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# Comparison of Multidrug Formulations for Anti-Hypertensive Treatment

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## Abstract

The multidrug therapy in the form of Orally Disintegrating Tablets (ODTs) is superior to control and treat high blood pressure and to decrease cardiovascular events in hypertensive patients than individual drug telmisartan, hydrochlorothiazide and amlodipine besylate to provide quick onset of action and improve drug adherence. ODT formulations of telmisartan and amlodipine besylate (F1), telmisartan and hydrochlorothiazide (F2), amlodipine besylate and hydrochlorothiazide (F3) were prepared by direct compression method and evaluated for pre-compression parameters and post-compression parameters. Formulation F1 showed the highest release of the drug, i.e., 80.7 ± 0.5%, whereas F2 and F3 showed 66.285 ± 0.3% and 65.182 ± 0.7% respectively for 15 min. All three formulations (F1, F2 and F3) passed the tests with disintegrating time within the limit of 20 s. The hardness of formulations was in the range of 4.33 to 5.33 kg/cm$^2$ and the friability of all the formulations were found to be within limit of 1%. The thickness and diameter of all the formulations were found to be 0.2-0.3 cm and 0.8 cm respectively. The % dissolution efficiencies were found in the order of F1>F3>F2. All formulations were found to be stable when were maintained at 40 ± 2°C/75 ± 5% RH and 50 ± 2°C/75 ± 5% RH for 6 months. This multidrug combination therapy may serve as an alternative for conventional single pill dosage form to treat hypertension.

**Keywords:** Dysphagia; Amlodipine besylate; Telmisartan; Hydrochlorothiazide; Dissolution; Disintegration

## Introduction

Orally Disintegrating Tablets (ODTs) are also known as orodispersible tablets, quick tablets, Fast Disintegrating Tablets (FDTs), fast dissolving tablets, rapid dissolving tablets, porous tablets, or rapidmelts. European Pharmacopoeia has recently utilized the term orodispersible tablet for tablets that disperse readily within 3 min before swallowing in the oral cavity. ODTs are disintegrated in less than one min but the time ranges from 5-30 s. ODTs help to increase the acceptability of bitter drugs by altering it to good taste and flavor to offer a pleasant mouth feeling. Some novel ODT technologies allow high drug loading and leaving minimal residue in the mouth. It also improves the bioavailability of a poorly soluble drug. They are characterized by high porosity, low density and low hardness. Some patented ODTs technologies include OraSolv®, Zydis®, FlashTab®, DuraSolv®, Wowtab®, etc. [1,2].

ODT is prepared to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for faster release; and providing ease of administration and better patient compliance. While formulating ODTs, most common challenges usually faced are palatability, mechanical strength, and hygroscopicity, the amount of drug, aqueous solubility and size [3,4].

Advantages of ODTs include it bypasses the Gastrointestinal Tract (GIT), hepatic portal systems and enhances the bioavailability of drugs that are administered orally. Without affecting the pH of the stomach and GIT enzymes, the drug remains protected and enhances patient compliance. It offers rapid drug delivery from the dosage forms and has a rapid onset of action. Moreover, the administration of a drug is easy through the buccal mucosa and suitable while travelling where water may not be available. It provides accurate dosing as com-pared to liquids and has good chemical stability.

Now-a-days, one of the primary treatment for hypertension is mainly dependent on β-blockers because of their ability to manage heart failure. Treatment of hypertension has been evolved from single drug therapy to combinations of drugs exhibiting the different mechanism of actions. Telmisartan acts by blocking angiotensin II receptors and has peroxisome proliferator activator receptor γ-agonistic activity. Amlodipine acts as calcium channel blocker CCB and is also found effective in events of stroke and myocardial infarction. Hydrochlorothiazide belongs to a class of thiazide diuretics that reduces blood pressure by volume depletion and is practiced in combination therapy with other antihypertensive drugs because of its synergistic effect [5-7].

