RESEARCH ARTICLE

Design of fast dissolving amlodipine besylate tablet formulations

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The demand for fast disintegrating tablets has been growing during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. Amlodipine besylate is used commonly for the treatment angina pectoris, commonly known as angina, which is chest pain due to ischemia of the heart muscle, generally due to obstruction or spasm of the coronary arteries. Hence, in the present work an attempt has been made to formulate fast dissolving tablets of amlodipine besylate by direct compression technique using various concentration of super disintegrants like cross carmellose sodium (Ac-Di-Sol), polyplasdone R-XL and sodium starch glycolate (SSG). The formulated tablets were evaluated for crushing strength, friability, thickness, diameter, weight variation, drug content, wetting time, water absorption ratio, disintegration time, and percentage of drug release. All formulations showed satisfactory result. Among them formulation F3 containing 3% of Ac-Di-Sol exhibited complete release within 12 minutes and disintegration time was within 10 seconds. Dissolution data was compared with innovator for similarity factor (*f2*) exhibited an acceptable value >50 (82). Accelerated stability study indicated no significant difference in assay and crushing strength. Hence, three production validation scale batches were designed based on lab scale best batch (F3) and charged for stability. All parameters were within the limit of acceptance. There was no chemical interaction between the drug and excipients during FT-IR study; considered in the present investigation.

Key words: *Amlodipine besylate, angina pectoris, fast dissolving tablet, innovator, validation scale batch*

INTRODUCTION

Oral drug delivery is the most widely utilized routes for administration that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage form. Among them the most popular solid dosage forms are tablets and capsules, which are simple and convenient to use. One of the important drawbacks of these dosage forms is difficulty to swallow for geriatric, pediatric, or psychiatric patients. Thus, great attention has been paid for designing of mouth dissolving drug delivery systems (MDDDS) with fast disintegrating and or dissolving properties to improve patient's compliance.[1] A fast dissolving tablet (FDT) system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in the form of liquid.[2,3] Recently, fast dissolving formulation is popular as novel drug delivery systems because they are easy to administer to the elderly patients and children having difficulty to swallow and also evident in travelling patients who may not have ready access to water.[4] As the tablet disintegrates in mouth, this could enhance the clinical effect of the drug through pre-gastric absorption through mouth, pharynx, and esophagus, as well as bioavailability of drug can be significantly increased by avoiding first pass liver metabolism.

Amlodipine besylate, chemically described as 3-Ethy l-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate monobenzene sulphonate,

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.100141

is a long-acting calcium channel blocker used in the treatment of chronic stable angina, vasospastic angina, and hypertension.[5,6] It inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Peak plasma concentrations are reached 6-12 hours following oral administration. Its estimated bioavailability is 64-90%. Numerous studies have been carried out for the designing and fabrication of FDT formulations using super disintegrants. Thus, an attempt has been made to formulate the FDT of amlodipine besylate by Ac-di-sol, polyplasdone R-XL, and sodium starch glycolate (SSG).

MATERIALS AND METHODS

Materials

Amlodipine besylate was procured from Zydus Cadila Healthcare Ltd, Ahmedabad, India. Cross carmellose sodium (Ac-Di-Sol) and SSG were purchased from Signet chemical corporation Mumbai, India. Polyplasdone R-XL was purchased from Orchid Healthcare, Chennai, India. Microcrystalline cellulose (Avicel-102), mannitol, and sodium saccharine were procured from SD Fine chemicals, Mumbai, India. Colloidal silicon dioxide (Aerosil-R 972) and glyceryl behenate were purchased from Tangmin industry Ltd, China. All chemicals and solvents used are of high analytical grade.

Method of preparation of FDT

Amlodipine besylate, Ac-di-sol, Polyplasdone R-XL, SSG, mannitol, and Avicel-102 were passed through #40 mesh and collected separately in polyethylene bag.[7] Direct compression technique was adopted for batch preparation of FDTs. The drug and diluents were mixed in a geometrical manner and blended for a period of 20 minutes. The resulted mixture lubricated with Aerosil-R 972 and with glyceryl behenate (sifted through #60 mesh) for 5 minutes in an octagonal blender (Mevish engineering, India). Finally the blend was compressed to formulate tablets using tablet compression machine (Cadmach Machinery Pvt. Ltd, India) with 6.5 mm circular flat punch. The composition of various formulations designed in the present study is given in Table 1.

