Research Article

# Formulation and Evaluation of Orally Disintegrating Tablets of Amlodipine Besylate Using Novel Co-Processed Superdisintegrants.

**P.V. Kamala Kumari*, Y. Srinivasa Rao, A. Lakshmi Devi, P.N. Mallikarjun**
Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India.
***Corresponding author's E-mail:** kamalaparavastu@gmail.com

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**ABSTRACT**

The demand for orally disintegrating tablets (ODT) has been growing the last decade especially for elderly and children who have swallowing difficulties. Amlodipine besylate is 3-Ethyl 5 methyl 2- (2-aminomethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3, 5-dicarboxylate monobenzene sulphonate.[1] Oral bioavailability of Amlodipine besylate is around 60% and having a half life of 30 to 35 hrs. In the present study an attempt was made to formulate oral disintegrating tablets of amlodipine besylate with a view to achieve a better disintegration and dissolution rate and further improving the bioavailability of the drug and increase the convenient means of administration to those patients suffering from angina pectoris. Oral disintegrating tablets (ODT) of Amlodipine besylate using natural superdisintegrants, synthetic superdisintegrants and coprocessed excipients were prepared by direct compression method. The superdisintegrants used in the study were crosspovidine and fenugreek seed powder in varying concentrations.[2] The prepared tablets were evaluated for pre and post compression parameters such as flow properties, hardness, friability, disintegration time, wetting time, estimation of drug content and *in vitro* drug release studies. The optimized formulation showed the minimum disintegration time of 16 secs and release maximum amount of drug in 30 min. Short term stability studies indicated no significant changes in hardness, friability, *in vitro* disintegration time, drug content and *in vitro* drug release.

**Keywords:** ODTs, Amlodipine besylate, superdisintegrants, coprocessed excipients, Angina pectoris.

## INTRODUCTION

Amongst the various routes of drug delivery, oral route is the most preferred by patients and clinicians.

Amongst all the oral administered dosage forms, tablets are the most preferred because of ease of administration, compactness and flexibility in manufacturing.[3-5]

Because of changes in various physiological functions associated with aging, including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy.

The pediatric and geriatric patients are of particular concern.

To overcome this, a renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose.

Orally disintegrating tablets may show greater patient acceptability and convenience. Orally disintegrating tablets can be defined as *"A solid dosage form containing medicinal substances which disintegrates rapidly, usually within few seconds, when placed upon the tongue".*

These products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids.[6,7]

According to the USFDA's Guidance for Industry, products labeled as ODTs should match the primary characteristics for this dosage form such as tablets must disintegrate rapidly in the oral cavity, with an *in-vitro* disintegration time of approximately 30 seconds or less, when based on the United States Pharmacopeia (USP) disintegration test method or an alternative method.

Tablets that take longer than 30 seconds to disintegrate or are dosed with liquids may be more appropriately considered to be chewable or oral tablets.

The weight of the tablet should not exceed 500 mg; however, if a tablet intended for use as an ODT weighs more than 500 mg, its ability to perform effectively as an ODT should be justified based on product performance.

**An Ideal ODT should meet the following criteria**

1. Must not require water for oral administration.

2. It should disintegrate and dissolve in the oral cavity within few seconds.

3. Should have sufficient strength to withstand the rigors of the manufacturing process.

4. Post-manufacturing handling.

5. Should allow high drug loading.

6. Should have a pleasant mouth feel.

7. Should be insensitive to environmental conditions such as humidity and temperature.

8. Should be adaptable and amenable to existing processing and packaging machineries.

## MATERIALS AND METHODS

### Infrared Absorption Spectrum

The Infrared absorption spectrum of Amlodipine was recorded with a KBr disc over the wave No. 4000 to 400 $cm^{-1}$.

### Identification of Pure Drug

Identification of Amlodipine besylate was carried out by Infrared Absorption Spectroscopy.

### Melting Point Determination

Melting point of Amlodipine besylate was determined by Open capillary Method.

### Post Formulation Studies

Amlodipine besylate ODTs were prepared by using natural superdisintegrants, synthetic super disintegrants and co processed excipients by direct compression method.[8,9]

### Preparation of Fenugreek Powder

It was a natural superdisintegrant and it is scientifically known as "*Trigonella fenugraceum*" commonly known as "fenugreek" is an herbaceous plant of *Leguminaceae.* It is one of the oldest cultivated plants and has found wide applications as a food additive and as a traditional medicine in every region.[10,11] Fenugreek seeds contain a high percentage of mucilage which can be used as disintegrant for use in orally disintegrating tablets. Mucilage is off-white cream yellow colored amorphous powder that quickly dissolves in warm water to form viscous colloidal solution.