For antihypertensive medications, multiple drug intolerance is overlooked because of non-adherence. Combination therapy for treatment of hypertension in the form of ODT formulations and would have the advantage to bypass the first pass metabolism and improve bioavailability of drugs. Many issues like demurral to consume lifelong medication, high dosing frequency; and other patient and physician related problems can be reduced by simplifying dosing regimens and providing fixed-dose combinations. A randomized controlled trial of combination therapy for treatment of hypertension is under investigation. As compared to monotherapy, so far combination therapy has shown promising results in reduction of cardio-vascular mortality and morbidity and helped to achieve systolic and diastolic blood pressure. Multidrug delivery system is used to formulate combination drugs with different pharmaco-kinetic profiles provide a reduction in dose, dosing frequency and side effects; and provide additive effects and single pill convenience. Also, because of lower doses of each antihypertensive drug in a combination, metabolic and clinical adverse effects are decreased.

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The objective of the present work was to formulate and characterize multidrug ODTs containing telmisartan, amlodipine besylate, and hydrochlorothiazide for anti-hypertension by con-trolling elevated blood pressure. It also provides quick onset of action due to combination therapy in the form of ODTs.

## Materials and Methods

### Materials

Telmisartan, amlodipine besylate, hydrochlorothiazide and aspartame were gifted by Micro Labs (Mumbai, India). Cross-povidone was purchased from Research Lab Fine Chem Indus-tries (Mumbai, India). Mannitol and microcrystalline cellulose were procured from Molychem (Mumbai, India). Talc and magnesium stearate was obtained from S. D. Fine Chem (Mumbai, India).

### Methods

**Preparation of ODTs:** The composition of ODT formulations is shown in Table 1. All the ingredients were passed separately through 60 mesh sieve. The small portions of the drug and diluents were mixed each time and blended into a uniform mixture. The ingredients were weighed and mixed in a geometric order. The final powder obtained was compressed with 8 mm size flat round punch using a rotary tablet machine (Karnavati, India). The composition of different formulations is shown in Table 1.

**Evaluation of powder blend:** The angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index were used to evaluate powder blend.

***Bulk density and tapped density*:** A weighed quantity of powered from each formulation was introduced into a 50 mL measuring cylinder. The initial volume of the powder was noted and 100 taps were made using tap densitometer (Thermonik, India). The tapped volume of the powder was noted. Bulk density and tapped density were calculated using the following formula;

Bulk density: Mass of the powder/Bulk volume of the packing;

Tapped density: Mass of the powder/Tapped volume of the packing.

***Carr's index*:** It was determined by Carr's compressibility index as given below:

Carr's index (%) = [(Tapped density - Bulk density) × 100]/Tapped density

***Angle of repose (θ)*:** It was determined by using a fixed height funnel method. The powder blend was poured through the funnel that was raised to a fixed height (h) and the radius (r) of the heap formed was measured. It was calculated by using the formula:

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

***Hausner's ratio*:** An index of ease of powder flow is Hausner's ratio, which was calculated by the formula:

Hausner's ratio = Tapped density/Bulk density

**Post-compression characterization of tablet:** Formulations F1, F2 and F3 were evaluated for organoleptic characteristics like color, odor, taste, diameter and thickness and physical characteristics like weight variation, hardness, friability, disintegration time, wetting time and dissolution studies.

***Weight variation*:** According to USP, 20 tablets were weighed individually and average weight was calculated. The average weight of the individual tablet was calculated and compared to the average [8].

***Thickness and diameter variation*:** Batch formulations F1, F2 and F3, from which ten tablets were randomly selected and their thickness and diameter were measured using a micrometer screw gauge (Mitutoyo, USA).

***Hardness and friability*:** Using Monsanto hardness tester, the hardness of the tablet formulations F1, F2 and F3 was measured. The five tablets were placed in friabilator (Electrolab, India) at a speed of 25 rpm for 4 min. Friability of tablets was measured by calculating pre-weighed tablets and reweighed after mentioned revolution. The percentage loss of weight was calculated using following formula [8].

