Original Article

Formulation and Stability Studies of Fast Disintegrating Tablets of Amlodipine Besylate

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ABSTRACT

Introduction: Among tablets, fast dissolving technology has gained considerable popularity due to their rapid onset of action. Amlodipine besylate (ADB) is a long-acting calcium channel blocker that is used in the treatment of angina and hypertension which are life-threatening conditions and require immediate relief. Currently, no fast dissolving tablet dosage form of ADB is commercially available. **Methods:** A total of seven fast disintegrating tablets of Amlodipine besylate (ADB) have been prepared by direct compression method employing various excipients (Disintegrants and binders) in different concentrations. Pre-compression and post-compression studies were performed along with the storage in the stability chambers under real (30 ± 2°C / 65 ± 5% RH) and accelerated conditions (40 ± 2°C / 75 ± 5% RH) for six months. The assay of ADB was performed using a validated UV spectrometric method at 361 nm. **Results:** The release of ADB from tablets has been found to be very fast with almost more than 85% drug released within 15 min. The release of drug from all the tablet formulations followed Higuchi model. **Conclusion:** The use of sodium bicarbonate as super disintegrant has greatly promoted the rapid release of the active drug. The binder has been shown to affect the tensile strength of the tablets. The stability studies for six months in aluminum blister packaging indicated no significant change in concentration in the majority of the formulations. This study provides basic groundwork related to the formulation of fast disintegrating tablets of ADB.

Key words: Amlodipine besylate, Direct compression, Drug release, Fast disintegrating tablets, Model dependent and independent methods, Pre-compression and post-compression studies.

INTRODUCTION

The tablet dosage form is one of the most popular and widely preferred drug delivery systems due to the advantages both to the manufacturer and the patient.[1,2] Among the different types of tablets available, fast dissolving technology has gained considerable popularity for the last two decades due to its ability to release the drug much quicker than the conventional drug delivery systems.[3,4] Fast disintegrating tablets, also called as core immediate-release tablets, are employed for a quicker response or therapeutic effect at the site of action. They can be prepared by different techniques such as direct compression,[4,5] lyophilization or sublimation,[6,7] effervescent method[8] and direct molding method.[9,10]

Amlodipine (AD) is a dihydropyridine calcium channel blocker, which is used alone or in combination with other medicines for the treatment of chronic stable angina, certain types of vasospastic angina and in the management of mild to moderate essential hypertension.[11,12] More prolonged half-life, high volume of distribution and gradual elimination highlight AD from other agents of this class. Amlodipine besylate (ADB) is a sparingly soluble orally administered drug

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with slow absorption as the rate of absorption is often controlled by the rate of dissolution.[4,11,13,14] Various salts of AD have been prepared, e.g. besylate, mesylate, maleate, etc. However, whichever salt is used, the strength of the dosage form is always determined with respect to AD.[12] Among all the salts available, the most commonly employed form is besylate, which is known to have better solubility than AD alone.[15,16]

Various strategies have been employed to increase the bioavailability of AD which includes the development of new formulations, use of different excipients and formulation techniques, etc.[17] Presently, no fast disintegrating tablet dosage form of AD is available in the market. The object of the present work is to develop fast disintegrating tablets of ADB that will increase the rate of dissolution of AD after oral administration. This study would help in improving the release characteristics and bioavailability of the drug. The study would involve the use of various disintegrants along with other excipients for the formulation of fast disintegrating tablets to achieve rapid disintegration and release. A number of parameters including compatibility, disintegration, dissolution, bulk and tap density, etc. would be studied to examine the appropriateness of the formulated tablets. The stability studies of the prepared dosage form would be carried out according to the guideline of the International Council for Harmonization (ICH).[18] This study would help the pharmaceutical scientists in the development of a stable and effective dosage form that could be used in emergency conditions like angina pectoris for rapid therapeutic effect.

MATERIALS AND METHODS

Materials

ADB (99%) was procured from Amsal Chem Pvt. Ltd. (India). Microcrystalline cellulose (Avicel PH-102) from JRS Pharma (Germany), dibasic calcium phosphate anhydrous ($CaHPO_4$) from Reephos Chemicals, (China), povidone K-30 (M_r 40,000–80,000) from Ash Land Pvt. Ltd. (USA), sodium bicarbonate ($NaHCO_3$) from Tata Chemicals Ltd. (India), sodium starch glycolate from Yung Zip Chemical Industries Company Ltd. (Taiwan) and magnesium stearate from Peter Greven GmbH and Co. KG (Germany). Freshly boiled glass-distilled water was used throughout the work. All other solvents and reagents used in the study were of analytical grade obtained from BDH / Merck.

Formulation of Fast Disintegrating Tablets of Amlodipine Besylate

On the basis of various ADB formulations reported in the literature,[4,19–23] a general formula for the formulation of fast disintegrating tablets was developed, which is presented in Table 1. In order to evaluate the effect of various formulation ingredients on the physico-chemical properties of the fast disintegrating tablets, six other formulations of ADB were prepared with varying concentration of the disintegrants and binder (Table 2). The concentration of each excipient was selected according to the ranges provided in the Handbook of Pharmaceutical Excipients[24] and IIG (Inactive Ingredients) Limit of Food and Drug Administration.[25]

Confirmation of the Purity

The pure powdered samples of the drug and excipients were subjected to FTIR spectrometry for the determination of their purity. Before analysis, each sample was thoroughly ground and mixed in a mortar and pestle for 5 min. The spectra were collected using an FTIR spectrometer (Spectrum One, Perkin Elmer, USA) through Universal Attenuated Total Reflection (UATR) diamond crystal sampling assembly. Each spectrum was collected in a range of 4000–650 cm^{-1} by performing 64 scans with a 4 cm^{-1} resolution and analyzed using the built-in Spectrum One software (version 6.2.0).