The seeds are dried for removing moisture after that they are grinded in a mixer and the powder was sieved with sieve no.#40. The powder sealed in a box and used as a superdisintegrant in the formulations.

### Preparation of Co-processed Superdisintegrants

The co-processed Superdisintegrants were prepared by solvent evaporation method. A blend of Crospovidone and fenugreek seed powder was added to 10 ml of ethanol.[12-14] The contents of the beaker were mixed thoroughly and stirred continuously till most of ethanol evaporated. The wet coherent mass was granulated through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60° C for 20 minutes. The dried granules were sifted through # 60 mesh sieve and stored in airtight container till further use.

### Direct Compression method for Tablet Preparation

Oral disintegrating tablets of Amlodipine besylate were prepared by direct compression method as shown in Table 1. For formulations F1 to F6 all the ingredients were passed through # 60 mesh separately.[15] Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg using tablet compression machine and for formulations F7 to F9 all the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg using tablet compression machine.

### Formulation

**Table 1:** Formulae of Amlodipine besylate orally disintegrating tablets

| S. No | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Amlodipine besylate(mg) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2 | Crospovidone | 2 | 4 | 6 | - | - | - | - | - | - |
| 3 | Fenugreek seed powder | - | - | - | 2 | 4 | 6 | - | - | - |
| 4 | Crosspovine + fenugreek | | | | | | | 2 | 4 | 6 |
| 5 | Mannitol | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 6 | Micro crystalline cellulose | 26 | 24 | 22 | 26 | 24 | 22 | 26 | 24 | 22 |
| 7 | Sodium saccharine | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 8 | Magnesium stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9 | Talc | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total wt of tablet (mg) | | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

### Evaluation of Tablets:

### Pre-compression Parameters

Angle of Repose, Bulk density and Tapped density, Hausner ratio, Carr's Compressibility index (%) were carried out as per standard procedures and observed for their compliance with standard values.

### Post-compression Parameters

#### *Shape and appearance*

Tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light.

***Uniformity of thickness*[16]**

Thickness and diameter of both core tablets and coated tablets were measured using a calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated.

***Hardness*[17]**

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in $Kg/cm^2$. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

***Friability***

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). Four tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The percentage friability was then calculated by,

$$F = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

***Weight Variation***

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

***Drug Content Uniformity***

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 10 ml of methanol was added and then the solution was subjected to sonication for about 1 hours. The solution was made up to the mark with methanol. The solution was filtered and suitable dilutions were prepared with medium. The drug content was estimated by recording the absorbance at 239 nm by using UV-Visible spectrophotometer.

***Wetting Time***

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

***Water Absorption Ratio*[18]**

It was tested by using double folded tissue paper and the petri dish contains 6ml of Saliva buffer pH 6.8. Firstly randomly taken tablets form the all formulations weight was calculated it was denoted as Wb and then the tablets were allowed to place on the tissue paper. After completely wet of the tablet weight was calculated and it was denoted as Wa. And by using the following formula water absorption ratio (R) was measured.

$R = 100 \{ (Wa – Wb) / Wb \}$

where,

Wb = Weight of tablet before absorption

Wa = Weight of tablet after absorption.

***In vitro dispersion time***

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a fast dissolving tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

***In vitro disintegration time***

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37°±2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In vitro dissolution studies***

Dissolution rate was studied by using USP type-II apparatus (LAB INDIA DS-8000 at 25 rpm) using 500ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of dissolution medium was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 239 nm and concentration of the drug was determined from standard calibration curve.

***Dissolution Efficiency Studies***

The dissolution efficiency (DE) of the batches was calculated as the area under the dissolution curve between time points $t_1$ and $t_2$ expressed as a percentage

of the curve at maximum dissolution over the same time period or the area under the dissolution curve up to a certain time t (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[19]

**Stability studies**

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

In the present study, the ODTs where packed in a suitable packing material and stored under the following conditions for a period of 90 days at 40±1°C and RH 75±5%.

