a gradual drug release extending up to 12 hours. Among all batches, F6 showed an optimized release profile (99.44% at 8 h) with controlled release kinetics. This justified its selection for the bilayer formulation.

For the bilayer tablet (Tables 8 and 9), Cinnarizine showed nearly complete release (98.85%) within 1.5 hours**,** confirming its immediate-release property. In contrast, Domperidone exhibited a sustained-release profile, with ~98.85% release achieved at 12 hours**.** This biphasic release behavior confirmed the suitability of the bilayer design in providing both rapid onset of action and prolonged therapeutic effect.

The optimized bilayer tablet showed hardness of 6.3 kg/cm² and friability of 0.885%, which ensured mechanical stability during handling (Table 7). Both layers met drug content requirements (Cinnarizine 99.15% and Domperidone 99.65%) (Table 8). The dissolution study (Table 9) established that the formulation provided rapid release of Cinnarizine for immediate therapeutic action, while Domperidone was released in a sustained manner for prolonged effect.

**Table 1: Composition of Cinnarizine fast dissolving tablets**

| **Ingredients(mg)** | **Formulation code** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **IF1** | **IF 2** | **IF 3** | **IF 4** | **IF 5** | **IF 6** | **IF 7** | **IF 8** | **IF 9** |
| Cinnarizine | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Sodium Starch glycolate | 10 | 15 | 20 | - | - | - | - | - | - |
| Croscarmellose sodium | - | - | - | 10 | 15 | 20 | - | - | - |
| Crospovidone | - | - | - | - | - | - | 10 | 15 | 20 |
| Microcrystalline cellulose | 50 | 45 | 40 | 50 | 45 | 40 | 50 | 45 | 40 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total weight | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 2: Various formulations of Domperidone controlled release tablets**

| **Excipients (mg)** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** |
|---|---|---|---|---|---|---|---|---|
| **Domperidone** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **HPMC K4** | 90 | 120 | - | - | - | - | 30 | 40 |
| **HPMC K15** | - | - | 90 | 120 | - | - | 30 | 40 |
| **Xanthan gum** | - | - | - | - | 90 | 120 | 30 | 40 |
| **PVP K30** | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **Talc** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Magnesium Stearate** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Lactose** | 70 | 40 | 70 | 40 | 70 | 40 | 70 | 40 |
| **Total Weight** | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Table 3: Results of post-compression parameters of all formulations**

| F. Code | Hardness test (kg/cm$^2$) | Friability (%) | Weight variation (%) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| IF1 | 2.9±0.2 | 0.854±0.025 | 102±4 | 2.2±0.2 | 96.65±1.25 |
| IF2 | 3.1±0.3 | 0.658±0.032 | 100±6 | 2.3±0.3 | 97.85±1.36 |
| IF3 | 3.2±0.2 | 0.882±0.045 | 103±8 | 2.2±0.2 | 98.25±1.74 |
| IF4 | 3.1±0.2 | 0.765±0.65 | 104±7 | 2.4±0.2 | 97.65±0.96 |
| IF5 | 3.3±0.1 | 0.736±0.074 | 98±4 | 2.5±0.5 | 96.65±1.88 |
| IF6 | 3.4±0.3 | 0.698±0.065 | 99±3 | 2.2±0.3 | 99.25±1.74 |
| IF7 | 3.2±0.5 | 0.674±0.066 | 102±5 | 2.3±0.5 | 97.32±1.63 |
| IF8 | 3.6±0.4 | 0.785±0.074 | 101±6 | 2.4±0.3 | 96.68±1.74 |
| IF9 | 3.5±0.2 | 0.795±0.036 | 99±3 | 2.3±0.6 | 97.52±1.66 |

**Table 4: Results of Disintegration time of instant layer of Cinnarizine**

| Formulation code | Disintegration time (sec.) (n=3) Mean ± SD |
|---|---|
| IF1 | 125±6 |
| IF2 | 110±8 |
| IF3 | 95±5 |
| IF4 | 110±3 |
| IF5 | 95±9 |
| IF6 | 63±4 |
| IF7 | 136±2 |
| IF8 | 112±5 |
| IF9 | 105±3 |