Formulation of Tablets by Direct Compression Technique

All the ingredients were passed separately through a sieve of mesh size 40 via an oscillator. The sieved drug and sodium bicarbonate were mixed together for 5 min in a bin blender (Thuf Engineering KIA, Karachi, Pakistan). Subsequently, all other excipients were added to this mixture one by one with a mixing time of 5 min each. The tablets of 200 mg (±3%) weight were prepared by direct compression using a compression machine (D type 16-station D3B, Manesty, England) at a speed of 12 rpm.

Packaging

All formulations were packed in Alu-Alu (Aluminum) blisters (Chinese Blister Machine, Taiwan). Each blister was placed in a secondary container which was a plain carton containing the formulation information.

Leakers Test

Randomly two consecutive cuts from the blister machine in doublet for each formulation were selected and subjected to leakage test (Model LT-101P, Electro Lab, India). The blisters were placed in the instrument containing 0.5% methylene blue solution as indicator. The perforated polypropylene discs were placed over the sample to avoid floating. The vacuum pressure was set at 200 mm Hg with a holding time of 1 min. The blisters were taken out and dried with a lint-free cloth.

The leakage of the blisters was checked visually by opening the samples and observing the color of the dye inside the blister.

Pre-Compression Studies

The blended mixture of powders was evaluated for various parameters such as.

Bulk and Tapped Density

A pre-weighed 100 ml empty cylinder was filled with the blended powder (i.e. ADB + excipients) up to the highest mark. The cylinder was weighed again without tapping. The cylinder was then manually tapped on a smooth surface 100 times from a height of 10 cm with a 2 s interval. It was weighed repeatedly after every 25 taps and the volume occupied was recorded. The procedure was repeated thrice for every formulation and the mean result was calculated. The bulk and tapped densities of the blended powders were calculated by using the following formulae:[26]

$$\text{Bulk density} = \frac{W_2 - W_1}{V_1}$$

$$\text{Tapped density} = \frac{W_2 - W_1}{V_2}$$

W_1 is the weight of the empty cylinder;
W_2 is the total weight (cylinder + powder);
V_1 is the total volume of the powder (untapped);
V_2 is the total volume of the powder (tapped).

Carr's Index or Compressibility Index

The % compressibility of the powdered material was calculated as follows:[26]

$$C = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio

Hausner Ratio (HR) was calculated by the following formula:[26]

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose

The blended powder was passed through a funnel that was attached vertically to a stand until a maximum cone height (H) was obtained. The diameter of the heap (D) was measured and angle of repose (θ) was calculated by the following formula:[26]

$$\tan(\alpha) = \frac{\text{Height}}{0.5\ \text{Base}}$$

Post-Compression Studies

The core tablets were evaluated for various quality control tests which are described as follows.

Organoleptic Studies

All formulations were evaluated for their organoleptic properties throughout the study including appearance (color, shape and size) and odor.

Weight Variation

A total of 20 tablets were selected randomly from each formulation and average weight was determined. Each tablet was then weighed individually and compared with the average weight and the deviation was calculated.[26]

Thickness and Breaking Force of the Tablets

The thickness and breaking force of the tablets were measured using a digital hardness testing instrument (PTB 111EP, Pharma Test, Germany). Thickness was measured in mm while breaking force was recorded in kilo poise unit.

Friability

The friability of the core tablets from each formulation was measured using an automated Friabilator (EF-2, ElectroLab, India) according to the method described in British Pharmacopoeia.[26] Since the weight of each tablet is 200 mg, therefore, a number of tablets equivalent to 6.5 g (i.e. ~33 tablets) were placed in the plastic chamber of the instrument. The chamber was rotated at a speed of 25±1 rpm for 4 min. (i.e. 100 rotations) and the tablets were dropped from a height of 6 inches on each rotation. The friability of each formulation was determined in triplicate and calculated using the following formula:

$$F = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Disintegration Test

The disintegration time for all tablets was determined according to the method described in British Pharmacopoeia.[26] A total of 6 tablets were placed individually in each tube of the disintegration apparatus (PTZ-S, Pharma Test, Germany) and the discs were placed over the tablets to avoid floating. The disintegration medium was distilled water maintained at a temperature of 37±2°C. The instrument was run until no solid mass was observed in any tube and the time was noted. The

disintegration time of each formulation was determined in triplicate.

Drug Assay

The assay was performed spectrometrically according to the method of Dahima *et al*.[27] and Ghenge *et al*.[22] Due to change in assay wavelength and use of different formulation ingredients, the method was validated prior to its application according to the guideline of ICH.[18]

A total of 20 pre-weighed tablets from each formulation were powdered in a mortar with the help of a pestle and an amount equivalent to 10 mg was weighed accurately. The weighed powder was dissolved in 100 ml of methanol. From this stock, 1 ml was taken and further diluted to 10 ml with methanol. The solution was filtered using Whatman No. 40 filter paper (Schleicher and Schuell, UK). The first few ml of the filtrate were discarded and the remaining were collected in a screw cap tube and closed tightly to prevent evaporation of the solvent. The drug content was analyzed spectrometrically (UV-1601, Shimadzu, Japan) at 361 nm using quartz cells of 10 mm path length and the concentration was calculated using the following formula:

$$\text{Concentration} = \frac{\text{Absorbance} \times \text{dilution factor}}{\text{A (1\%, 1 cm)} \times \text{1 cm}}$$

$$\%\ \text{Recovery} = \frac{\text{Concentration found}}{\text{Concentration added}} \times 100$$

Content Uniformity

A total of 10 tablets from each formulation were selected randomly. Each tablet was powdered finely in a mortar with pestle and an amount equivalent to 10 mg was taken and assayed as described above.

Dissolution Studies

The release rate of ADB from each formulation was determined by 7 vessels dissolution testing apparatus II (Paddle method) (PT-DT70, Pharma Test, Germany). The dissolution test was performed using 900 ml of 0.01 N HCl (pH 2.0) at 37±0.5°C. The Teflon paddles were rotated at a speed of 50 rpm for 15 min. A 5 ml sample of the solution was withdrawn after every 3 min interval and an equivalent amount of the dissolution medium was added to maintain the sink conditions. The samples were filtered through 0.45 μ membrane filter (Micropore, USA), the absorbance was measured at 361 nm and the drug content was determined as described in the assay section. The dissolution profiles of the test formulations were compared with the conventional tablets of ADB purchased from the local pharmacy.

