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Formulation and In-Vitro Evaluation of Fast Dissolving Tablets of Amlodipine Besylate-using Different Super Disintegrants

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ABSTRACT

Amlodipine Besylate is used commonly for the treatment angina pectoris, commonly known as angina, is chest pain due to ischemia of the heart muscle, generally due to obstruction or spasm of the coronary arteries (the heart's blood vessels). Dosing for elderly patients is improved by mouth dissolving tablets it also provides convenience to whom that has trouble in swallowing tablets. The target of these new oral dissolving/disintegrating dosage forms has ODTs Direct Compression method was employed for blending of drug with polymers in the given ratio as a 9 formulations. The prepared powder blends were then compressed into tablets using the necessary Superdisintegrants (CCS, CP, and SSG) and Excipients. The tablets were evaluated for Weight variation, thickness, hardness, friability, Drug Content and Disintegrating Time (Sec) were subjected to a 10 minutes in vitro drug release studies (USP dissolution rate test apparatus II, 50rpm, 37^{0}C ±0.5^{0}C) using phosphate buffer, pH 6.8 as a dissolution medium (900ml). The amount of Amlodipine besylate released from the tablet formulations at different time intervals was estimated using a UV spectroscopy method. The formulations that showed a considerable retardation of the drug release are considered promising. Among the nine formulations, F9 formulation containing drug to Sodium Starch Glycollate (SSG) in the ratio 1:1 is optimized based on its ability to till 7 mins of in vitro dissolution time, and its % Cumulative Drug Release Of The 99% of dissolution study.

***Key Words**: Amlodipine besylate, Sodium Starch Glycollate, Angina pectoris.*

INTRODUCTION

A fast dissolving tablet system can be defined as a dosage form for oral administration, which, when placed in the mouth, rapidly dispersed or dissolved and can be swallowed in the form of liquid. Recently fast dissolving formulation has been popular as Novel Drug Delivery Systems because they are easy to administer and lead to better patient compliance. Pediatric and geriatric patient has difficulty in swallowing the conventional dosage forms these dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the swallowed as a solution to be absorbed from the gastrointestinal tract [1, 20-21].

Angina pectoris, commonly known as angina, is chest pain due to ischemia of the heart muscle, generally due to obstruction or spasm of the coronary arteries (the heart's blood vessels). Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine 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 extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells [22].

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MATERIALS AND METHODS

Materials:

Amlodipine besylate was a gift sample from MSN Laboratories Ltd, Hyderabad, Microcrystalline Cellulose, Magnesium Stearate were used and supplied by Bright Labs, Hyderabad, Mannitol, Sodium Starch Glycolate, Cros povidone was used and supplied by Signet chemicals, Hyderabad, Croscarmellose Sodium from Bright Scientific Traders, Hyd, Talc was supplied by SD chemicals, Hyderabad.

Methodology:

Preformulation Studies:

Standardization of Amlodipine besylate by UV-Visible Spectrophotometry:

Standard calibration of Amlodipine besylate in 6.8 Phosphate buffer:

100mg of Amlodipine besylate was accurately weighed and dissolved in100ml of 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbance was measured at 238nm as shown in fig 1and **Table 1**.

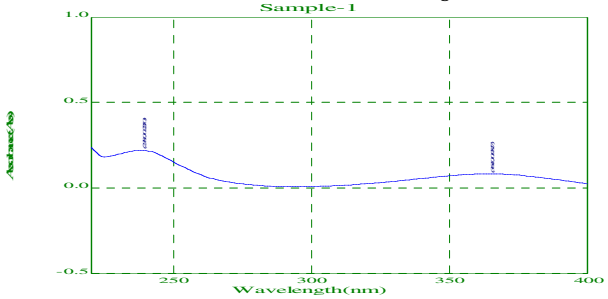

Fig. 1: λmax of Amlodipine besylate in pH 6.8 Phosphate buffer (238nm)

Table No. 1: Standard graph of Amlodipine besylate in pH 6.8 Buffer

S.No	Concentration	Absorbance
1	2	0.097
2	4	0.158
3	6	0.219
4	8	0.286
5	10	0.343
6	15	0.491
7	20	0.651
8	25	0.832