% Friability = (Initial weight of tablets – Final weight of tablets/ Initial weight of tablets) × 100

***Wetting time*:** A piece of tissue paper of 10 $cm^2$ was folded twice and placed in a small petri dish containing phosphate buffer pH 6.8. A tablet of each formulation was placed in 3 different petri plates and time taken to completely wet the paper was measured using a stop watch.

***Disintegration test*:** ODTs get dispersed in the buccal cavity in the presence of saliva. As the volume of saliva in the mouth is limited the apparatus is modified. In a cylindrical vessel, 6 mL of phosphate buffer pH 6.8 was placed with 10 mesh screen and the tablet was placed on the sieve. The whole apparatus was placed on a shaker and 6 tablets of each formulation were randomly selected. Time taken by the tablet to disintegrate was noted and its average value was determined [8].

***In vitro dissolution studies*:** Dissolution studies were performed using paddle method at 50 rpm in 900 mL of phosphate buffer pH 6.8 as a dissolution medium which was maintained at 37°C ± 2°C. At specific time intervals, 10 mL of aliquots were withdrawn and replaced with fresh media and analyzed at 239 nm, 226 nm, and 239 nm for amlodipine besylate, hydrochlorothiazide and telmisartan respectively at 1, 2, 5, 10 and 15 min.

**Accelerated stability studies:** Stability Studies were performed for formulations F1, F2 and F3 under accelerated conditions in stability chamber with controlled conditions. Each formulation was packed in Alu/Alu blister and was incubated at two different elevated temperature and relative humidity (RH) which were maintained at 40 ± 2°C/75 ± 5% RH and 50 ± 2°C/75 ± 5% RH for 6 months. During 6 months, the formulations were evaluated for the change in appearance, odor, friability, hardness. The content of formulations was determined by performing disintegration, dissolution and assay after 6 months as per ICH guidelines. After 3 and 6 months, loss on drying was carried out on all the three formulations (F1, F2 and F3). The assay was performed for all the formulations by spectroscopic analysis on UV-visible spectrophotometer and absorbance was measured at 239 nm, 226 nm, and 239 nm for amlodipine besylate, hydro-chlorothiazide and telmisartan respectively. The percentage

| Ingredient | F1 (mg) | F2 (mg) | F3 (mg) |
|---|---|---|---|
| Telmisartan | 40 | 40 | - |
| Amlodipine besylate | 5 | - | 5 |
| Hydrochlorothiazide | - | 25 | 25 |
| Cross-povidone | 8 | 8 | 8 |
| Directly compressible mannitol | 80 | 80 | 80 |
| Microcrystalline cellulose | 52 | 52 | 52 |
| Aspartame | 6 | 6 | 6 |
| Magnesium stearate | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 |
| Total weight of each tablet | 195 | 215 | 180 |

**Table 1:** Composition of ODT.

was determined by formula as below and drug concentration in the tablet was measured [9,10].

Percentage of formulation= Absorbance of individual drug in sample formulation × 100/Absorbance of Standard formulation

Acceptable limits were found to be 99-101%.

## Results

The present study was carried out to develop ODTs of three different formulations, F1, F2 and F3 containing two different APIs by the direct compression method.

### Preformulation study

Amlodipine besylate, hydrochlorothiazide and telmisartan possessed similar color, odor and texture as stated in USP 2016. The melting point of amlodipine besylate, hydrochlorothiazide and telmisartan were found to be 178˚C, 265˚C and 260˚C respectively by capillary fusion method.

### Pre-compression parameters

The angle of repose, bulk density, tapped density; Hausner's ratio and Carr's index are shown in Table 2.

### Post-compression parameters

Post-compression parameters like weight variation, thickness, diameter, hardness, friability, disintegration and wetting time are shown in Table 3.

### Dissolution rate profile

Percentage release of amlodipine besylate, telmisartan and hydrochlorothiazide from formulations F1, F2 and F3 are shown in Figure 1.