Model-Dependent Method

The dissolution profiles of different formulations of the same drug are described by the model dependent methods which are based on different mathematical calculations.[28–31] In order to evaluate the appropriate drug release kinetic model illustrating the dissolution profile of the formulations, different model dependent methods have been used and are as follows:

Zero-order: $C_0 - C_t = k_0 t$

First-order: $\ln (C_0 / C_t) = kt$

Higuchi: $C_t = k_H t^{1/2}$

Hixson-Crowell: $C_0^{1/3} - C_t^{1/3} = kt$

Korsmeyer-Peppas: $C_t / C_0 = kt^n$

where C_0 = initial concentration;

C_t = concentration at time t;

k_H = Higuchi dissolution constant;

k = release rate constant;

n = slope.

Model-Independent Method

The dissolution similarities have been evaluated by calculating similarity factor, f_2, at different time intervals using the following equation:[32,33]

$$f_2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

where n= The number of time intervals;

R = The dissolution value of the standard at time t;

T = The dissolution value of the test at time t.

Stability Studies

All blister packed tablet formulations of ADB were stored in a stability chamber at 30±2°C/65±5% RH (Model YWER-A1001P, Dongguan Yuanyao Electronics Technology Co., Ltd., China) and 40±2°C/75±5% RH (Model NEC 2530RS, Newtronic Lifecare Equipment Pvt. Ltd., India) for six months. Each formulation was assayed at 0, 1, 2, 3, 4, 5 and 6 months of storage in triplicate.

RESULTS AND DISCUSSION

Confirmation of the Purity of Amlodipine Besylate and Excipients

The purity of ADB and excipients was confirmed by FTIR spectrometry. The spectra of pure drug and excipients are reported in the supplementary file (S- Figures 1–7). All spectra of the pure compounds were found identical to the reference standards indicating that the chemicals were of the highest purity.

Formulation of the Tablets

Fast disintegrating tablets of ADB have been prepared by direct compression method (Table 2). The concentration of ADB has been kept constant in each formulation i.e. 13.86 mg, which is equivalent to 10 mg of AD while varying concentrations of the binder and disintegrants have been used (Table 2). Each ingredient was selected on the basis of its suitability in the formulation. The formulations have been studied for various pre-compression and post-compression parameters that are discussed in the following sections.

Pre-Compression Studies

Flow and Compressibility Properties

Flowability of any powder is important for producing a uniform blend and consistent dosage forms having similar masses.[34,35] Physical properties of the powder are found to have more impact on its flowability as compared to chemical properties. A total of seven fast disintegrating tablets have been formulated. The flow and the compression ability of the powder mixtures have been analyzed by determining the angle of repose, tapped and bulk density, Carr's index and Hausner's ratio and are reported as follows:

Angle of Repose

Although the angle of repose (θ) is not a direct measure of powder flowability still it is used widely. Powders having θ values of greater than 50°C are considered to have unsatisfactory flow whereas a value near to 25°C makes them good free-flowing material.[35] In this study, all formulations showed an average θ of around 37°C indicating a moderate flow pattern of blended powders in all the formulations (Table 3).

Tapped and Bulk Density

Tapped and bulk densities are not only required to determine powder compressibility but they are also important in the overall tableting process as they are related to the correct mechanical strength, porosity and dissolution characteristics.[34,35] The tapped and bulk densities of all the formulations have been found to be close to each other indicating good flow and compression properties (Table 3).

Carr's or Compressibility Index

The simplest way of measurement of the compressibility of a blend of different excipients and drug is through Carr's or compressibility index, which is an indication of the ease with which a material can be compressed.[4,36] The values of compressibility index are reported in Table 3 that indicate average flow behavior

Table 1: A general formula for the formulation of ADB tablets (standard).

Ingredients	Percentage (*w/w*)
Active Pharmaceutical Ingredient	
Amlodipine besylate	6.93[a]
Diluents	
Microcrystalline cellulose	59.57
Dibasic calcium phosphate anhydrous	22.50
Disintegrants	
Sodium bicarbonate	5.0
Sodium starch glycolate	3.0
Binder	
Povidone K-30	2.0
Lubricant	
Magnesium stearate	1.0

[a] Equivalent to 5% of AD.

Table 2: Different formulations of fast dissolving tablets of ADB.

Ingredients	mg per tablet						
	Standard	F1[a]	F2[a]	F3[a]	F4[a]	F5[a]	F6[a]
Amlodipine besylate[b]	13.86	13.86	13.86	13.86	13.86	13.86	13.86
Microcrystalline cellulose[c]	119.14	121.14	117.14	121.14	117.14	123.14	115.14
Dibasic calcium phosphate	45	45	45	45	45	45	45
Sodium bicarbonate	10	10	10	10	10	6	14
Sodium starch glycolate	6	4	8	6	6	6	6
Povidone K-30	4	4	4	2	6	4	4
Magnesium stearate	2	2	2	2	2	2	2
Total weight[c]	200	200	200	200	200	200	200

[a]F= Formulation.
[b]13.86 mg of ADB is equivalent to 10 mg AD.
[c]The total weight of each formulation was adjusted by the change in the concentration of microcrystalline cellulose.

Table 3: The pre-compression parameters for the powder blends of various formulations of ADB.

Parameters	Formulations						
	Standard	F1	F2	F3	F4	F5	F6
Angle of repose (θ)	37.14°	37.14°	38.23°	36.02°	37.14°	36.38°	36.86°
Bulk density(g/ml)	0.4782	0.4456	0.4566	0.4621	0.4535	0.4580	0.4581
Tapped density (g /ml)	0.6550	0.6365	0.6254	0.6508	0.6298	0.6366	0.6190
Compressibility index (%)	26.99	29.99	26.99	28.99	27.99	28.05	25.99
Hausner's ratio	1.36	1.42	1.36	1.40	1.38	1.39	1.35

Table 4: The post-compression parameters of all tablet formulations of ADB.

