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STUDY THE INFLUENCE OF SUPERDISINTEGRATING AGENTS ON DRUG RELEASE OF AMLODIPINE BESYLATE TABLETS BY STEAM GRANULATION TECHNIQUE

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ABSTRACT

In the present work of Amlodipine Besylate polo shape tablets were prepared by direct compression technique with various concentrations of super disintegrants such as Cross Carmellose Sodium, Sodium Starch Glycolate and crospovidone. Microcrystaline Cellulose was used as the direct compressible vehicle. Talc was used as glidant to improve the flow property of formulations. Magnesium Stearate used at very low concentration as anti-adherent which found to be having a deleterious effect on the dissolution. The disintegration time decreases with the increase concentration of superdisintegrants then Cross Povidone having less disintegration time compare to all formulations. 8 % Cross Povidone having less disintegration time compare to 2, 4 and 6 %. The maximum increase in the dissolution rate was observed with Cross Povidone amongst the three superdisintegrants. The less disintegrating time of Cross Povidone due to the thickness of the tablet was increased. Cross Povidone containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly so formulationF12 producued better drug release compare to all formulations. The rapid increase in dissolution of Amlodipine besylate with the increase in croscarmellose sodium may be due to rapid swelling and disintegrating tablets rapidly into apparently primary particles. While tablets formulated with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling into primary particle but more slowly due to the formation of a viscous gel layer by sodium starch glycolate. Cross povidone containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly so formulation F12 produced better drug release compare to all formulations. Thus difference in the size distribution generated with different superdisintegrants might have contributed to difference in the % drug release values with the same amount of superdisintegrants in the tablet.

Keywords: Disintegrate, Super disintegrants, Glycolate.

INTRODUCTION

Oral formulation has been the preferred and most common route of drug delivery around the globe. The popularity of this dosage form is owing to its ease of administration and good patient compliance. From drug development and formulation perspective, a solid dosage form offers superior stability compared to intravenous formulations. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used in a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration. But for many drugs, formulation of solid dosage form can be an inefficient mode for administration as approximately 40% or more of the NCE being generated through drug discovery programs have problem in water-solubility [1]. For drugs with poor aqueous solubility, dissolution is the rate limiting step for its bioavailability.

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration, compact in nature, easy to manufacture and it can be deliver in accurate dose.

One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and

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nervous systems and in schizophrenic patients which leads to poor patient compliance [2].

Difficulties in swallowing of tablet and capsule are also occurring when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention [3].

MATERIALS AND METHODS

Materials

Amlodipine Besylate was gift sample from symed labs ltd, India. Cross povidone, Sodium starch glycolate, Cross carmellose sodium, Microcrystalline cellulose Magnesium stearate, Talc were obtained from CDH, Delhi, India and all other reagents used were of analytical grade and obtained from S.D. Fine chemicals, Mumbai, India.

Methods

Fast dissolving tablets containing 10 mg of Amlodipine Besylate were prepared by direct compression method the various formulas used in the study are shown in table 1 Super disintegrating agents like Cross Carmellose Sodium, Cross Povidone, Sodium Starch Glycolate were used in different ratios (2%w/w, 4%w/w, and 6%w/w, 8%w/w), Micro Crystalline Cellulose was used as diluent. The blend was lubricated with talc and Magnesium Stearate, blend was compressed into tablets with 16 station rotary tableting machine (cadmach machinery, Mumbai, India) using 5 mm flat punches.

EVALUATION OF TABLETS

Weight variation test

Twenty tablets were collected and were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated using the formula

$$\% \text{ weight variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \text{ X 100}$$

Thickness

The thickness of the formulated tablets was measured by Vernier Calipers.

Hardness test

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The lower plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was calculated by deducting the initial pressure from the final pressure.

Friability

Friability of the tablets was determined using Roche friabliator. 20 tablets were weighed and placed in the friabliator, and were subjected to 25 revolutions per 4 mins. Tablets were then de-dusted, reweighed and percentage loss was calculated. Friability is obtained by the following formula.