**Table 5: Results of post compression properties of Domperidone tablets**

| F. code | Thickness (mm) | Hardness (kg/cm$^2$) | Weight variation (mg) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 3.2±3 | 5.6±0.3 | 202±5 | 0.745±0.032 | 95.65±0.25 |
| F2 | 3.3±2 | 5.5±0.2 | 198±3 | 0.658±0.045 | 96.74±0.36 |
| F3 | 3.4±4 | 5.8±0.4 | 206±4 | 0.885±0.063 | 98.98±0.14 |
| F4 | 3.6±3 | 5.6±0.6 | 205±6 | 0.746±0.036 | 97.65±0.65 |
| F5 | 3.5±2 | 5.7±0.2 | 204±5 | 0.663±0.015 | 98.88±0.14 |
| F6 | 3.7±3 | 5.5±0.5 | 203±3 | 0.558±0.022 | 97.65±0.33 |
| F7 | 3.5±4 | 5.6±0.3 | 199±4 | 0.743±0.036 | 99.88±0.74 |
| F8 | 3.4±3 | 5.7±0.2 | 196±3 | 0.698±0.041 | 99.36±0.33 |

**Table 6: *In-vitro* drug release study of tablets**

| Time | % Cumulative drug release | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (hr) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 0.5 | 58.98 | 43.36 | 41.36 | 38.85 | 37.85 | 34.65 | 31.15 | 28.85 |
| 1 | 76.65 | 57.74 | 54.69 | 50.36 | 43.36 | 40.36 | 38.85 | 37.74 |
| 1.5 | 88.95 | 79.95 | 76.65 | 73.32 | 65.58 | 59.98 | 53.32 | 53.32 |
| 2 | 98.85 | 98.12 | 87.74 | 82.25 | 76.66 | 71.36 | 68.85 | 61.15 |
| 3 | - | - | 99.12 | 81.14 | 83.32 | 86.65 | 73.36 | 69.95 |
| 4 | - | - | - | 98.78 | 92.25 | 93.32 | 80.12 | 76.65 |
| 6 | - | - | - | - | 99.15 | 98.85 | 88.85 | 85.45 |
| 8 | - | - | - | - | - | 99.44 | 93.39 | 93.32 |
| 12 | - | - | - | - | - | - | 99.05 | 95.58 |

**Table 7: Post-compression parameters of optimized formulation**

| Formulation | Hardness test ($kg/cm^2$) | Friability (%) | Weight variation | Thickness (mm) |
|---|---|---|---|---|
| 1. | 6.3 | 0.885 | Passes | 4.9 |

**Table 8: Results of Drug content analysis**

| Formulation | Cinnarizine (% Label Claim) | Domperidone (% Label Claim) |
|---|---|---|
| In-house Bilayer tablet | 99.15 | 99.65 |

**Table 9: Results of Dissolution rate studies of bilayer tablets**

| Time (Hour) | % Drug Release | |
|---|---|---|
| | Cinnarizine | Domperidone |
| 0.5 | 33.65 | 13.36 |
| 1 | 65.58 | 20.36 |
| 1.5 | 98.85 | 36.65 |
| 2 | - | 49.98 |
| 4 | - | 69.95 |
| 6 | - | 73.36 |
| 8 | - | 88.85 |
| 10 | - | 94.45 |
| 12 | - | 98.85 |

## CONCLUSION

The present study successfully developed and evaluated bilayer tablets of Cinnarizine and Domperidone to achieve immediate as well as sustained drug release in a single dosage form. The optimized formulation exhibited satisfactory post-compression parameters, drug content uniformity, and excellent mechanical strength. The Cinnarizine layer showed rapid disintegration and complete drug release within 1.5 hours, ensuring quick onset of action, while the Domperidone layer provided a sustained drug release for up to 12 hours, maintaining therapeutic activity over

an extended period. The bilayer tablet design proved to be an effective strategy to combine two drugs with distinct release profiles, thereby improving patient compliance, reducing dosing frequency, and enhancing therapeutic efficacy in the management of motion sickness–associated nausea and vomiting.

## DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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