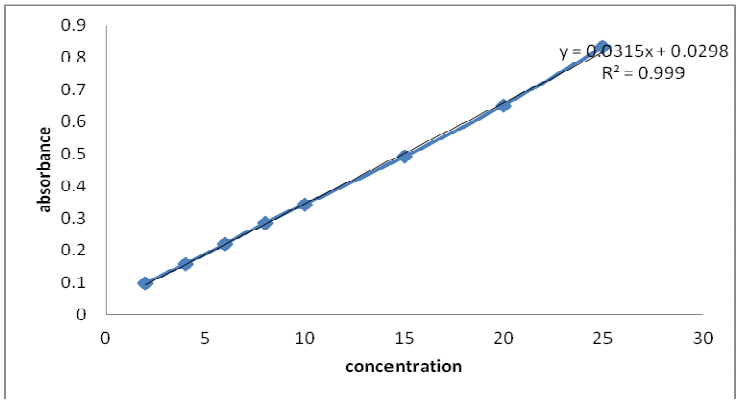

Fig. 2: Standard graph of Amlodipine besylate in pH 6.8 Buffer

Drug- Excipient Compatibility by FTIR studies:

In the preparation of ODT tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of the drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy (AGILENT TECHNOLOGIES) was employed to ascertain the compatibility between Amlodipine besylate and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure:

Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR (Agilent Technologies). FT-IR spectrum of Amlodipine besylate was compared with the spectrum of Amlodipine besylate and polymer. Disappearance of Amlodipine besylate peaks or shifting of peak in any of the spectra was studied [2,3,4].

FTIR Studies:

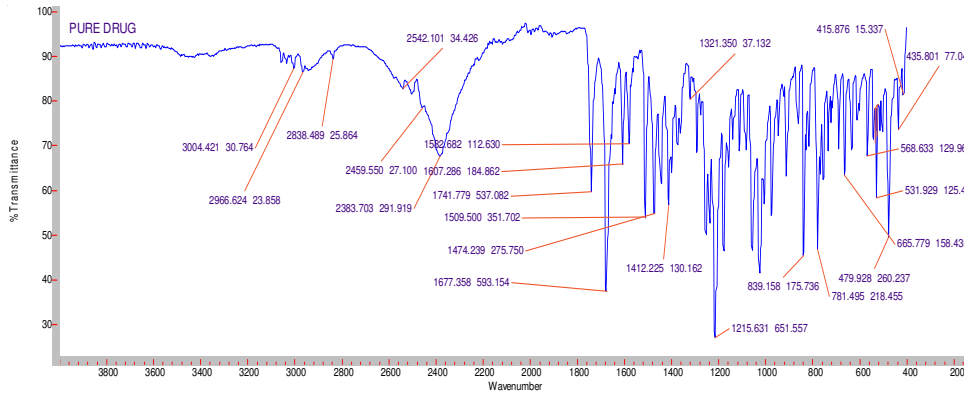

Fig. 3: FTIR Graph of Pure Drug (Amlodipine besylate)