The tablets were withdrawn after period of 15, 45, and 90 days and analysed for physical characterization (visual defects, hardness, friability, disintegration, dissolution, etc) and drug content.

## RESULTS AND DISCUSSION

The present study was aimed at formulating ODTs of Amlodipine besylate. This is a novel approach for increasing the patient compliance with a faster onset of action as compared to the conventional formulation mainly used at present.

**Identification of Amlodipine besylate**

**FTIR Studies**

FTIR is one of the most widely used methods for checking the compatibility between substances and for the identification of drug. Amlodipine besylate, super disintegrants, excipients and the selected formulation were analyzed using infrared spectrophotometer.

All the samples were scanned at the resolution of 4 cm-1 over the wave length region 4000-400 $cm^{-1}$ using KBr disk method.

This KBr disks are formed by taking drug and KBr in a ratio of 1:100 respectively.

Then this mixture was mixed well in motor for three to five minutes. A very small amount of this mixture was uniformly spread and sandwich between the pellets and pressed using KBr pellet press at a press of 20.000 psi for 1 min. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region.

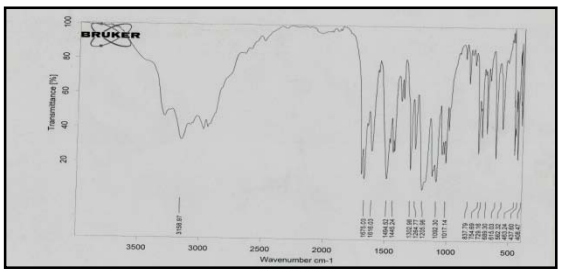


**Figure 1:** FTIR of Amlodipine besylate

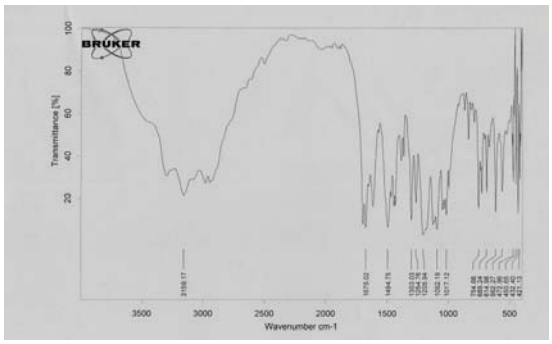


**Figure 2:** FTIR of Amlodipine besylate and fenugreek seed powder

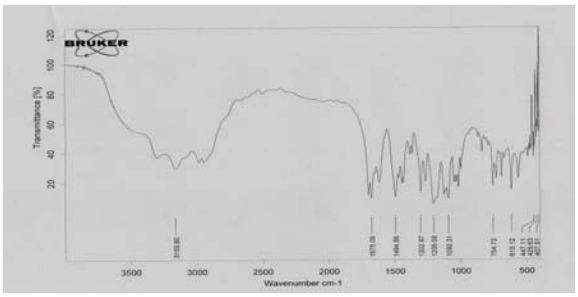


**Figure 3:** FTIR of Amlodipine besylate and crospovidone

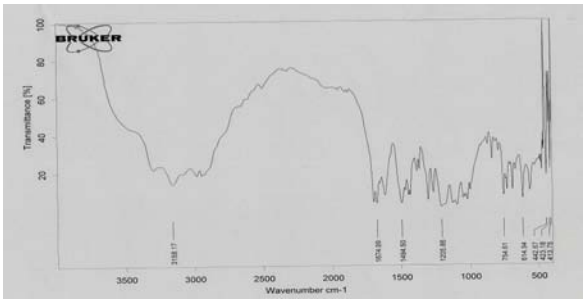


**Figure 4:** FTIR of Amlodipine besylate, crospovidone and fenugreek seed powder

The possible interaction between the drugs and the excipients was studied by FTIR spectroscopy. IR spectra of showed characteristic peaks at 3159.80 $cm^{-1}$ (unsubstituted have two bands, NH group stretch), 1675.99 $cm^{-1}$ (strong C=0 carbonyl bond stretch), 1494.75$cm^{-1}$ [weak multiple bands C=C stretch].