Micromeritic properties of blended powder

Prior to compression, granules were evaluated for their micromeritic parameters.[8] Angle of repose was determined by funnel method. Bulk density (BD) and tapped density (TD) were determined by cylinder method, and Carr's index (CI) was calculated using the following equation:

$$CI = (TD-BD)/TD \times 100 \quad (1)$$

Hausner's ratio (HR) was calculated by the following equation:

$$HR = TD/BD \quad (2)$$

Physiochemical characterization of tablets

The physical properties such as crushing strength, friability, thickness, diameter, weight variation, drug content, wetting time, water absorption ratio and disintegration time for each formulation were determined.

Crushing strength

Tablet crushing strength was determined by randomly selected 10 tablets using a digital crushing strength tester (Erweka TBH-28) and the data reported is the mean of three individual determinations.[9]

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap, or break. Preweighed randomly selected twenty tablets were placed in a Roche friability tester and operated for 4 min at 25 rpm. Compressed tablets should not loose more than 1% of their weight.[10]

Thickness and diameter

Tablet thickness and diameter were measured by Vernier callipers (Mitatoyo, Japan).[11]

Weight variation

A weight variation test was performed according to USP30 NF25 on 20 tablets by taking samples from a batch after production of every 100 tablets and randomly from a total batch of 300 tablets using an electronic balance (Contech Instruments CA 224, India).[12]

Drug content

The drug content in terms of assay of each batch was determined in triplicate. For each batch, a number of 20 tablets were weighed and crushed to fine powder using mortar and pestle. An accurately weighed 10 mg of the powder was taken and suitably dissolved in methanol and analyzed by HPLC after making appropriate dilutions. The procedure was carried out on Shimadzu LC-10AT (Octadecylsilyl silicagel; 250 × 4.00 mm) with flow rate of 1.5 ml/minute at ambient temperature.

Wetting time and water absorption ratio

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 6.5 cm to that 10 ml of purified water containing an eosin dye solution (0.05% w/v) was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for dye to reach the upper surface of the tablet and to completely wet was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R = (W_a - W_b)/W_b \times 100 \quad (3)$$

Where W_a and W_b are tablet weight after and before water absorption, respectively.[12]

Disintegration time

Many reports suggest that conventional DT apparatus may not give correct values of DT for FDTs. FDT is required to disintegrate in small amounts of saliva within a minute without chewing the tablet. In a simplest method to overcome these problems, 6 mL of phosphate buffer of pH 6.8 was taken in a 25-mL measuring cylinder. Temperature was maintained at 37 ± 2°C. A FDT was put into it and time required for complete disintegration of the tablet was noted.[13]

In vitro dissolution study

The procedure was determined using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method).[14-15] The dissolution test was performed using 900 ml of 0.1N HCl (pH-1.2) at 37 ± 0.5°C and 50 rpm. A sample of 10 ml of the solution was withdrawn from the dissolution apparatus at 2 minute interval with the replacement of fresh dissolution medium for 20 minute. The samples were passed through a 0.45-μm membrane filter and diluted to a suitable concentration with phosphate buffer. The absorbance of these solutions was measured at 237 nm using a Shimadzu UV-1601 UV/V is double beam spectrophotometer.

Comparison of dissolution profile

The similarity factor ($f2$) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profile.[16] The dissolution profiles are considered to be similar when $f2$ is between 50 and 100. The dissolution profiles of product was compared to Innovator (Norvasc, Pfizer Ltd.USA) using $f2$ which was calculated from the following formula,

$$f2 = 50 \times \log \{[1 + (1/n) \sum_{t=1}^{n} | R_t - T_t |^2]^{-0.5} \times 100\} \quad (4)$$

Where, n is the number of dissolution sample times and R_t and T_t are the individual or mean percent dissolved at each time point, t, for the innovator and test dissolution profiles.[17]

Table 1: Composition of tablet formulations (mg)