Parameters	Formulations						
	Standard	F1	F2	F3	F4	F5	F6
Thickness (mm)	3.58-3.61	3.61-3.63	3.62-3.65	3.56-3.61	3.59-3.62	3.58-3.63	3.60-3.63
Weight variation (mg)	197-202	195-202	195-203	197-206	195-205	196-204	195-203
Breaking force (Kp)	10.6-12.2	13.4-14.3	10.9-11.3	13.7-14.8	14.5-15.4	14.1-15.1	10.4-10.9
Friability (%)	0.05	0.03	0.04	0.07	0.02	0.06	0.09
Disintegration time (s)	13	12	13	13	12	18	10
Content uniformity (%)	94-99	92-101	94-105	96-109	95-104	91-100	91-106

of the blends, which has been found adequate for the formulation of uniform dosage units.

Hausner's Ratio

Another important parameter used to determine powder compressibility and flowability is the Hausner ratio. A ratio of greater than 1.6 indicates cohesive and less free-flowing powders whereas values less than 1.6 or around 1.2 points towards more free-flowing powders.[35] In this study, the ratios for all formulations have been found in the range of 1.35–1.42 indicating good flow and compression properties of the powder blends (Table 3).

Post-Compression Studies

Organoleptic Studies

The fast disintegrating tablets of ADB have been evaluated for their organoleptic properties such as color, shape, size and odor either alone or in comparison with each other. Organoleptic studies are considered important for identification, stability and consumer acceptance.[37] All formulations appeared white in color with oval shape, plain from both sides and odorless indicating uniformity in all batches. A shade card was used to visually identify any color variations. No change in color as well as in appearance has been observed for any formulation at the time of tableting as well as during storage. Similarly, no odor has been sensed for any formulation throughout the course of the study.

Weight Variation of the Tablets

The weight of the tablets determines that a tablet is being made with the proper amount of drug.[37] All core tablets must comply in weight with the tolerance limit given in the official compendia. In this study all fast disintegrating tablets of ADB have been prepared with a total weight of 200 mg (Table 2). According to British Pharmacopoeia[26] and the United States Pharmacopeia,[38] the variation allowed for tablets of such weight is ±7.5%. The average percent variation found in the tablets of each formulation is within ±3% indicating good flowability of the powdered blends from the hopper to dies (Table 4).

Thickness of the Tablets

The consistent thickness of the tablets within the same or different batches is an indication of adequate blending with uniform tooling during the compression process. Moreover, the thickness is an important quality control test for tablet packaging as very thick tablets

Table 5: Validation data for the analysis of ADB by UV spectrometric methoda.

Parameter	Data
λ_{max}	361 nm
Molar absorptivity (ε)	5.98×10^{3} M^{-1} cm^{-1}
A (1%, 1 cm)	110
Linearity	
Range	0.3–1.0×10^{-4} M (1.70–5.67 mg%)
Correlation coefficient	0.99966
Slope	5984
Intercept	0.01772
SE[b] of slope	0.00411
SE[b] of intercept	0.00455
SD[c] of intercept	0.01204
Recovery range (%)[d]	98.91–101.74
Accuracy (%)[e] ± SD[c]	100.03 ± 0.9630
Precision (%RSD)[f]	0.9627
LOD[g] (M)	6.64×10^{-6}(0.38 mg%)
LOQ[h] (M)	2.01×10^{-5}(1.14 mg%)

a *n* = 5.
b SE = standard error.
c SD = standard deviation.
d Recovery (%) = (amount found / amount added) × 100, where amount found was calculated from: (mean absorbance of 5 determinations – intercept) / slope.
e Accuracy (%) = Mean recovery range.
f %Relative standard deviation = (SD / Mean) × 100.
g Limit of Detection = 3.3 × (SD of intercept / slope).
h Limit of Quantification = 10 × (SD of intercept / slope).

affect packaging either in blister or plastic containers.[37] Generally, tablets are required to be kept within a variation of ±5%.[37] All formulations in this study showed identical thickness with values in the range of 3.56–3.65 mm, indicating consistent manufacturing process (Table 4).

Tablet Breaking Force and Friability

The mechanical integrity of a tablet to withstand mechanical shocks of handling during manufacture, packaging and shipping can be determined by its breaking force/hardness and through friability test.[37,38] The strength of a tablet plays a vital role in its dissolution and bioavailability as well as in marketing.[37,39] The highest tablet breaking force of 15.4 Kp has been found in tablets formulated with an increased amount of the binder (Povidone K-30), i.e. formulation 4 (Table 4). On the contrary, the lowest tablet breaking force has been observed in formulation 6, i.e. 10.4 (Table 4). It is interesting to note that the amount of povidone is minimum in formulation 3 but still the lowest breaking force has been observed in formulation 6. This could be due to the presence of a high amount of sodium bicarbonate and low amount of microcrystalline cellulose in addition to povidone as compared to formulation 4 (Table 2). Microcrystalline cellulose is also known to have binder properties[24] whereas sodium bicarbonate is a super disintegrant and is known to affect tablet compaction.[40]

Along with the breaking force, it is important that a core tablet must possess a certain amount of resistance to friability in order to withstand mechanical stresses to chipping and surface abrasion.[37,38] Similar results to that of tablet breaking force have been noted in the friability test. All formulations showed a friability of less than 0.1% indicating the excellent resistance of the formulations to mechanical stresses (Table 4). The highest friability has been observed in tablets of formulation 6 while the lowest in formulation 4 (Table 4).