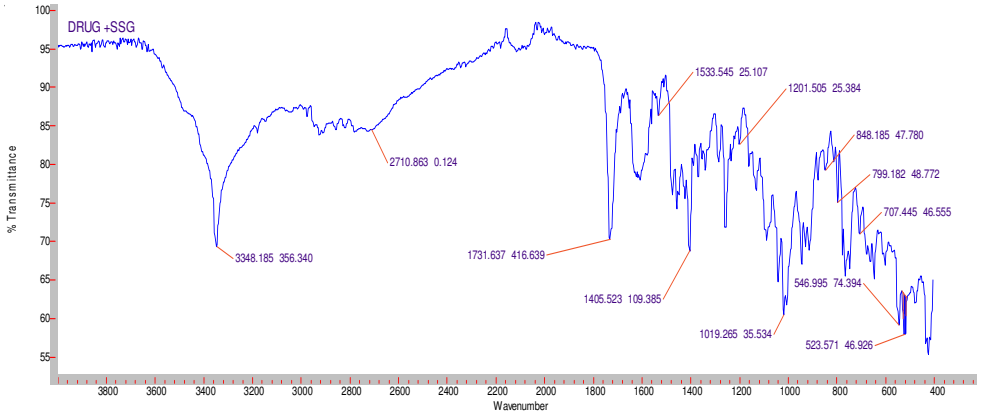

Fig. 4: FTIR Graph of Amlodipine besylate + SSG

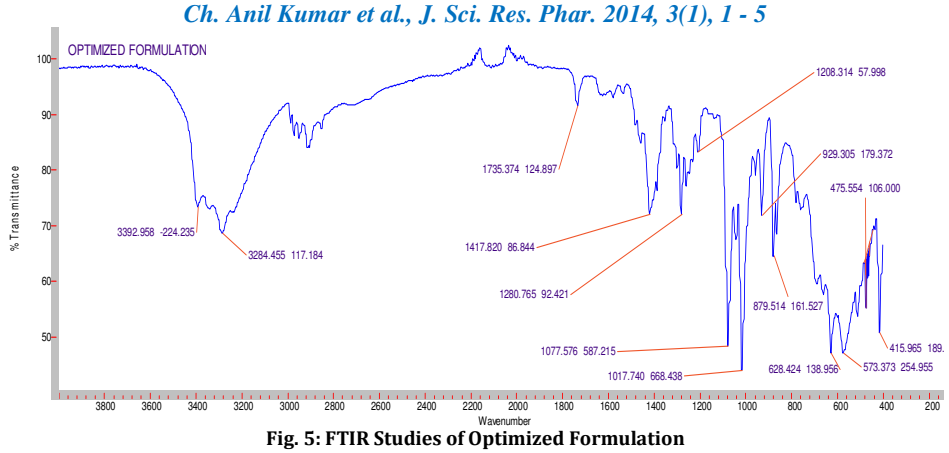

Fig. 5: FTIR Studies of Optimized Formulation

Angle of repose:

The angle of repose of the blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend was measured. The angle of repose was calculated using following formula

$$\tan \theta = h/r \quad \text{..... Eqn. (1)}$$

Where, "h" is the height of the heap and "r" is the radius of the heap of granules.

Carr's compressibility index:

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10mL of measuring cylinder. Initial bulk volume was measured, and the cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated by using the following formula:

Carr's compressibility index (%) = [(Tapped density-Bulk density) X100]/Tapped density.Eqn.(2)

Pre-compression parameters of Direct Compression method mean SD(n=3):

Table No. 2: Precompression Parameters

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's Ratio*
F1	0.49± 0.030	0.56± 0.04	28.43 ± 1.20	16 ± 1.41	1.20 ± 0.03
F2	0.52 ± 0.023	0.60 ± 0.02	30.1 ± 1.70	17 ± 1.20	1.21 ± 0.04
F3	0.54 ± 0.013	0.62 ± 0.01	30.72 ± 0.88	15 ± 2.51	1.19 ± 0.03
F4	0.52 ± 0.017	0.63 ± 0.01	29.25 ± 1.56	17 ± 1	1.20 ± 0.05
F5	0.53 ± 0.020	0.63 ± 0.01	30.02 ± 1.20	15 ± 1.51	1.19 ± 0.06
F6	0.53 ± 0.013	0.64 ± 0.02	30.1 ± 1.70	17 ± 1.20	1.20 ± 0.03
F7	0.55 ± 0.023	0.65 ± 0.01	30.20 ± 0.88	15 ± 2.51	1.18 ± 0.03
F8	0.50 ± 0.015	0.63 ± 0.01	28.43 ± 1.48	20 ± 1.58	1.26 ± 0.03
F9	0.52 ± 0.032	0.63 ± 0.02	30.72 ± 1.22	17 ± 1.55	1.21 ± 0.04

Preparation of tablets:

Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as a lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a poly bag. Prior to compression, the blends were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 100mg of Amlodipine besylate [5-11] (**Table 3**).