% Friability= Initial weight – final weight × 100

Disintegration Time

The disintegration time was determined in distilled water at 37 ± 0.5^0 C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai) [3].

Drug content determination

Five tablets were collected, powdered and powder containing the equivalent of 10 mg of Amlodipine besylate was dissolved in 10 ml of methanol. Then solution was filtered, suitably diluted and analyzed for Amlodipine besylate by measuring the absorbance spectro photometrically at 239nm [4].

In vitro Dissolution studies

In vitro dissolution studies for Amlodipine Besylate fast dissolving tablets were performed in 6.8 P^H phosphate buffer using USP type II dissolution test apparatus with a paddle stirrer, the stirring speed employed was 75 rpm, and the temperature was maintained at 37°C ± 0.5°C. Samples were withdrawn at different time intervals and replaced with fresh dissolution medium, solutions were filtered and determined the Amlodipine Besylate content by UV–visible Spectrophotometrically at 239 nm [5].

Drug-Excipient Compatibility studies

The physico-chemical compatibility studies of Amlodipine Besylate and the various excipients used in the work were studied by IR spectroscopy. The samples were scanned under diffuse reflectance mold, plotted the graph by KBr pellet method and spectra were recorded in wavelength region between 4000 cm^{-1} to 400 cm^{-1}.The spectra obtained from various formulations were compared and reported [6].

The results of in-vitro drug release studies were reported in table 6. the comparative in -vitro release profile was depicted in figure 6.1. The percentage of drug release for formulations F1, F2, F3 and F4 were 79.05±0.05, 86.29±0.06, 90.07±0.01 and 91.41±0.09 at the end of 30 minutes. The percentage of drug release were found in the following order F4>F3>F2>F1.

The drug release kinetics were analysed by invitro release data was fitted into various release equations which were tabulated in table no 6.4. The drug release followed first order kinetics ,the plots were made as shown in figure 6 [10].

The results of invitro drug release studies were reported in table 7. The comparative invitro release profile was depicted in figure 7 . The percentage of drug release for formulation F5, F6, F7 and F8 were 80.88±0.01,

82.48±0.02, 88.22±0.07 and 90.56±0.05 at the end of 30 mins. The percentage drug release was in the following order F8>F7>F6>F5.

The drug release kinetics were analysed by invitro release data was fitted into various release equations which were tabulated in table no .8. The drug release followed first order kinetics, the plots were made as shown in figure 8 [11-14].

The results of invitro drug release studies were reported in table 9. The comparative invitro release profile was depicted in fig 9. The percentage of drug release for formulation F9, F10,F11 and F12 were 81.46±0.01, 86.28±0.09, 95.41±0.08 and 98.51±0.07 at the end of 30 mins. The percentage ofdrug release was in the following order F12>F11>F10>F9.

The drug release kinetics were analysed by invitro release data was fitted into various release equations which were tabulated in table no 10. The drug release followed first order kinetics,the plots were made as shown in fig 11

In the present workof Amlodipine Besylate polo shape tablets were prepared by direct compression technique with various concentration ofsuperdisintegrants such as Cross Carmellose Sodium, Sodium Starch Glycolate and crospovidone. Microcrystaline Cellulose was used as the direct compressible vehicle. Talc was used as glidant to improve the flow property of formulations. Magnesium Stearate used at very low concentration as anti-adherent which found to be having a deleterious effect on the dissolution.The disintegration time decreases with the increase concentration of superdisintegrants then Cross Povidone having less disintegration time compare to all formulations. 8 % Cross Povidone having less disintegration time compare to 2, 4 and 6 %. The maximum increase in the dissolution rate was observed with Cross Povidone amongst the three superdisintegrants.The less disintegrating time of Cross Povidone due to the thickness of the tablet was increased.

Cross Povidone containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly so formulation F12 producued better drug release compare to all formulations.