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amlodipine besylate	10	10	10	10	10	10	10	10	10
AC-di-sol	2	4	6	-	-	-	-	-	-
Polyplasdone R-XL			-	2	4	6		-	-
SSG	-	-	-	-	-	-	2	4	6
Avicel-102	90	88	86	90	88	86	90	88	86
Mannitol	43	43	43	43	43	43	43	43	43
Sodium saccharine	1	1	1	1	1	1	1	1	1
Aerosil R 972	2	2	2	2	2	2	2	2	2
Sodium behenate	2	2	2	2	2	2	2	2	2
Total weight (mg)	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION

Micromeritic properties of blended powder

Result shows that all the formulations produced optimal flow properties calculated in terms of compressibility. Table 2 depicts micromeritic properties of the designed formulations. The angle of repose ranged from 27.38 ± 0.07 to 30.52 ± 0.09, which indicates optimal flow ability. In addition to that the tapped density and bulk density for all formulation granules ranged between 0.68 ± 0.02 to 0.73 ± 0.002 and 0.57 ± 0.04 to 0.61 ± 0.18, respectively, whereas Hausner's ratio was obtained between 1.16 to 1.21.

Physiochemical characterization of tablets

The physical properties of the designed tablets are presented in Table 3. These properties were studied by determining crushing strength, friability, thickness, diameter, weight variation, drug content, wetting time, water absorption ratio, and disintegration time. Crushing strength of prepared tablets ranged from 69.3 ± 0.73 newton to 72.7 ± 0.83 newton. The results were compared and concluded on the basis of amount of superdisintegrants and Avicel-102 used. It was observed that those formulations contained SSG exhibited higher hardness than others.[18] Moreover, the amount of Avicel-102 at 58% in all formulations showed higher crushing strength. The European and United States Pharmacopeia state that a loss up to 1% is acceptable for friability. Prepared tablets passed the friability test as values were ranged from 0.01% to 0.04% indicating the ability of tablet to withstand abrasion in handling packaging and shipment. The thickness for all tablets ranged between 2.80 ± 0.20 to 2.83 ± 0.25 mm and diameter was similar for all tablets. In a weight variation test, the pharmacopoeial limit for the percentage

Table 2: Micromeritic properties of prepared powder blend

Formulations	Bulk density	Tapped density	Angle of repose	Hausner´s ratio	Carr´s index
F1	0.58 ± 0.01	0.68 ± 0.02	27.72 ± 0.11	1.17	14.7
F2	0.59 ± 0.12	0.70 ± 0.01	28.23 ± 0.03	1.18	15.71
F3	0.60 ± 0.04	0.72 ± 0.11	29.45 ± 0.26	1.2	16.66
F4	0.59 ± 0.11	0.70 ± 0.23	28.31 ± 0.05	1.18	15.71
F5	0.61 ± 0.04	0.71 ± 0.03	30.26 ± 0.27	1.16	14.08
F6	0.57 ± 0.04	0.69 ± 0.12	28.46 ± 0.46	1.21	17.39
F7	0.59 ± 0.02	0.68 ± 0.04	27.38 ± 0.07	1.15	13.23
F8	0.60 ± 0.06	0.73 ± 0.002	29.45 ± 0.34	1.21	17.8
F9	0.61 ± 0.18	0.73 ± 0.24	30.52 ± 0.09	1.19	16.43

