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Formulation and Evaluation of fast dissolving tablets containing Amlodipine Besylate

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Abstract: In the present work, fast dissolving tablet of Amlodipine besylate was formulated with quick onset of action. The main objective of this study was to formulate and evaluate fast dissolving tablets of amlodipine besylate to achieve a better dissolution rate and further improving the bioavailability of the drug. Fast dissolving tablets prepared by direct compression and using super-disintegrants in different concentration and evaluated for the pre-compression parameters. The prepared tablets were evaluated for post compressional. Among all, the formulation F8 containing 8% w/w super-disintegrant Croscarmellose sodium, Crospovidone and Microcrystalline Cellulose was considered to be best formulation, which release up to 96.50 % in 10 min.

Key words: Amlodipine besylate, superdisintegrants, disintegration time, *In vitro* dissolution test

Introduction

Recent advance in novel drug delivery system, aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration. Difficulty in swallowing is experienced by patient such as pediatric and geriatric. Fast dissolving tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing. Amlodipine besylate is a dihydropyridine calcium antagonist (calcium ion-channel blocker) that inhibits the trans-membrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It binds to both dihydropyridine and non dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extra cellular calcium ions into these cells through specific ion channels. Direct compression is one of the techniques requiresthe incorporation of a super-disintegrants into the formulation the use or highly. The basic approach used in development of FDT was the use of superdisintegrants like cross linked Croscarmellose Sodium, and Crospovidone etc. which provide instantaneous disintegration of tablet after placed on tongue, thereby releasing the drug in saliva.

Material and Methods

Amlodipine besylate was obtained as a gift sample from Dr. Reddy labs, Hydrabad (India). Crospovidone, Microcrystalline cellulose and Croscarmellose sodium were gift sample from Curex Pharma, Jalgaon. Sodium saccharine was obtained as gift sample from Emcure Pharma, Pune and vanilla flavour were gift samples from Merck Ltd, Mumbai, India. All chemicals and reagents used were of analytical grade.

Preparation of fast dissolving tablets

Fast dissolving tablets of Amlodipine besylate were prepared by direct compression method incorporating in different superdisintegrants i.e., Crospovidone (CP), Croscarmellose Sodium (CCS). The Amlodipine Besylate equivalent to 10mg, Sodium saccharine and Microcrystalline Cellulose were mixed thoroughly in glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture according to each formulation in the tablets and finally Magnesium stearate, Talc and Vanilla flavour was added. The whole mixture was passed through Sieve No. 80 twice. Tablets were prepared using 4 mm round flat-faced punch of the rotary tablet machine. Compression force was constant for all formulations are showed in Table 1.

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Table 1. Formulations of fast dissolving tablets

Sr.No.	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Amlodipine Besylate	10	10	10	10	10	10	10	10
3	Crospovidone	2	4	6	8	0	0	0	0
4	Crosscrarmilose Sodium	0	0	0	0	2	4	6	8
5	Sodium saccharine	36	34	32	30	36	34	32	30
6	Microcrystalline Cellulose	100	100	100	100	100	100	100	100
7	Magnesium Stearate	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
8	Talc	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
9	Flavour (Vanilla)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

Precompression parameters

Angle of Repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using formula. $\theta = tan^{-1}$ (h/r) Where, θ is angle of repose, h is height of pile and r is the radius of the base pile.

Bulk Density

Apparent bulk density *(LBD)* was determined by pouring blend into a graduated cylinder. The bulk volume *(Vo)* and weight of powder *(M)* was determined. The bulk density was calculated using the formula.

$$LBD = \frac{weight\ of\ the\ powder\ (M)}{volume\ of\ the\ packing\ (Vo)}$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight of powder blend (M) as measured. The tapped density (TBD) was calculated using the formula.

$$TBD = \frac{height\ of\ the\ powder\ (M)}{tapped\ volume\ of\ the\ packing\ (Vt)}$$

Carr's Compressibility Index

The simplex way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was determined by Carr's compressibility index (C) which is calculated by using the following formula.

$$C = [(TBD - LBD/TBD)] \times 100$$

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$Hausner\ ratio = Tapped\ density\ (TBD)/\ Bulk\ density\ (LBD)$$

Where *TBD* is tapped density and *LBD* is bulk density.

Lower hausner ratio (<1.25) indicate better flow properties than higher ones (>1.25).

Table 2. Precompression parameters

Formulation code	Angleof Repose (θ)	Tapped density(g/cc)	Bulk Density(g/cc)	Carr's index	Haunser Ratio
F1	25.12	0.75	0.65	13.04	1.15
F2	26.35	0.73	0.63	13.79	1.16
F3	27.84	0.71	0.65	8.26	1.09
F4	24.21	0.75	0.64	14.53	1.17
F5	25.12	0.73	0.63	13.79	1.16
F6	26.45	0.76	0.66	13.04	1.15
F7	27.84	0.72	0.62	13.79	1.16
F8	26.35	0.71	0.61	13.79	1.16

Post compression parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results as shown in Table 3.

Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the table 3 and none deviate by more than twice the percentage. The mean and standard deviation were determined.

Table 3. Post compression parameters

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)
F1	3.1	3.7	0.42	153.6
F2	3.1	3.8	0.51	155.4
F3	2.95	3.1	0.73	156.1
F4	3.3	3.1	0.30	151.6
F5	3.15	3.2	0.48	150.2
F6	2.95	3.6	0.68	153.9
F7	3.15	3.5	0.32	154.8
F8	3.3	3.1	0.53	154

Thickness
The thickness and diameter of the tablets was determined using a Micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

Hardness Test
The hardness of the tablet was determined using Monsanto Hardness Tester.

Friability Test
Six tablets from each batch were examined for friability using Roche Fribilator and the equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated.

$$Percent friability = \frac{Initial weight - Final weight}{Initial weight} \times 100$$

Water Absorption Ratio
A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation.

$$R = \frac{wa - wb}{wawb} \times 100$$

Where, Wb and Wa are the weight before and after water absorption, respectively.

Wetting Time
A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 9 cm) containing 6ml pH 6.8 phosphate buffer, A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

Content Uniformity Test
Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 10mg of Amlodipine besylate was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, the absorbance was measured at wavelength 279 nm using double beam UV-Visible spectrophotometer (IP, 2007). Content uniformity was calculated using formula

$$\% \text{ Purity} = 10\ C \frac{\text{Absorbance of unknown (Au)}}{\text{Absorbance of Standard (As)}}$$

Where, C - Concentration

***In vitro* Disintegration Time**
Initially the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time.

***In vitro* Dissolution Testing**
Dissolution study was conducted for all the formulation using USP type-II apparatus (Electrolab, Mumbai, India.). The dissolution test was performed using 900 ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 37°C ± 0.5°C. Ten ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 279 nm.

Table 4. Results of *In vitro* dispersion time, wetting time and water absorption ratio of Amlodipine besylate tablets

Formulation Code	*In vitro* dispersion time (sec)	Wetting time (sec)	Water absorption Ratio
F1	82.8	91.33	0.069
F2	98.33	107.33	0.062
F3	105.16	118.33	0.065
F4	114	136.66	0.072
F5	64.50	85.00	0.068
F6	111.66	126.00	0.061
F7	53.66	70.66	0.067
F8	88.16	102.00	0.071

Table 5. *In vitro* drug release studies of fast dissolving tablets for F1 to F4

Sr. No	Time (Min)	% cumulative drug release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	2	37.21	38.78	41.67	48.13
3	4	49.31	56.88	61.21	65.35
4	6	60.21	68.04	70.45	76.12
5	8	71.71	76.56	80.87	87.02
6	10	80.21	88.15	91.57	93.02

Table 6. *In vitro* drug release studies of fast dissolving tablets for F5 to F8

Sr. No.	Time (Min)	% cumulative drug release			
		F5	F6	F7	F8
1	0	0	0	0	0
2	2	39.54	42.50	48.13	48.39
3	4	56.89	62.12	65.35	64.25
4	6	69.22	70.54	76.12	74.02
5	8	80.01	83.53	87.00	86.32
6	10	90.53	92.56	93.00	96.50

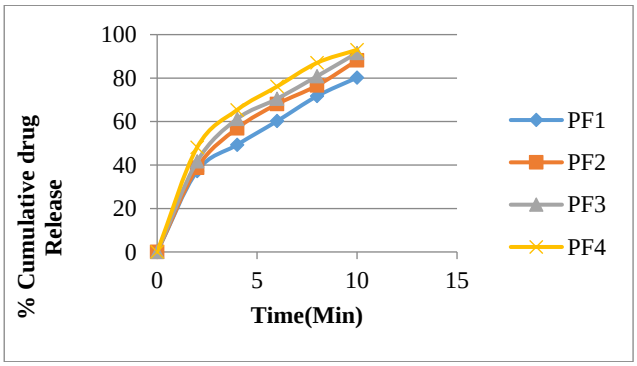

Figure 1. *In-vitro* drug release studies of fast dissolving tablets for F1 to F4

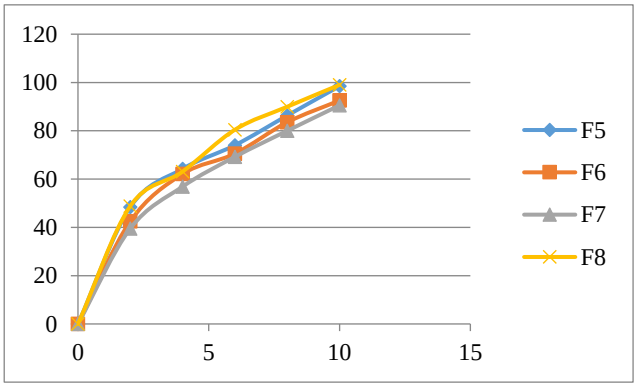

Figure 2. *In vitro* Drug Release Studies of fast dissolving tablets

Characterization of Amlodipine besylate tablet FT-IR studies

Infrared spectrum was taken for the pure Amlodipine besylate. FT-IR studies was carried by KBr disk method using computer mediated Fourier transformed infrared spectroscopy (FTIR).