The rapid increase in dissolution of amlodipine besylate with the increase in croscarmellose sodium may be due to rapid swelling and disintegrating tablets rapidly into apparently primary particles. While tablets formulated with sodium starch glycolate, disintegrate by rapid uptake of water, followed by rapid and enormous swelling into primary particle but more slowly due to the formation of a viscous gel layer by sodium starch glycolate.Cross povidone containing tablets rapidly exhibits high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrates the tablets rapidly so formulation F12 produced better drug release compare to all formulations. Thus difference in the size distribution generated with different superdisintegrants might have contributed to difference in the % drug release values with the same amount of superdisintegrants in the tablets.

Table 1. Composition of Amlodipine Besylate tablets formulated with various super disintegrating agents by steam granulation technique

	Formulation code(mg)											
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Amlodipine besylate	10	10	10	10	10	10	10	10	10	10	10	10
Cross carmallose sodium	2	4	6	8	-	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	2	4	6	8	-	-	-	-
Cross povidone	-	-	-	-	-	-	-	-	2	4	6	8
Micro crystalline cellulose	86	84	82	80	86	84	82	80	86	84	82	80
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1

Table 2. Evaluation of Amlodipine Besylate tablets containing Cross Carmellose Sodium

	Formulations			
Parameters	**F1**	**F2**	**F3**	**F4**
Average weight	97±0.87	98±0.54	100±0.75	99±0.3+7
Hardness(kg/cm^2)	3.0±0.12	3.2±0.08	3.4±0.23	3.6±0.17
Thickness (mm)	2.27±0.03	2.35±0.01	2.41±0.04	2.46±0.07
Friability (%)	0.64±0.02	0.62±0.04	0.66±0.08	0.64±0.01
Drug content (%)	96.6±0.16	97.2±0.31	99.2±0.24	98.2±0.36
Disintegration time (sec)	32	26	24	21

The average weight of tablets F1, F2, F3, F4 are as follows 97 ± 0.87, 98 ± 0.54, 100 ± 0.75, 99 ± 0.37, Hardness of tablets F1, F2, F3, F4 are 3.0 ± 0.12, 3.2 ± 0.08, 3.4 ± 0.23, 3.6 ± 0.17, thickness of tablets F1, F2, F3, F4 are 2.27 ± 0.03, 2.35 ± 0.01, 2.41 ±0.04, 2.46 ± 0.07, % friability of tablets F1, F2, F3, F4 are 0.64 ± 0.02, 0.62 ± 0.04, 0.66 ±0.08, 0.64 ± 0.01, drug content of F1, F2, F3, F4 were found to be 96.6 ± 0.16, 97.2 ± 0.13, 99.2 ± 0.24, 98.2 ± 0.36, and disintegration time of F1, F2, F3, F4 was found to be 32, 26, 24, 21secs respectively. From the above results all the formulations showed uniform weight, hardness, friability, thickness and drug content within limit [7].

Table 3. Evaluation of Amlodipine Besylate tablets containing Sodium Starch Glycolate

PARAMETERS	FORMULATIONS			
	F5	**F6**	**F7**	**F8**
Average weight	97±0.76	100±0.34	98±0.56	101±0.79
Hardness(kg/cm^2)	3.0±0.12	3.2±0.16	3.5±0.32	3.7±0.14
Thickness(mm)	2.34±0.06	2.31±0.01	2.47±0.03	2.52±0.05
Friability (%)	0.72±0.12	0.7±0.16	0.71±0.09	0.67±0.32
Drug content (%)	95.5±0.12	96.2±0.45	96.7±0.56	97.2±0.32
Disintegration time (sec)	35	32	27	24

The average weight of the tablets F5, F6, F7, F8 are as follows 97 ± 0.76, 100 ± 0.34, 98 ± 0.56, 101 ± 0.79, Hardness of F5, F6, F7, F8 were found to be 3.0 ± 0.12, 3.2 ± 0.16, 3.5 ± 0.32, 3.7 ± 0.14, Thickness were found to be2.34 ± 0.06, 2.31 ± 0.01, 2.47 ± 0.03, 2.52 ± 0.05, % Friability of F5, F6, F7, F8 were found to be 0.72 ± 0.12, 0.7 ± 0.16, 0.71 ± 0.09, 0.67 ± 0.33,Drug content of F5, F6, F7, F8 were found to be 95.5 ± 0.12, 96.2 ± 0.45, 96.7± 0.56, 97.2 ± 0.32, ana the Disintegration time of F5, F6, F7 F8 were found to be 35, 32, 27, 24.., respectively. From the above results all the formulations showed uniform weight, hardness, friability, thickness, disintegration time and drug content were within limits [8].