Data are represented as mean ± standard deviation (SD), n = 3

Table 3: Physical characterization of the designed formulations

Evaluation parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Crushing strength (Newton)	45.3 ± 0.73	49.8 ± 0.54	46.5 ± 0.71	47.3 ± 0.85	48.5 ± 0.46	47.9 ± 0.56	47.9 ± 0.61	50.7 ± 0.83	49.98 ± 0.92
Friability (% w/w)	0.02 ± 0.004	0.01 ± 0.002	0.02 ± 0.001	0.1 ± 0.021	0.03 ± 0.008	0.04 ± 0.08	0.03 ± 0.008	0.01 ± 0.07	0.03 ± 0.06
Thickness (mm)	2.81 ± 0.20	2.82 ± 0.22	2.80 ± 0.23	2.80 ± 0.20	2.82 ± 0.41	2.81 ± 0.27	2.82 ± 0.31	2.80 ± 0.28	2.83 ± 0.25
Diameter (mm)	6.50 ± 0.22	6.50 ± 0.24	6.50 ± 0.26	6.50 ± 0.21	6.50 ± 0.21	6.51 ± 0.19	6.50 ± 0.20	6.50 ± 0.29	6.50 ± 0.23
Weight variation (mg)	150.2 ± 0.31	150.2 ± 0.52	151.3 ± 0.27	151.7 ± 0.73	150.26 ± 0.23	151.6 ± 0.36	151.1 ± 0.42	150.3 ± 0.41	151.2 ± 0.56
Drug content (%)	99.78 ± 1.23	100.02 ± 0.98	101.3 ± 0.56	99.93 ± 0.99	100.17 ± 1.13	99.87 ± 1.03	99.93 ± 0.83	101.73 ± 0.92	100.48 ± 0.42
Wetting time (Sec.)	31 ± 0.34	25 ± 0.12	16 ± 1.02	35 ± 0.43	29 ± 0.72	21 ± 0.28	43 ± 0.48	33 ± 0.43	27 ± 1.01
Water absorption ratio (%)	80.21 ± 0.35	84.27 ± 0.73	90.12 ± 0.28	76.64 ± 1.01	82.11 ± 0.82	85.71 ± 0.29	69.46 ± 0.39	73.49 ± 0.52	77.46 ± 0.64
Disintegration time (Sec.)	28 ± 0.46	22 ± 0.83	10 ± 1.10	31 ± 1.03	24 ± 0.73	15 ± 0.94	36 ± 0.72	27 ± 1.02	21 ± 1.02
% Drug release (10 Mnt.)	78.12 ± 0.92	89.27 ± 0.62	99.73 ± 1.02	72.68 ± 0.78	79.18 ± 0.37	80.52 ± 0.28	66.59 ± 0.92	70.28 ± 0.47	80.36 ± 0.67

Data are represented as mean ± standard deviation (SD), $n = 3$

deviation for tablets of more than 150 mg is ± 3.5 %. The average percentage deviation of all tablet formulations was found to be within the above limit and hence all formulations passed the test for uniformity of weight as per official requirements. Average weight of each formulation tablets ranged from 150.2 ± 0.31 mg to 151.7 ± 0.73 mg. Uniformity in drug content was found among different formulations of the tablets, and the percentage of drug content was more than 99% in all cases. During this study various disintegrants were used at 1%, 2%, and 4% levels. The results shows that concentration dependent disintegration time was observed in batches prepared using superdisintegrants. Among them Ac-Di-Sol based formulations (F3 at 4% level) exhibited lesser disintegration time (10 ± 1.10 seconds). Because the fibrous nature of Ac-Di-Sol gives it out-standing water wicking capabilities and it cross-linked chemical structure creates an insoluble hydrophilic, highly absorbant material with good swelling properties, hence, it facilitates faster disintegration.[19] Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 69.46 ± 0.39 to 90.12 ± 0.28% and 16 ± 1.02 to 43 ± 0.48 seconds, respectively.[20]

In vitro dissolution study

Different grades of superdisintegrants ranging 1, 2, and 4 percentages were used to formulate FDT of amlodipinie besylate tablets and those formulations were subjected to *in vitro* drug dissolution studies. All formulation released 20% of drug within 2 minutes and 100% within 16 minutes. Formulations based on Ac-di-sol at 3% level showed complete release within 12 minutes, whereas polyplasdone and SSG-based formulations released complete drug within 14 and 16 minutes, respectively. Result showed that Ac-di-sol-based

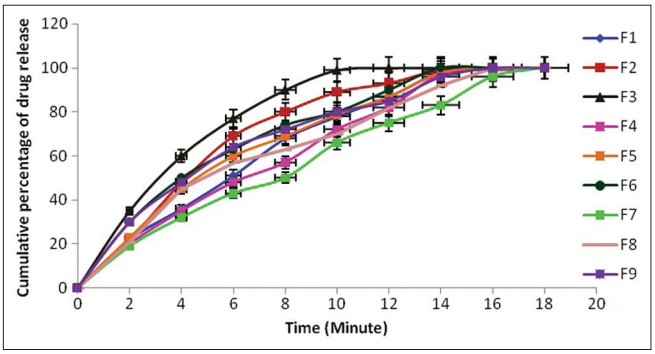

Figure 1: *In vitro* release profile of all formulations

formulations exhibited quicker drug release among all disintegrants. This could be due to higher water uptake and formation of channel in the tablet.[20] Hence, on the basis of above result, F3 was selected as promising formulation for further studies [Figure 1].