### Dissolution efficiency

Percentage dissolution efficiency of amlodipine besylate, telmisartan and hydrochlorothiazide from formulations F1, F2 and F3 are shown in Figure 2.

### Accelerated stability studies

Formulations F1, F2 and F3 were stored in an aluminium blister packs and subjected to 40 ± 2°C/75 ± 5% RH and 50 ± 2°C/75 ± 5% RH for six months. The content of formulations was determined and dissolution was carried out as per ICH guidelines as shown in Tables 4 and 5. The percentage loss on drying of all formulations is shown in Table 6. All parameters were found to be satisfactory. From this, we concluded that the active ingredients were stable in the formulations.

## Discussion

Several people are suffering from hypertension comprising of hypertensive phenotypes for which combination therapy has been suggested. The therapy should provide pharmacologic action on two or more different physiologic sites and is expected to be more effective. The results of the present study for hypertension combination therapy formed as ODT composed of amlodipine besylate that

| Formulations | Precompression parameters | | | | |
|---|---|---|---|---|---|
| | Angle of repose (Θ) | Bulk density (g/mL) | Tapped density (g/mL) | Hausner's ratio | Carr's index (%) |
| F1 | 27.02 ± 0.02 | 0.31 ± 0.85 | 0.46 ± 0.06 | 1.5 ± 0.19 | 32.61 ± 0.64 |
| F2 | 33.42 ± 0.1 | 0.32 ± 0.05 | 0.51 ± 0.76 | 1.6 ± 0.08 | 37.25 ± 0.78 |
| F3 | 26.10 ± 0.38 | 0.32 ± 0.62 | 0.54 ± 0.33 | 1.7 ± 0.87 | 40.74 ± 0.91 |