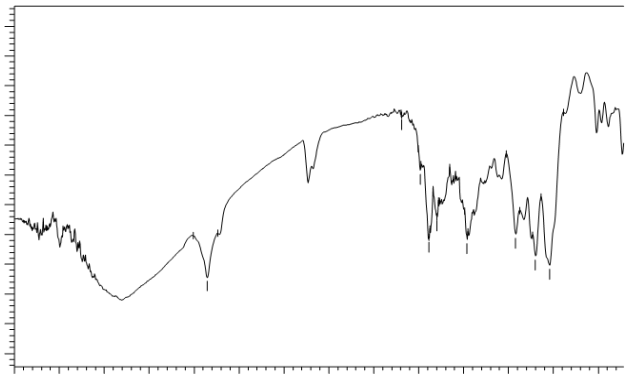

Figure 3. FTIR spectra of Amlodipine Besylate

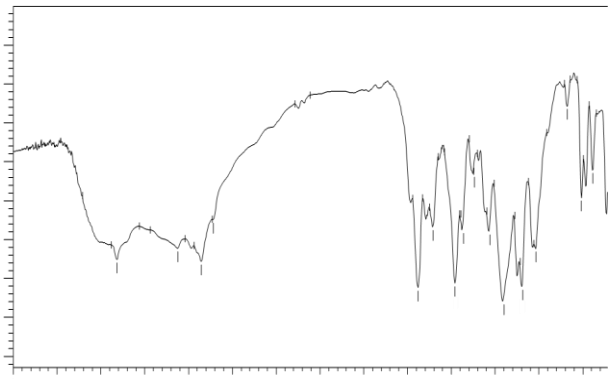

Figure 4. FTIR spectra of Formulations of fast dissolving tablets

Results and Discussion

Amlodipine besylate fast dissolving tablets were prepared by direct compression method was carried out by using superdisintegrants like Crospovidone, Croscarmellose sodium and Microcrystalline Cellulose in different concentration. Angle of repose: range from 25.12 to 26.35° show good flow. Bulk density and tapped density: range from 0.71 to 0.75 (g/cc), and 0.61 to 0.65 (g/ml), respectively. Compressibility index and Hausner ratio range from 13.04 to 13.79 and 1.09 to 1.17 respectively. The results for recompressed parameters as shown in Table 2. Weight variation test range from 150.2 mg to 156.1mg as per IP specification. Friability: less than 0.73 % the results indicate that the percentage losses were not more than 1.0 %. So the tablet complies as per IP specifications. Thickness: range from 2.95 to 3.30 mm; the results indicate that the tablets are suitable for packing. Hardness of tablet was found to be between 3.10 to 3.60 kg/cm^2. The results indicate that the tablets are mechanically strong and are in limit. Disintegration time: in between 13 to 20 seconds the results indicate that disintegration time of tablets is within 1minute. Wetting time: in between 91.33 to 102.11 second and water absorption ratio was found to be 0.069 to 0.072. The post compressed parameters are showed in Table 3. Dissolution Study in 6.8 pH phosphate buffer: formulation of F1, F2, F3, F4, and F5 have a recorded drug release 80.21 %, 88.15 %, 91.57 % and 93.02 % at the end of 10 min the results was showed in Figure 1, formulation F5, F6, F7 and F8 have a recorded drug release 90.53 %, 92.56 %, 93.00 % and 96.50 % at the end of 10 min the result was showed in Figure No. 1 and 2. FTIR studies: The FTIR spectra of the pure drug and Formulations, the result was showed in Figure No. 3 and 4 there is no any interactions between drug and excipients. Storage condition: Tablets were stored at 40° C ± 2° C/75 % for a storage period of 0 days, 30 days, 60 days, and 90 days, Hardness was increases with time increases but, in all cases, hardness was within the limit.

Disintegration time: at various storage conditions increases but maximum 15 seconds which is less than 1min (specification of IP). Dissolution studies shows there was no significant difference in dissolution data of formulations at initial and after specified storage period.

Conclusion

Fast dissolving tablets of Amlodipine besylate can be successfully prepared by direct compression techniques using selected super disintegrants for the better patient compliance and effective therapy. The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was found in order i.e. Crospovidone and Croscarmellose sodium.

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