Comparison of dissolution profile

The dissolution profile of the selected formulation batch F3 was compared with the theoretical dissolution profile (Innovator, Norvasc; Pfizer Ltd.) using the similarity factor *f*2 test to assure the best batch. The results of the similarity tests showed that formulation F3 containing 4 percentage of Ac-di-sol had an *f*2 value > 50 i.e. 82, indicating the closest fit to the dissolution profile of innovator [Figure 2].

Drug polymer interaction study

The drug-excipient interaction were studied using FTIR (FTIR 8400S, Schimazu).[21,22] IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer with KBr pellets. The spectra were scanned over 3600-400 cm^{-1} range. It was found that there

was no chemical interaction between amlodipine besylate and excipients used as cited in Figures 3-5.

Stability study of best batch

Long term, intermediate, and accelerated stability testing were carried out based on the ICH guidelines considering 25 ± 2°C/60 ± 5% RH, 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH, respectively. One hundred tablets of batch F3 were securely packed in aluminium blister and placed in humidity chamber. The samples were evaluated for crushing strength and drug assay at a regular interval of 3 months during the study of 24 months. There was no significance change in crushing strength and drug assay as shown in Table 4. Thus, F3 formulation batch confirmed its stability.[23,24]

Stability study of production batch

From the above mentioned results, further studies like *in vitro* dissolution, comparison of dissolution profile, drug polymer interaction, and accelerated stability study, the batch number F3 was selected as optimized laboratory scale, which was subjected for production batch. Hence, reproducible production validation scale batches with same qualitative and quantitative composition of F3, namely F10, F11, and F12 containing each of 1000 tablets were prepared. Tablets were packed in Polyvinyl chloride/ Polyvinylidene chloride (PVC/ PVDC) and charged for stability testing according to ICH guidelines for the study of crushing strength, dissolution, loss on drying, presence of related substances, assay,

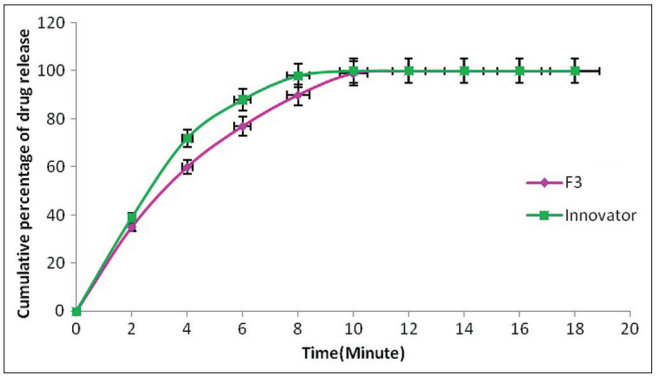

Figure 2: Comparative *in vitro* dissolution study between best batch (F3) and innovator