- ✓ The FTIR spectra of Amlodipine showed prominent peaks at 3158.97$cm^{-1}$ (unsubstituted have two bands, NH group stretch), 1675.03 $cm^{-1}$ (strong C=0 carbonyl stretch), 1494.52$cm^{-1}$ (C=C stretch). (Figure 1)
- ✓ The FTIR spectra of Amlodipine and crospovidone showed prominent peaks at 3159.80$cm^{-1}$ (unsubstituted have two bands, NH group stretch), 1675.09 $cm^{-1}$ (strong C=0 carbonyl stretch), 1494.56$cm^{-1}$ (C=C stretch). (Figure 2)
- ✓ The FTIR spectra of Amlodipine and fenugreek seed powder showed prominent peaks at 3159.17$cm^{-1}$ (unsubstituted have two bands, NH group stretch), 1675.02 $cm^{-1}$ (strong C=0 carbonyl stretch), 1494.75$cm^{-1}$ (C=C stretch). (Figure 3)

- ✓ The FTIR spectra of Amlodipine and coprocessed superdisintegrant showed prominent peaks at 3158.17cm$^{-1}$ (unsubstituted have two bands, NH group stretch), 1674.99 cm$^{-1}$ (strong C=0 carbonyl stretch), 1494.50cm$^{-1}$ (C=C stretch). (Figure 4)

## EVALUATION

### Preformulation Studies of Pure Drug

#### *Identification of Drug*

The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum Amlodipine given in British pharmacopoeia.

#### *Melting Point Determination*

Melting point of Amlodipine besylate was found to be in the range of 178-179 °C with decomposition as reported in pharmacopoeia, thus indicating purity of the drug sample.

#### *Pre-formulation parameters*

The angle of repose of all the formulations were found to be in the range of 24.34 to 25.28 thus falling in the official limit range of 25$^{o}$ to 30$^{o}$ which indicates that all the formulation blend have excellent flow property. Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed. The loose bulk density was found to be in the range of 0.47 to 0.520 gm/cm$^{3}$ and tapped bulk density was found to be in the range of 0.542 to 0.611 gm/cm$^{3}$. Hausnerratios of entire formulation showed 1.15 to 1.17 thus indicating that formulation have good flowing property which is ideal for ODTs. Carr's consolidation index or compressibility index (%) for the entire formulations were ranged from 13.2 to 15 which lies in the official limits i.e. 11 to15, indicating the blend has good flow property for compression.

### Post Compression Evaluation Parameters

#### *Shape and Appearance*

Formulations prepared were randomly picked from each batch examined under lens for shape and in presence of light for color. Tablets showed standard concave surfaces with circular shape. Tablets were white and light yellow in color.

#### *Hardness*

Tablet crushing strength, the critical parameter was controlled as the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage, depends on its hardness. Hence, hardness for all formulation batches prepared was found to be between 3.2 to 4.0 Kg/cm$^{2}$. This ensures good handling characteristics of all batches

#### *Average Weight*

As material was free-flowing, tablets were obtained of uniform weight due to uniform die fill with acceptable variation as per I.P. standards. The weight variation was found in all designed formulations in the range 98.01 to 100.3 mg. All the tablets passed weight variation test as the average percentage weight variation was within ±10% i.e. in the pharmacopoeia limits.

#### *Friability*

To achieve % friability within limits for an Oral disintegrating tablet is a challenge to the formulator since all methods of manufacturing of Oral disintegrating tablet are responsible for increasing the % friability values. The % friability values for all formulation batches prepared was found to be between 0.40 and 0.69 %. Thus all the formulations was less than 1% ensuring that the tablets were mechanically stable.

#### *Uniformity of Thickness*

Thickness of the tablets was measured using calibrated dial calipers by picking three tablets randomly from all the batches. The results of thickness for tablets are shown in Table 3. The mean thickness of all formulations of batches between 2.1 mm to 2.45 mm. The standard deviation values indicated that all the formulations were within the range.

#### *Drug content Uniformity*

The percentage of drug content for all formulation was found to be 95.9 to 99.2 which lie in the IP limit.

#### *Wetting Time*

The values of wetting time were found to be in the range of 38 to 124 seconds. The wetting time is least for F9, so it will release the drug faster than other formulations.

#### *in vitro Dispersion Time*

*In vitro* dispersion time was found to be in the range of 47-58 seconds.

#### *in vitro Disintegration Test*

This is the most important test with respect to ODT formulations. Among all formulations F9 was selected as the best formulation as it gave the least *in vitro* disintegration time of 16 seconds.