**Table 2:** Evaluation of powder blend.

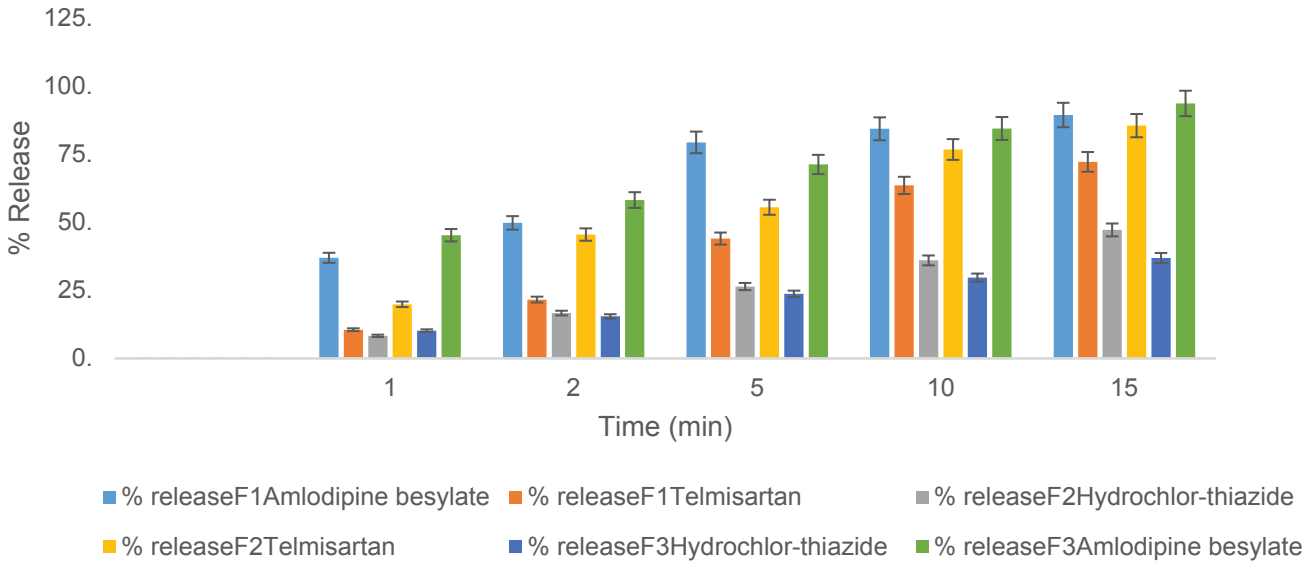


**Figure 1:** Drug release profile.

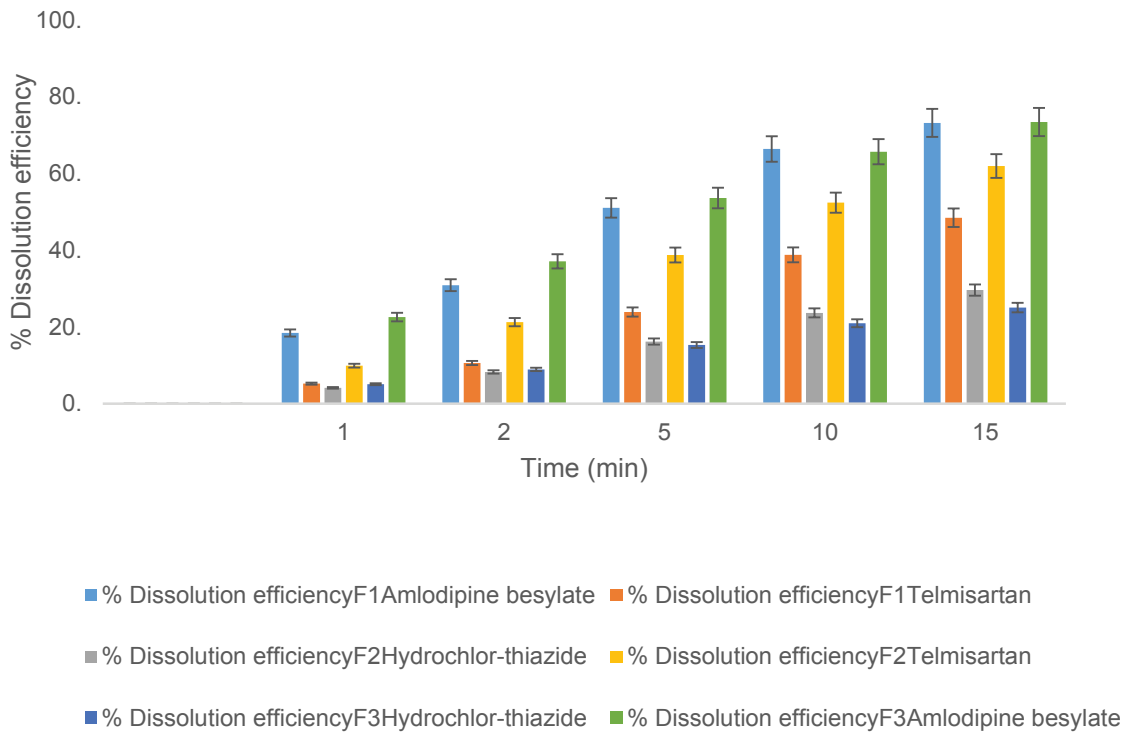


**Figure 2:** % Dissolution efficiency.

| Test Parameter | Formulation | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Weight variation (mg) | 195 ± 5 | 215 ± 5 | 180 ± 5 |
| Hardness (kg/cm$^2$) | 4.33 ± 0.5 | 5.33 ± 0.5 | 4.66 ± 0.5 |
| Friability (%) | 0.315 ± 0.7 | 0.681 ± 0.4 | 0.337 ± 0.9 |
| Thickness (cm) | 0.2 ± 0.1 | 0.3 ± 0.1 | 0.2 ± 0.1 |
| Diameter (cm) | 0.8 ± 0.1 | 0.8 ± 0.1 | 0.8 ± 0.1 |
| Disintegration (s) | 9 ± 2 | 12 ± 2 | 7 ± 2 |
| Wetting time (s) | 20 ± 3 | 25 ± 2 | 17 ± 4 |