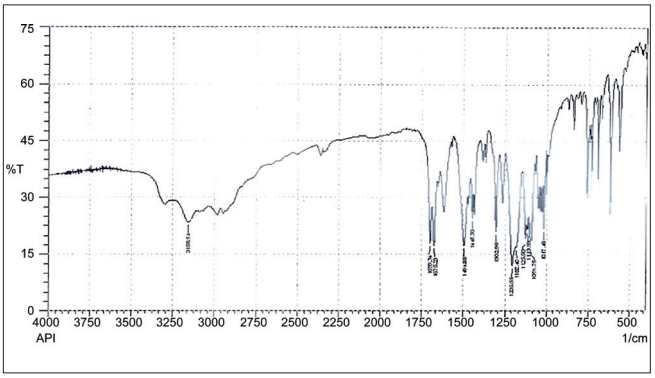

Figure 3: Infrared spectra of amlodipine besylate

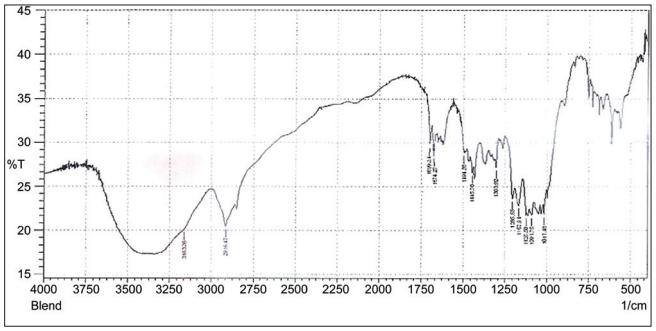

Figure 4: Infrared spectra of blend

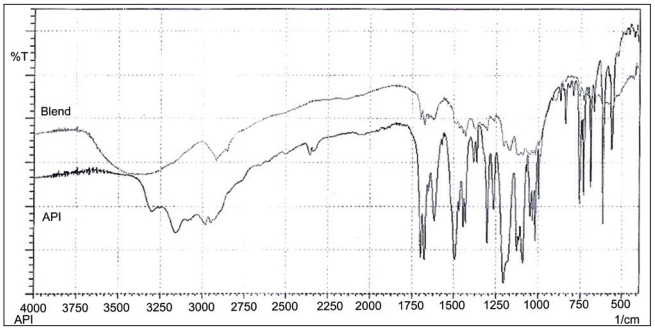

Figure 5: Comparative infrared spectra between amlodipine besylate and blend

Table 4: Stability study of best batch

Long term stability study (25 ± 2°C and 60 ± 5% RH)				
Days (Month)	3	6	9	12
Drug assay (%)	99.39 ± 0.21	99.19 ± 0.43	100.46 ± 0.62	99.32 ± 0.07
Crushing strength (newton)	45.35 ± 1.25	46.06 ± 1.08	45.62 ± 1.37	44.33 ± 1.53
Intermediate stability (30 ± 2°C and 65 ± 5% RH)				
Days (Month)	3	6	9	12
Drug assay (%)	99.47 ± 0.35	99.01 ± 0.12	99.38 ± 0.06	98.27 ± 0.72
Crushing strength (newton)	45.39 ± 1.05	45.88 ± 1.42	44.07 ± 1.03	44.11 ± 1.17
Accelerated stability (40 ± 2°C and 75 ± 5% RH)				
Days (Month)	1	2	3	6
Drug assay (%)	99.45 ± 0.47	99.38 ± 0.72	99.52 ± 0.05	99.03 ± 0.15
Crushing strength (newton)	45.56 ± 1.27	44.88 ± 1.03	44.69 ± 1.08	43.11 ± 1.13

Data are represented as mean ± standard deviation (SD), *n* = 3

and microbial limit test. The parameters and results are explained in Tables 5-7.

Dissolution for validation scale batches were carried out in 1000 ml phosphate buffer of pH 6.8 using USP- II (paddle apparatus) at 75 rpm maintained temperature of 37 ± 0.5°C. The dissolution profiles of F10, F11, and F12 were found to be similar with that of dissolution profile of optimized initial samples. Moreover, the impurity profile was observed to be well within the specification limit of less than known impurity, 0.1% for unknown maximum single impurity, and 0.8% for total impurity. The tests for salmonella were negative as well as the colony forming units were within the specified limit. Hence, the results of the stability studies confirm the designed F3 is a stable formulation and can be produced in large scale. Thus, the formulation and development in this direction leads to design promising FDT tablet containing amlodipine besylate intended to be used clinically for the treatment of angina pectoris and hypertension.