#### *in vitro Dissolution Studies*

All the selected formulations which passed the *in vitro* disintegration test were subjected to *in vitro* release studies using IP dissolution apparatus in 6.8 phospate buffer. Depending on the *in vitro* disintegration test formulation F9 was selected as optimized formulation.

F9 formulation released the maximum amount of drug 99.24% (Figure 5, Figure 6, and Figure 7). These results are in tune with those obtained for the disintegration time for the respective formulation.

#### *Accelerated Stability Studies*

The selected formulation F9 was subjected to accelerated stability studies and the formulation where evaluated for appearance, hardness, friability, drug content, *in vitro*

disintegration time and *in vitro* dissolution test. The formulations were stored at different conditions. All the formulations were analyzed after every 30, 65, and 90 days. All the formulations show no change in all the above parameters thus successfully passes the accelerated stability study which was conducted for 90 days.

### Dissolution Studies

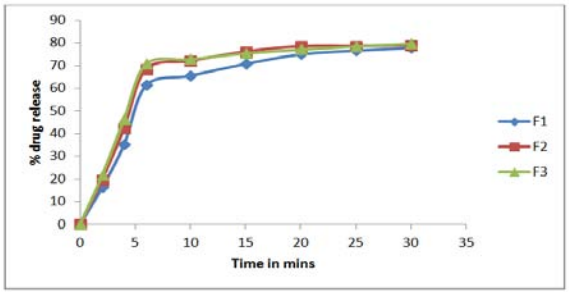


**Figure 5:** Zero Order Release Plots For Formulations F1, F2, F3

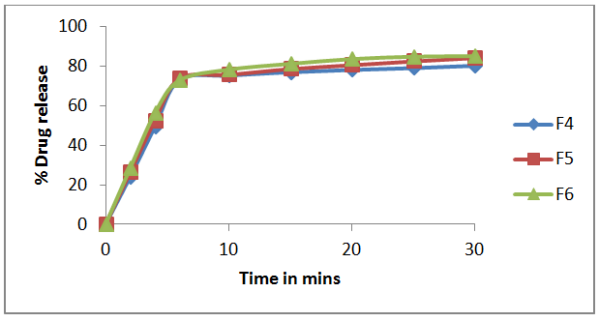


**Figure 6:** Zero Order Release Plots for Formulations F4, F5, F6

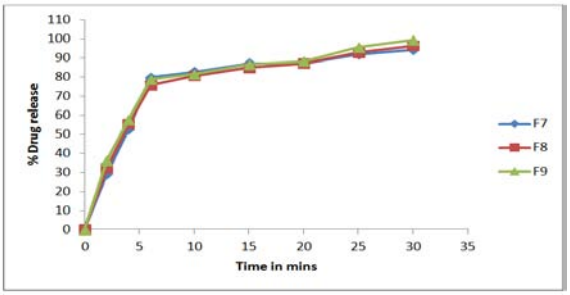


**Figure 7:** Zero Order Release Plots For Formulations F7, F8, F9

### Stability Studies

Optimized formulation was exposed for accelerated conditions as per ICH guidelines. The stability study was carried out at 40°C/75% RH for formulation F9 up to 3 months. At every 1 month time interval, the devices were analyzed for drug content uniformity and *in vitro* drug release. The results of accelerated stability study showed that there was no change in the formulation after one month. *In-vitro* drug release study showed that after 1, 2 and 3 months; values obtained were 99.24%, 98.48% and 97.62% respectively. After 1 month accelerated stability study the assay result was stable.

## CONCLUSION

In the present study, an attempt was made to prepare ODTs of Amlodipine besylate to increase its dissolution by its faster disintegration and finally improves its bioavailability.[20] The ODTs of Amlodipine besylate were prepared by direct compression method. In this dosage form natural superdisintegrants, synthetic superdisintegrants and co processed superdisintegrants in different ratios are used. The data obtained from this study reveals that use of co-processing of superdisintegrants significantly enhance the Dissolution & Disintegration of Amlodipine tablet than that of alone superdisintegrants. Specially the effects of co-processed superdisintegrants have better potential than other superdisintegrants having disintegration time in 16sec and release maximum amount of drug 99.24%. It showed no significant changes in physicochemical properties, drug content, disintegration property and *In vitro* dissolution pattern after storage at at 40±2°C / 75±5% RH during stability studies for three months. Thus, the objective of the present investigation to design and prepared ODTs of Amlodipine was achieved.

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