Table 4. Evaluation of Amlodipine Besylate tablets containing Cross Povidone

PARAMETERS	FORMULATIONS			
	F9	**F10**	**F11**	**F12**
Average weight	98±0.34	99±0.67	100±0.19	100±0.53
Hardness(kg/cm^2)	3.0±0.13	3.3±0.08	3.5±0.23	3.9±0.37
Thickness(mm)	2.46±0.04	2.43±0.01	2.48±0.03	2.51±0.06
Friability(%)	0.7±0.01	0.6±0.05	0.65±0.02	0.72±0.12
Drug content (%)	98±0.21	99.7±0.35	99.5±0.51	100±0.79
Disintegration time (sec)	28	25	24	21

The results of physico-chemical evaluation of tablets were resulted in table 4.The average weight of the tablets F9, F10, F11, F12 are as follows 98 ± 0.34, 99 ± 0.67, 100 ± 0.19, 100 ± 0.53, Hardness of F9, F10, F11, F12 3.0 ± 0.13, 3.3 ± 0.08, 3.5 ± 0.23, 3.9 ± 0.37, % friability of F9, F10, F11, F12 were found to be 0.7 ± 0.01, 0.6 ± 0.05, 0.65 ± 0.02, 0.72 ± 0.12,Drug content of F9, F10, F11, F12 were found to be 98 ± 0.21, 99.7 ± 0.35, 99.5 ± 0.51, 100 ± 0.79,and the disintegration time of F9, F10, F11,F12 were found to be 28, 25, 24, 21sec respectively.,. From the above results all the formulations showed uniform weight, hardness, friability, thickness and drug content within limit [9].

Table 5. In vitro dissolution data of Amlodipine Besylate tablets containing various concentrations of Cross Carmellose Sodium

TIME (mins)	% DRUG RELEASE			
	F1	F2	F3	F4
0	0	0	0	0
5	28.52±0.08	30.52±0.02	40.46±0.06	42.86±0.08
10	36.81±0.03	39.69±0.08	48.22±0.04	80.22±0.01
15	50.88±0.07	55.86±0.03	68.55±0.03	65.24±0.09
20	59.69±0.04	60.52±0.07	72.43±0.01	78.69±0.03
25	62.22±0.01	72.48±0.05	83.29±0.08	82.88±0.04
30	79.05±0.05	86.29±0.06	90.07±0.01	91.41±0.09

Table 6. Dissolution kinetics of Amlodipine Besylate tablets formulated with various concentrations of Cross Carmellose Sodium

Formulations	Correlation coefficient (r) value		Release rate constant K_1 (Min^{-1})
	Zero order	First order	
F1	0.865	0.925	0.041
F2	0.847	0.958	0.045
F3	0.825	0.941	0.062
F4	0.869	0.936	0.072

Table 7. Dissolution data of Amlodipine Besylate tablets containing various concentrations of Sodium Starch Glycolate

TIME (mins)	% Drug Release			
	F5	F6	F7	F8
0	0	0	0	0
5	29.88±0.04	30.31±0.06	32.21±0.03	39.82±0.06
10	35.13±0.03	41.23±0.03	42.66±0.04	45.83±0.02
15	45.53±0.07	45.55±0.01	50.59±0.01	52.44±0.04
20	52.43±0.02	50.43±0.05	65.81±0.09	67.84±0.01
25	69.63±0.06	72.57±0.08	70.51±0.05	80.25±0.03
30	80.88±0.01	82.48±0.02	88.22±0.07	90.56±0.05

Table 8. Dissolution kinetics of Amlodipine Besylate tablets formulated with various concentrations of Sodium Starch Glycolate

Formulations	Correlation coefficient (r) value		Release rate constant K_1 (Min^{-1})
	Zero order	First order	
F5	0.925	0.947	0.048
F6	0.934	0.950	0.05
F7	0.939	0.954	0.06
F8	0.915	0.938	0.07

Table 9. Dissolution data of Amlodipine Besylate tablets containing various concentrations of Cross Povidone.