Table 5: Stability study of reproducible batch F10

Batch no.	**F10**	**Reason for study**		**Stability**				
Pack details	**10's clear blisters PVC/PVDC**	**Condition**		**40°C ± 2°C and 75% ± 5% RH**				
Name of test			**Limit**	**Initial**	**1st month**	**2nd month**	**3rd month**	**6th month**
Description			*	Complies	Complies	Complies	Complies	Complies
Average weight (Mass) (mg)			150.00 mg ± 7.5%	150.3	150.8	150.5	151.8	151.9
Disintegration time (min' sec")			NMT 15 min.	10"	10"	12"	13"	16"
Thickness (mm)			2.80 ± 0.30 mm	2.80 ± 0.11	2.80 ± 0.14	2.80 ± 0.15	2.80 ± 0.16	2.80 ± 0.18
Resistance to Crushing (Newton)			NLT 15 newton	46 ± 1.01	46 ± 2.03	45 ± 0.97	45 ± 1.24	44 ± 0.97
Dissolution			NLT 80%	99.5 -101.4	99.8-100.4	98.7-99.8	97.7-98.5	97.2-98.0
Related	Impurity D		NMT 0.3%	ND	ND	ND	ND	ND
Substances	Impurity A		NMT 0.15%	ND	ND	0.046	0.05	0.053
	Impurity E		NMT 0.15%	ND	ND	ND	ND	ND
	Impurity F		NMT 0.15%	ND	ND	ND	ND	ND
	Unspecified impurity		NMT 0.10%	0.011	0.012	0.013	0.015	0.018
	Total impurities		NMT 0.8%	0.053	0.055	0.059	0.065	0.071
Assay			95.0% to 105.0%	101.4	100.6	99	98.3	97.7
Microbiological		TAMC	NMT 10^3 cfu/g	38	40	42	44	42
Limit test		TYMC	NMT 10^2 cfu/g	<10	<10	<10	<10	<10
		Escherichia coli	Should be absent/g	Absent	Absent	Absent	Absent	Absent
NMT	Not more than		NLT	Not less than				
ND	Not detected		NA	Not applicable				
TAMC	Total Aerobic microbial count		TYMC	Total yeast and mould count				

Impurity D: 3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-6-methylpyridine- 3,5-dicarboxylate
Impurity A: 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[[2-(1,3-dioxo- 1,3-dihydro-2H-isoindol-2-yl)ethoxy]methyl]-6-methyl-1,4- dihydropyridine-3,5-dicarboxylate
Impurity E: 3-Ethyl 5-ethyl 4-(2-chlorophenyl)-6-methyl-2-[[2- [(2-aminoethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate
Impurity F: 3-Methyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-[[2- [(2-aminoethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate

Table 6: Stability study of reproducible batch F11

Batch no.	**F11**	**Reason for study**	**Stability**				
Pack details	**10's clear blisters PVC/ PVDC**	**Condition**	**40°C ± 2°C and 75% ± 5% RH**				
Name of test		**Limit**	**Initial**	**1st month**	**2nd month**	**3rd month**	**6th month**
Description		*	Complies	Complies	Complies	Complies	Complies
Average weight (Mass) (mg)		150.00 mg ± 7.5%	150.2	150.6	150.9	151.4	151.8
Disintegration time (min' sec")		NMT 15 min.	11"	11"	12"	14"	17"
Thickness (mm)		2.80 ± 0.30 mm	2.80 ± 0.19	2.80 ± 0.12	2.80 ± 0.18	2.80 ± 0.15	2.80 ± 0.21
Resistance to crushing (Newton)		NLT 15 newton	46 ± 1.32	46 ± 0.92	46 ± 1.05	45 ± 1.24	44 ± 0.72
Dissolution		NLT 80%	99.59-100.4	99.8-100.4	98.7-99.9	98.7-99.2	97.2-98.4
related	Impurity D	NMT 0.3%	ND	ND	ND	ND	ND
substances	Impurity A	NMT 0.15%	ND	ND	0.036	0.04	0.058
	Impurity E	NMT 0.15%	ND	ND	ND	ND	ND
	Impurity F	NMT 0.15%	ND	ND	ND	ND	ND
	Unspecified impurity	NMT 0.10%	0.009	0.011	0.014	0.015	0.019
	Total impurities	NMT 0.8%	0.049	0.052	0.055	0.062	0.068
Assay		95.0% to 105.0%	100.4	100.6	99.6	98.8	98.2
Microbiological	TAMC	NMT 10^3 cfu/g	32	39	40	42	43
Limit test	TYMC	NMT 10^2 cfu/g	<10	<10	<10	<10	<10
	Escherichia coli	Should be absent/g	Absent	Absent	Absent	Absent	Absent
NMT	Not more than	NLT	Not less than				
ND	Not detected	NA	Not applicable				
TAMC	Total aerobic microbial count	TYMC	Total yeast and mould count				

Impurity D: 3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-6-methylpyridine- 3,5-dicarboxylate.
Impurity A: 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[[2-(1,3-dioxo- 1,3-dihydro-2H-isoindol-2-yl)ethoxy]methyl]-6-methyl-1,4- dihydropyridine-3,5-dicarboxylate.
Impurity E: 3-Ethyl 5-ethyl 4-(2-chlorophenyl)-6-methyl-2-[[2- [(2-aminoethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate.