**Table 3:** Evaluation of tablet.

| Test Parameter | Formulation | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Color | White | White | White |
| Odor | No | No | No |
| Friability (%) | 0.426 ± 0.5 | 0.731 ± 0.5 | 0.451 ± 0.6 |
| Hardness (kg/cm$^2$) | 4.30 ± 0.5 | 5.29 ± 0.5 | 4.53 ± 0.5 |
| Disintegration time (s) | 8 ± 2 | 10 ± 2 | 9 ± 2 |
| Drug content (%) | 100.75 ± 0.25 | 99.47 ± 0.23 | 99.83 ± 0.27 |
| % Drug release | 75.53 ± 0.34 | 64.48 ± 0.29 | 62.67 ± 0.32 |

**Table 4:** Stability study of formulations F1, F2 and F3 at 40±2°C/75±5% RH after 6 months.

acts as CCB, telmisartan acts by blocking angiotensin II receptors and hydrochlorothiazide as a diuretic. By controlling elevated blood pressure, it will also help to prevent complications related to cardiovascular. The rationale behind the combination therapy is to control blood pressure by acting multiple mechanisms of actions.

The multidrug antihypertensive combination was used to develop a new formulation of ODT with a combination drug therapy by adopting the conventional approach of direct compression in much simpler

| Test Parameter | Formulation | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Color | White | White | White |
| Odor | No | No | No |
| Friability (%) | 0.435 ± 0.5 | 0.811 ± 0.5 | 0.561 ± 0.6 |
| Hardness (kg/cm$^2$) | 4.28 ± 0.5 | 5.11 ± 0.5 | 4.49 ± 0.5 |
| Disintegration time (s) | 7 ± 2 | 9 ± 2 | 8 ± 2 |
| Drug content (%) | 99.85 ± 0.25 | 99.13 ± 0.23 | 99.54 ± 0.27 |
| % Drug release | 72.42 ± 0.37 | 62.53 ± 0.36 | 60.42 ± 0.32 |

**Table 5:** Stability study of formulations F1, F2 and F3 at 50 ± 2°C/75 ± 5% RH after 6 months.

| Formulation | 3 months at 40±2°C/75±5% RH | 6 months at 40±2°C/75±5% RH |
|---|---|---|
| F1 | 5.23 ± 0.2 | 4.84 ± 0.3 |
| F2 | 6.49 ± 0.3 | 7.23 ± 0.2 |
| F3 | 8.57 ± 0.2 | 8.91 ± 0.3 |

**Table 6:** Loss on drying percentage at different time intervals.

and cost-effective manner. This will aid the availability of economical and patient compliant product for efficient pharmaceutical therapy. Formulations F1 and F3 showed excellent and F2 showed a good flow of pre-compressed powder. Using direct compression technique this powder blend was compressed and evaluated for physical properties which are shown in Table 3. On performing post-compression studies all 3 formulations were found to be disintegrated within 15 s with a medium as phosphate buffer pH 6.8 and wet-ting time was found to be less than 30 s. The hardness was in the range of 4.33-5.33 kg/cm$^2$ and the friability of all the formulations were found to be within 1%. The thickness and diameter of all 3 formulations were found to be 0.2-0.3 cm and 0.8 cm. From dissolution rate profile is was found out that F1 showed 80.7 ± 0.5% whereas F2 showed 66.285 ± 0.3%

and F3 showed 65.182 ± 0.7% of drug release within 15 min. The % dissolution efficiencies of F1 were found to be 60.84 ± 0.5%, F2 with 45.79 ± 0.2% and F3 with 49.25 ± 0.3%. On performing stability studies, the formulations were found to be stable under accelerated conditions.

## Conclusion

Multidrug ODTs with combinations of amlodipine besylate, hydrochlorothiazide and telmisartan were prepared by direct compression method. All three formulations were disintegrated within 15 s. All other physicochemical parameters were within limits. So, combination therapy is useful to treat hypertension with a diuretic, CCB and angiotensin II receptor antagonist drugs. Hence, this combination therapy may serve an important role in antihypertensive treatment.

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