Disintegration Test

The disintegration of tablets is an important parameter to ensure lot-to-lot uniformity.[37] It is used as a quality assurance tool to confirm complete disintegration of solid oral dosage forms within the recommended time period when placed in a liquid medium under the investigational conditions as described in the particular official monographs.[26,38]

Magnesium stearate is known to cause a delay in tablet disintegration.[24] Therefore, it was used in an equal concentration in all the formulations to nullify any hindrance in the disintegration of the tablets. All tablets of ADB have been found to disintegrate within 20secs indicating towards the rapid availability of the active drug for absorption (Table 4). Formulation 6 has been found to be the quickest of all showing a disintegration time of only 10 secs, which is due to the presence of highest amount of super disintegrant i.e. 14 mg of sodium bicarbonate (Table 2).

Validation of the assay method

The assay of pure ADB and its fast disintegrating tablets has been performed spectrometrically at a wavelength of 361 nm. The method has been validated according to the guideline of ICH18 and the data are reported in Table 5. The calibration curve and overlay spectra of ADB are reported in Figure 1. The active drug has been calculated with reference to the parent molecule i.e. 13.86 mg of ADB is equivalent to 10 mg of AD. The method has been found to be accurate and precise for the assay of ADB either alone (Table 5) or in tablet dosage form (Table 6). None of the excipients have been found to interfere with ADB at the assay wavelength of 361 nm indicating the selectivity of the assay method for the active drug. A typical UV of spectrum of fast

Table 6: Accuracy and precision of the proposed method for the assay of ADB from tablet dosage form.

Formulation	Amount labeled (mg)	Amount found (mg)[a,b]	Recovery (%)[a,b]	Mean recovery (%) ± SD	Relative accuracy error (%)[c]	RSD (%)
Standard	10	9.81	98.14	99.35±0.637	–1.21	0.641
1	10	9.97	99.69		+0.34	
2	10	9.92	99.16		–0.19	
3	10	9.98	99.80		+0.45	
4	10	9.90	98.99		–0.36	
5	10	9.99	99.89		+0.54	
6	10	9.98	99.81		+0.46	

[a] *n* = 3.
[b] The formula for amount found and recovery are same as in Table 5.
[c] Relative accuracy error (%) = (Recovery – Mean recovery)/ (Mean recovery) × 100.

disintegrating tablets of ADB is shown in dotted line in Figure 1b.

Content Uniformity

Uniformity of content in each unit is one of the most concerned requirements of a tablet dosage form. All quality control parameters would be considered void if the tablet-to-tablet distribution of the drug substance is not uniform. The uniformity of the dosage units largely depends on the formulation process. Therefore, process design needs to be implemented in a manner that must provide correct potency and little content variability. Weight variation test is considered acceptable if the drug is present in an amount excess of 25 mg.[38] In this study, the weight of active drug in all the formulations is less than 25 mg, therefore, content uniformity test has been performed to check the distribution of ADB. The results showed that all randomly selected tablets of each formulation have been prepared with uniformity in their content and the active drug is found to be within ±15% limit (Table 4) indicating acceptable manufacturing process.

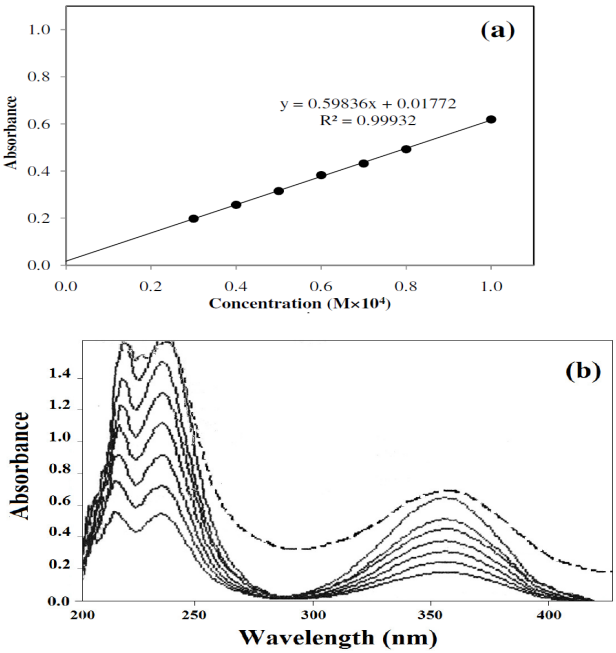

Figure 1: The calibration curve (a) and overlay spectra (b) of ADB. The dotted line in (b) indicates the spectrum of ADB in fast disintegrating tablets.

Dissolution Studies

The rate of drug absorption and its efficacy is related to the dissolution of the tablet. Therefore, it is important to estimate the amount of the drug that would be released from the tablet when placed in an environment of GIT37. There are many factors that can impact the rate at which a tablet disintegrates and the drug substance dissolves. These factors can be grouped into two broad categories, i.e. drug substance and drug product factors. For drug substance factors, salt form, polymorphic form, particle size, and surface area all play an important role in the dissolution of the drug. For drug product factors, the dissolution will be affected by the formulation process (granulation, etc.) and the excipients used.[41]

In this study, all fast disintegrating tablets showed a drug release of greater than 70% within 6 min (Table 7). On the contrary, at the same time, the conventional immediate release tablets of ADB showed a release of only ~48% at the same time (Table 7). This indicates that the formulated fast disintegrating tablets are much more efficient in drug release as compared to the conventional release tablets of ADB (Figure 2). The amount of disintegrant present in the tablet has been found to play an important role in the release of the drug.

Table 7: Comparison of percent release of ADB from fast disintegrating tablets versus its conventional release commercial tablets.

Time (min)	Cumulative drug release (%) ± SD[a]							
	Commercial Tablet	Standard	F1	F2	F3	F4	F5	F6
3	26.02±2.952	47.05±4.777	45.34±5.557	47.62±3.676	47.85±4.111	44.45±4.604	41.90±3.061	51.10±2.564
6	47.68±5.913	76.38±3.898	74.39±3.569	77.24±3.551	75.58±3.726	72.66±3.907	70.54±3.087	82.35±2.431
9	64.48±2.898	85.48±5.107	83.88±2.615	86.44±4.244	84.95±4.320	82.54±4.648	79.64±2.382	90.50±2.176
12	76.66±1.354	88.55±3.933	87.41±2.822	89.75±3.863	88.78±4.542	85.93±3.631	83.44±1.875	93.75±2.157
15	82.44±3.786	90.14±3.599	89.11±2.496	91.45±3.234	90.80±3.760	87.65±3.575	85.19±1.551	95.35±1.675

a $n = 6$ for each formulation.