CONCLUSION

The present investigation shows that the various superdisintegrants can effectively be used to design fFDT of amlodipine besylate utilizing direct compression technique. The use of superdisintegrants for preparation of FDT is highly effective and commercially feasible. These superdisintegrants accelerate disintegration or dissolution of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The physiochemical characterizations of all formulations were found to be satisfactory. Result shows formulation F3 based on Ac-Di-Sol exhibited complete release within 12 minutes. From dissolution study and similarity factor (*f2*) value, formulation F3 was selected as best laboratory scale grade batch. Hence, reproducible production scale batches of size 1000 tablets were designed and charged for stability study. Parameters were checked and found to be within the specified limit. Further, *in vivo* and pharmacokinetic studies have to be carried out.

ACKNOWLEDGEMENT

Authors are thankful to scientific and research committee team of Jeypore College of pharmacy, Biju Patnaik University of Technology, Odisha. SN thanks to NIC for providing research facilities to him.

Table 7: Stability study of reproducible batch F12

Batch no.	**F12**	**Reason for study**	**Stability**				
Pack details	**10's clear blisters PVC/PVDC**	**Condition**	**40°C ± 2°C and 75% ± 5% RH**				
Name of test		**Limit**	**Initial**	**1st month**	**2nd month**	**3rd month**	**6th month**
Description		*	Complies	Complies	Complies	Complies	Complies
Average weight (Mass) (mg)		150.00 mg ± 7.5%	150.5	150.5	150.7	150.9	151.2
Disintegration time (min' sec")		NMT 15 min.	12"	12"	13"	14"	16"
Thickness (mm)		2.80 ± 0.30 mm	2.79 ± 0.82	2.80 ± 0.12	2.80 ± 0.18	2.80 ± 0.22	2.80 ± 0.28
Resistance to crushing (Newton)		NLT 15 newtons	46 ± 1.28	45 ± 2.02	45 ± 0.42	44 ± 1.30	44 ± 0.52
Dissolution		NLT 80%	99.57-100.3	99.2-99.4	98.7-99.2	97.4-98.2	97.1-98.0
Related	Impurity D	NMT 0.3%	ND	ND	ND	ND	ND
Substances	Impurity A	NMT 0.15%	ND	ND	0.016	0.042	0.043
	Impurity E	NMT 0.15%	ND	ND	ND	ND	ND
	Impurity F	NMT 0.15%	ND	ND	ND	ND	ND
	Unspecified impurity	NMT 0.10%	0.009	0.01	0.012	0.014	0.016
	Total impurities	NMT 0.8%	0.043	0.046	0.051	0.052	0.057
Assay		95.0% to 105.0%	100.4	99.4	98.7	98.2	97.4
Microbiological	TAMC	NMT 10^3 cfu/g	35	37	40	42	44
Limit test	TYMC	NMT 10^2 cfu/g	<10	<10	<10	<10	<10
	Escherichia coli	Should be absent/g	Absent	Absent	Absent	Absent	Absent
NMT	Not more than	NLT	Not less than				
ND	Not detected	NA	Not applicable				
TAMC	Total aerobic microbial count	TYMC	Total yeast and mould count				

Impurity D: 3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-6-methylpyridine- 3,5-dicarboxylate.
Impurity A: 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[[2-(1,3-dioxo- 1,3-dihydro-2H-isoindol-2-yl)ethoxy]methyl]-6-methyl-1,4- dihydropyridine-3,5-dicarboxylate.
Impurity E: 3-Ethyl 5-ethyl 4-(2-chlorophenyl)-6-methyl-2-[[2- [(2-aminoethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate.
Impurity F: 3-Methyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-[[2- [(2-aminoethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate

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How to cite this article: Roy H, Parida KR, Nandi S, Panda SK, Mohapatra DK. Design of fast dissolving amlodipine besylate tablet formulations. Asian J Pharm 2012;6:51-9.

Source of Support: Nil. **Conflict of Interest:** None declared.