Formulation Chart:

Table No. 3: Formulation Chart

S.No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Amlodipine esylate**	10	10	10	10	10	10	10	10	10
2	**MCC**	71	69	67	71	69	67	71	69	67
3	**Mannitol**	10	10	10	10	10	10	10	10	10
4	**CCS**	4	6	8	---	---	---	---	---	---
5	**CP**	---	---	---	4	6	8	---	---	---
6	**SSG**	---	---	---	---	---	---	4	6	8
7	**Talc**	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	**Magnesium stearate**	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Total weight	100	100	100	100	100	100	100	100	100

Evaluation of Tablets:

A) Weight Variation Test:

From each batch twenty tablets were selected in a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

B) Hardness and Friability Test:

For each formulation the hardness was determined by using the Monsanto hardness tester and Friability of the tablets was

checked by using Roche Friabilator. This device subjects tablets to the combined effect of abrasion and shock by utilizing a plastic chamber which revolves at 25 RPM dropping the tablets at a distance of 6 inches with an each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed and then % Friability was calculated.

C) Water Absorption Ratio and Wetting Time:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet of known weight was put on the paper and the time required for complete wetting of the tablet was measured. The wetted tablet was then weighed; water absorption ratio R was determined using t

$$R = \frac{Wb - Wa}{Wb} \times 100$$

Where; Wb is weight of the tablet before water absorption
Wa is weight of the tablet after water absorption

D) Drug Content Uniformity Study:

Five tablets were weighed individually and powdered. The powder equivalent to 50 mg of Amlodipine besylate was weighed and extracted in 6.8 phosphate buffer (100 ml) and the concentration of drug was determined by measuring absorbance at 238 nm by spectrophotometer.

Postcompression Parameters: mean SD (n=3):

Table No. 4: Postcompression parameters

Formulation	Hardness (Kg/Cm²)	Friability %	Thickness (mm)	Weight varitation	Distegration Time(Sec)
F1	3.5 ± 0.21	0.71±0.12	2.21 ±0.16	109 ± 1.28	36±3
F2	3.8 ± 0.14	0.69±0.13	2.33 ±0.14	108 ± 1.32	28±1
F3	3.7 ± 0.15	0.39±0.17	2.32 ±0.17	104 ± 0.86	20±2
F4	3.6 ± 0.11	0.81±0.12	2.29 ±0.12	109 ± 1.78	48±1
F5	3.7 ± 0.12	0.64±0.16	2.30 ±0.15	102 ± 1.32	38±3
F6	3.9 ± 0.10	0.31±0.15	2.42 ±0.10	101 ± 0.56	29±1
F7	3.7 ± 0.12	0.62±0.18	2.31± 0.10	102 ± 1.97	35±3
F8	3.8 ± 0.18	0.47±0.17	2.32 ± 0.17	105 ± 0.85	28±1
F9	3.6 ± 0.10	0.65±0.15	2.36 ± 0.15	106 ± 1.73	21±2

***In-Vitro* Drug Release Study:**

Dissolution rate was studied 6.8 phosphate buffer as dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5ºC; aliquot of dissolution medium was withdrawn at every 2 minute interval and filtered. The absorbance of a filtered solution was checked by UV spectrophotometric method at 238nm and concentration of the drug was determined from the standard calibration curve. Dissolution rate was studied for all designed formulations [12-19].

***In –vitro* drug release studies details:**

Apparatus used : USP XXIII dissolution test apparatus
Dissolution medium : 6.8 phosphate buffer at λ max 238 nm
Dissolution medium volume : 900ml
Temperature : 37±0.5ºC
Speed of basket paddle : 50rpm
Sampling intervals : 2min
Sample withdrawn : 5ml
Absorbance measured : 238nm.