Table 8: Model dependent methods and determination of coefficients of linearization of ADB release for different formulations.

Formulations	Time (min)	Model Dependent Methods									
		Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas	
		k_0	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	k_{KP}	R^2
Conventional	03	2.46	0.954	0.195	0.997	1.50	0.977	0.250	0.993	0.176	0.884
	15	0.117		5.74		2.10		0.008		3.03	
Standard	03	1.76	0.776	0.109	0.932	2.71	0.952	0.156	0.887	0.104	0.796
	15	0.067		0.0030		2.30		0.0046		0.947	
F1	03	1.83	0.776	0.114	0.937	2.60	0.957	0.163	0.895	0.10	0.801
	15	0.073		0.0033		2.28		0.0048		0.936	
F2	03	1.74	0.778	0.107	0.943	2.71	0.953	0.153	0.896	0.105	0.796
	15	0.060		0.0027		2.33		0.0040		0.957	
F3	03	1.74	0.784	0.106	0.950	2.76	0.958	0.153	0.904	0.106	0.795
	15	0.067		0.0030		2.30		0.0044		0.947	
F4	03	1.85	0.791	0.117	0.933	2.56	0.958	0.166	0.892	0.097	0.802
	15	0.086		0.0040		2.23		0.0060		0.915	
F5	03	1.93	0.797	0.125	0.927	2.42	0.959	0.170	0.889	0.091	0.807
	15	0.10		0.0047		2.18		0.0073		0.894	
F6	03	1.63	0.763	0.097	0.961	2.95	0.947	0.140	0.906	0.113	0.790
	15	0.03		0.0014		2.43		0.0020		1.000	

Among all the tablets, formulation 6 has been found to be the quickest and formulation 5 as the slowest in drug release as compared to other formulations, which is due to the highest and lowest amount of super disintegrant (sodium bicarbonate) present in these formulations, respectively (Table 2). Similar patterns of release with respect to the concentration of another disintegrant (sodium starch glycolate) and binder (povidone K-30) have been observed in the remaining formulations but with less significant differences in the rate of release (Figure 2). Model-dependent release methods have been applied to the dissolution profile of the standard and other prepared formulations (F1–F6) (Table 8). The results obtained from these models indicate that all formulations follow Higuchi model as the best fit. The regression values (R^2) for all fast disintegrating formulations have been obtained in the range of 0.947 to 0.959 (Table 8). After Higuchi model, the second best fit model was found to be first-order where R^2 values are in the range of 0.927 to 0.961 (Table 8). In the case of conventional release tablets of ADB, first-order model has been found to be the best fit for its release (Table 8). The similarity factor (f_2) between the standard and other prepared formulations has also been calculated and is

reported in Table 9. According to FDA,[42,43] model-independent approach is better to compare the dissolution profile of different formulations of the same drug. The values obtained for the test tablets (F1–F6) are compared with the standard formulation and the data interpretation has been made by a simple evaluation method. If the f_2 values are in the range of 50 to 100, the dissolution profile for the test formulations is considered to be similar to the reference or standard formulation.[32,33] All values are found to be greater than 50 and are in the range of 61.37–99.40 (Table 9), which indicates that the formulations prepared with varying excipient concentration have same dissolution profile as compared to that of the standard formulation. However, the f_2 values of F5 and F6 are found to be lower as compared to the others (F1–F4) which could be due to the different concentration of super-disintegrant (sodium bicarbonate) in the prepared formulations to those of the standard tablets (Table 2). On the contrary, the comparison of all seven test formulations with the conventional release tablets of ADB showed f_2 values of less than 50 indicat-

Table 9: The f_2 values for standard (Std) and other prepared formulations (F1–F6) of ADB.

Time (min)	f_2 Value					
	Std v/s F1	Std v/s F2	Std v/s F3	Std v/s F4	Std v/s F5	Std v/s F6
3	85.15	96.94	94.74	78.00	63.98	69.02
6	82.61	93.91	94.54	70.70	64.38	60.92
9	86.18	92.94	97.26	75.39	61.37	64.57
12	91.01	90.29	99.40	77.62	64.18	63.80
15	92.13	89.18	96.07	78.51	64.80	63.79

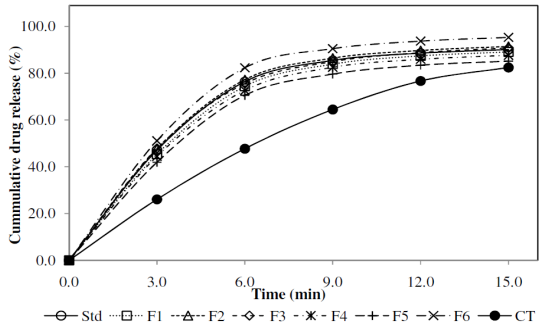

Figure 2: The release profile of ADB from fast disintegrating and conventional tablets (CT).

Table 10: Stability of ADB in different fast disintegrating tablets stored at real and accelerated conditions in Alu-Alu blisters for 6 months.