In vitro dissolution studies:

Table No. 5: % Cumulative Drug Release of the Formulations (f1-f9)

S.No	Time(mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	1	60	66	52	57	54	66	50	52	58
3	3	70	71	67	65	69	74	62	70	74
4	5	77	75	75	76	73	86	74	78	83
5	7	89	94	86	89	89	95	92	93	99
6	10	92	96	94	93	95	98	94	96	--

Dissolution release profiles of Formulations:

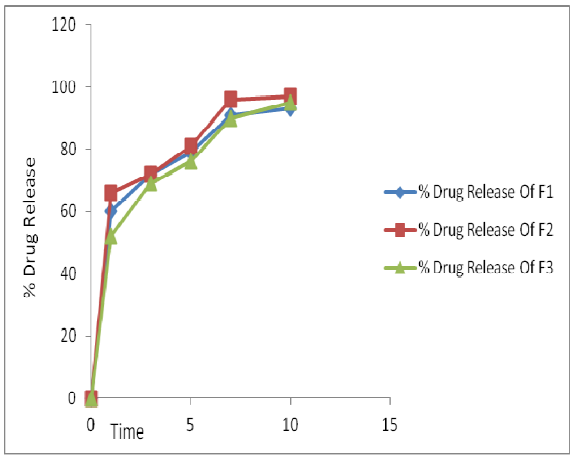

Fig. 6: Dissolution profiles of Formulations F1-F3 (Using Cross Caramellose Sodium)

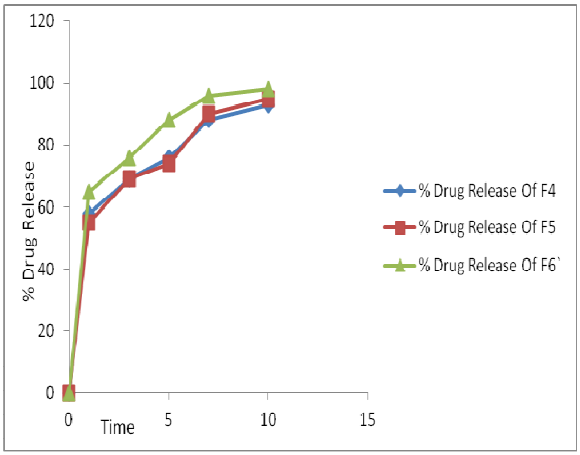

Fig. 7: Dissolution profiles of Formulations F4-F6 (Using Cross Povidone)

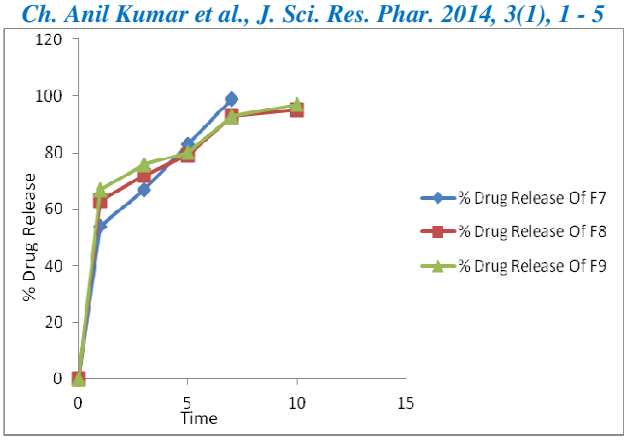

Fig. 8: Dissolution profiles of Formulations F7-F9 (Using Sodium Starch Glycollate)

RESULTS AND DISCUSSION

Amlodipine besylate has a UV absorbance of 238 NM. Solutions ranging from 5 to 25 µg/ml were prepared using 6.8 Phosphate buffers separately, absorbance was measured for each solution at λ max of 238nm using LABINDIA Double beam UV/ visible spectrophotometer, and graph was plotted for absorbance versus concentration of Amlodipine besylate. Standard graph of Amlodipine besylate in 6.8 pH Buffer at λ max 238nm. The drug compatibility studies were done by using FTIR and there is no interference to the drug and exipients. Precompression Parameters and post compression parameters were done and they were within the range.

CONCLUSION

The fastest dissolving tablets of Amlodipine besylate were prepared successfully using Polymers in different ratios of by using Superdisintegrants. We can conclude Out of nine formulations formulated using various Superdisintegrants like CCS, CP, and SSG among these Formulation F9 containing 5 % Sodium Starch Glycollate (SSG) showed maximum drug release within 7 minutes of dissolution study. These formulations showed disintegrating times of 39 seconds respectively. Thus based on Disintegrating times and dissolution profiles, Formulations F9 is optimized to be the best among all the nine.

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