Time (months)	Formulation ± SD[a]													
	STANDARD		F1		F2		F3		F4		F5		F6	
	30° / 65%	40° / 75%	30° / 65%	40° / 75%	30° / 65%	40° / 75%	30° / 65%	40° / 75%	30° / 65%	40° / 75%	30° / 65%	40° / 75%	30° / 65%	40° / 75%
0	100.60 ±2.018	100.25 ±1.115	100.08 ±1.425	101.40 ±1.333	100.30 ±2.002	100.36 ±0.775	102.85 ±1.606	100.41 ±0.780	100.04 ±0.757	100.35 ±0.650	102.20 ±1.122	100.37 ±0.580	100.39 ±0.455	101.00 ±0.755
1	100.05 ±1.110	102.05 ±1.410	100.15 ±0.205	100.35 ±0.480	99.97 ±0.652	100.41 ±0.854	99.15 ±1.078	102.07 ±1.350	99.15 ±1.209	102.00 ±1.320	101.01 ±0.654	100.30 ±0.320	100.31 ±1.785	102.20 ±1.155
2	101.01 ±0.801	100.70 ±1.058	101.15 ±1.895	101.03 ±0.950	101.40 ±1.450	101.22 ±1.045	100.21 ±0.500	100.26 ±0.915	100.05 ±1.110	100.90 ±0.880	101.60 ±0.545	101.22 ±1.095	100.24 ±1.350	100.77 ±0.654
3	99.94 ±1.150	101.20 ±1.035	100.12 ±1.050	102.20 ±1.750	100.90 ±0.750	100.21 ±1.165	101.50 ±1.050	100.17 ±0.900	98.25 ±0.750	100.50 ±1.014	101.00 ±1.005	100.90 ±0.850	101.15 ±0.640	100.15 ±0.370
4	100.06 ±1.006	100.50 ±0.650	100.90 ±1.035	101.01 ±1.323	100.40 ±1.390	100.20 ±0.689	100.10 ±0.565	100.90 ±0.695	99.35 ±1.475	100.30 ±0.680	100.70 ±0.790	97.35 ±0.965	100.09 ±1.254	98.72 ±1.035
5	100.30 ±0.702	98.85 ±0.854	100.40 ±0.550	99.30 ±0.460	99.00 ±1.010	101.07 ±1.222	101.40 ±1.052	100.50 ±0.450	98.55 ±1.858	98.10 ±0.500	102.11 ±1.650	94.05 ±0.880	99.89 ±1.750	96.89 ±0.860
6	99.65 ±1.315	95.90 ±1.230	100.10 ±0.985	96.90 ±0.890	97.85 ±1.825	98.10 ±0.625	100.33 ±0.660	99.01 ±0.317	97.00 ±1.355	95.50 ±0.321	98.12 ±1.240	92.30 ±0.940	100.75 ±1.660	95.35 ±1.060

a n =3 for each formulation per month.

ing a significant difference between the releases of test and commercial tablets of ADB.

Stability Studies

Randomly, a number of tablets from each formulation packed in Alu-Alu blisters were selected and kept in the stability chamber at real time (30±2°C / 65±5% RH) and accelerated conditions (40±2°C / 75±5% RH). Prior to blistering, leakage test has been performed to make sure that the tablets are packed properly. Shelf-life of any dosage form is determined on the basis of 10% degradation of the active drug with respect to time.[34]

The assay data of the stability of ADB in fast disintegrating tablets indicated no concentration change in the standard as well as in formulations 1, 3 and 6 (Table 10). Around 2–3% loss has been observed in formulations 2, 4 and 5 after six months of storage at 30°C / 65% RH. This appears to be in the range of experimental error. Under accelerated conditions (40°C / 75% RH), all formulations including the standard showed a loss within 5%. Thus, a change in temperature under the same humidity conditions appears to affect the drug that undergoes degradation to various levels within 5%. This loss could be due to the effect of temperature on the drug in the presence of moisture which may involve some hydrolytic reaction[44] in the molecule and/or an effect of excipients under these storage conditions. However, this loss can be considered within the permitted value of shelf life (t_{90}) and the tablets are still acceptable for clinical use.

None of the tablets showed degradation of 10% or more at real and accelerated conditions after six months of storage (Table 8). The results indicated that all the fast disintegrating tablets of ADB are stable with the excipients of the formulations for a considerable period of time. Moreover, the Alu-Alu blisters are also found to be suitable for the packaging of fast disintegrating tablets of ADB.

CONCLUSION

The fast disintegrating tablets of ADB have been prepared by direct compression method. The study of pre and post compression parameters indicated a consistent manufacturing process that produced tablets with optimal physical characteristics. The excipients selected for the preparation of these tablets have shown an impact on the physicochemical characteristics of the formulations. All such effects are found to be concentration dependent; therefore, the use of optimum concentration of each excipient in the formulation is of highest consideration. The use of sodium bicarbonate as super disintegrant has greatly increased the disintegration and dissolution of the tablets resulting in the rapid release of the active drug. The binder has been shown to affect the tensile strength of the tablets. The stability studies at real and accelerated conditions for six months in aluminum blister packaging indicated no significant change in concentration in the majority of the formulations.

This study provides basic groundwork related to the formulation of fast disintegrating tablets of ADB. However, further work related to the bioavailability of ADB in such tablets would help in improving the formulation characteristics as well as its clinical efficacy. A detailed analysis of the degradation products formed during storage under normal and stressed conditions would also help in better understanding of the nature and mechanism of ADB degradation in the tablet dosage form and in the development of a formulation with optimum safety, stability and efficacy. Variations in the nature and content of excipients may further improve the physical and chemical characteristics of the tablets.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AD: Amlodipine; **ADB:** Amlodipine besylate; **HR:** Hausner ratio; **ICH:** International Council for Harmonization.

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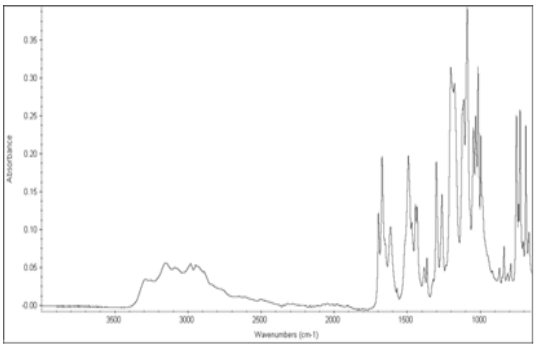
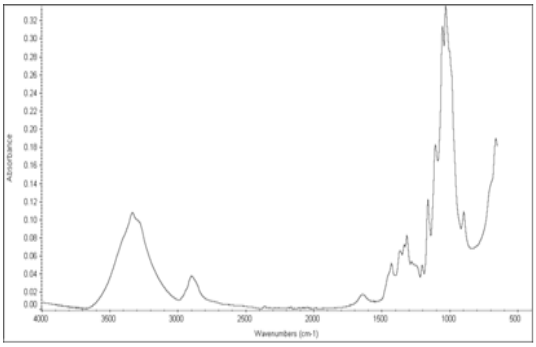
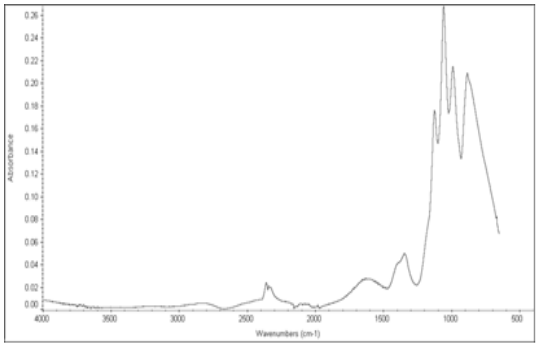


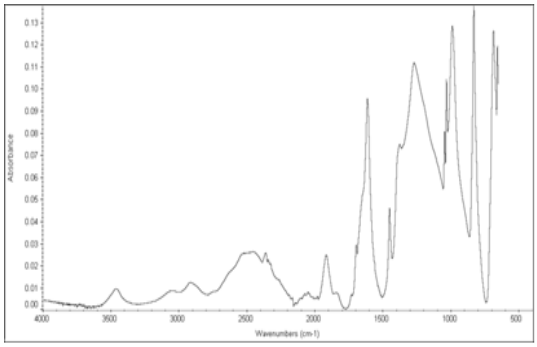
Supplementary Figure 1: FTIR spectrum of ADB.



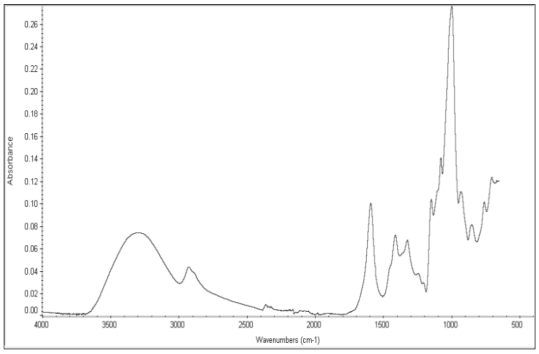
Supplementary Figure 2: FTIR spectrum of microcrystalline cellulose.



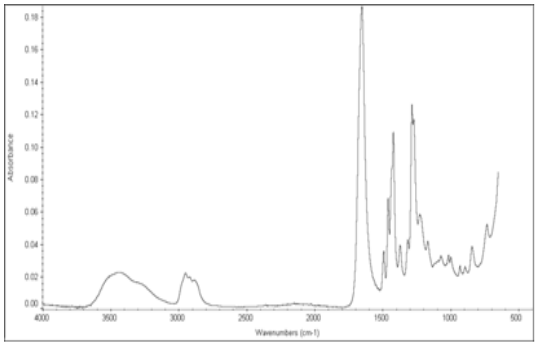
Supplementary Figure 3: FTIR spectrum of dibasic calcium phosphate anhydrous.



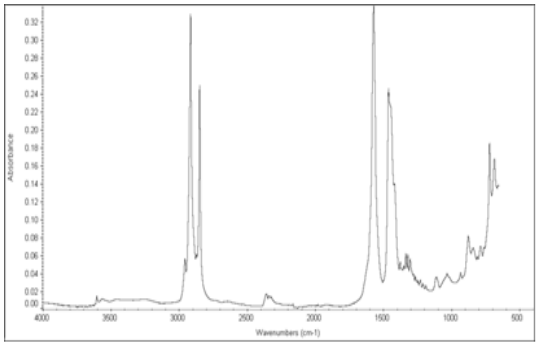
Supplementary Figure 4: FTIR spectrum of sodium bicarbonate.



Supplementary Figure 5: FTIR spectrum of sodium starch glycolate

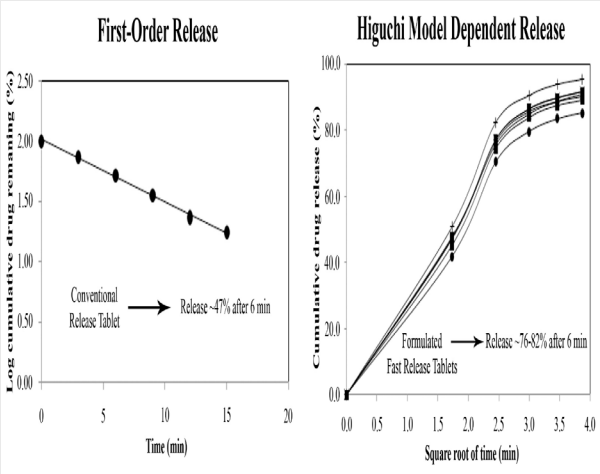


Supplementary Figure 6: FTIR spectrum of povidone K-30.



Supplementary Figure 7: FTIR spectrum of magnesium stearate.

PICTORIAL ABSTRACT



SUMMARY

- A total of seven fast disintegrating tablets of Amlodipine besylate (ADB) have been prepared by direct compression method employing various excipients (Disintegrants and binders) in different concentrations. The release of ADB from tablets has been found to be very fast with almost more than 75% drug released after 6 min as compared to only around 47% to the conventional tablets. The release of drug from all the tablet formulations followed the Higuchi model whereas the first-order release is being followed by the conventional tablets. The use of sodium bicarbonate as super disintegrant has greatly promoted the rapid release of the active drug. The binder has been shown to affect the tensile strength of the tablets. The stability studies for six months in aluminum blister packaging indicated no significant change in concentration in the majority of the formulations.

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