TIME (mins)	% DRUG RELEASE			
	F9	F10	F11	F12
0	0	0	0	0
5	38.22±0.01	43.92±0.06	46.69±0.03	40.66±0.03
10	46.67±0.08	50.55±0.03	52.58±0.06	55.59±0.06
15	52.23±0.06	59.66±0.02	60.19±0.02	68.42±0.01
20	61.84±0.03	68.56±0.09	74.62±0.05	79.47±0.09
25	75.68±0.09	75.47±0.04	85.44±0.04	89.62±0.05
30	81.46±0.07	86.28±0.09	95.41±0.08	98.51±0.07

Table10. Dissolution kinetics of Amlodipine Besylate tablets formulated with various concentrations of Cross Povidone

Formulations	Correlation coefficient (r) value		Release rateconstant K_1 (Min^{-1})
	Zero order	First order	
F9	0.885	0.955	0.044
F10	0.852	0.958	0.046
F11	0.871	0.952	0.068
F12	0.860	0.956	0.091

Fig 1. FT- IR spectra of pure drug (Amlodipine Besylate)

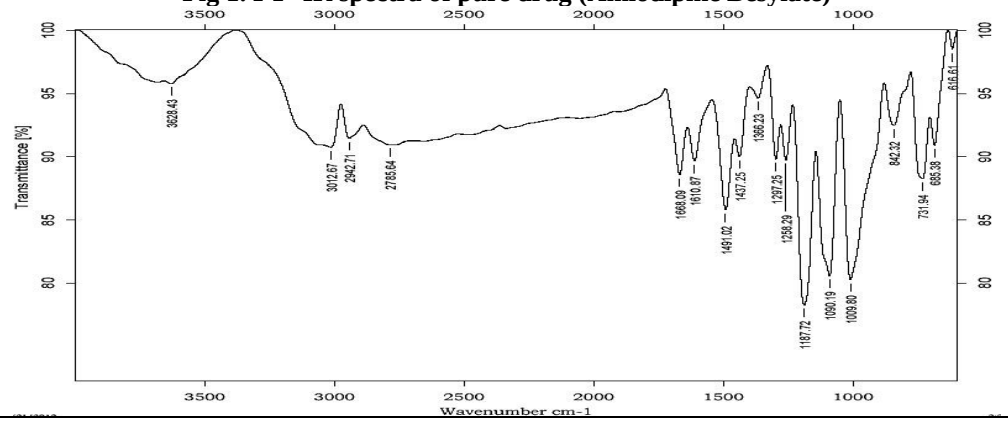


Fig 2. FT-IR spectra of drug +Cross povidone

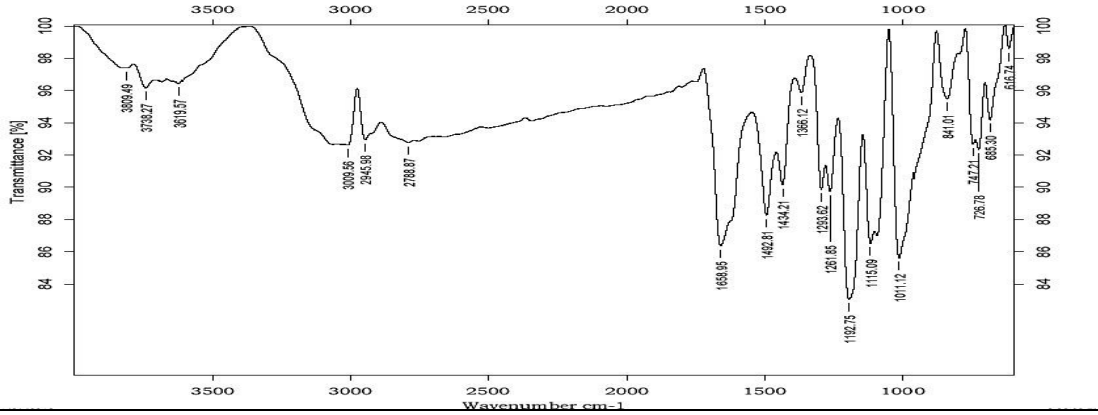


Fig 3. FT-IR spectra of drug + Cross Carmellose Sodium

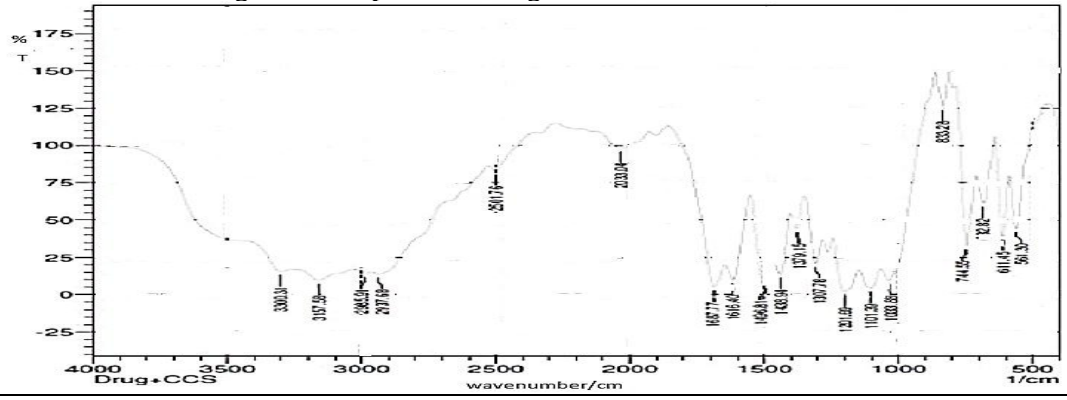


Fig 4. FT-IR spectra of drug + Sodium Starch Glycolate

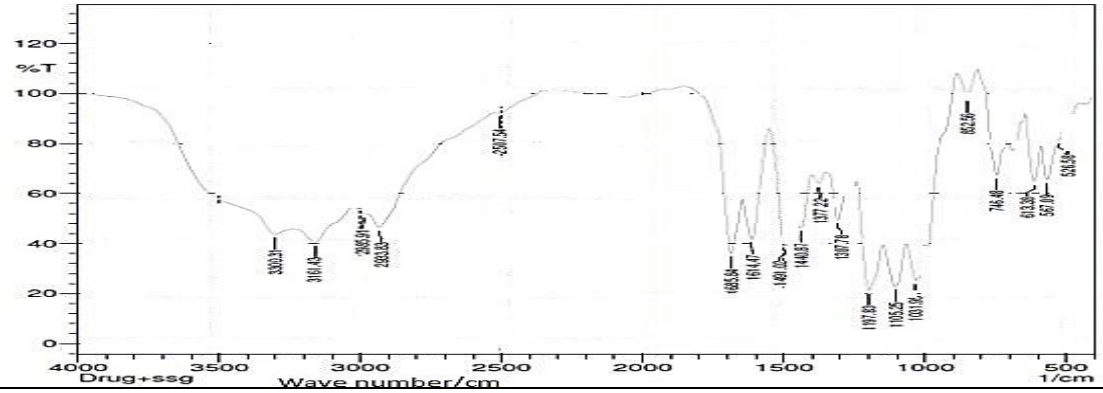


Fig 5. In vitro release profiles of Amlodipine Besylate tablets containing various Concentrations of Cross Carmellose Sodium

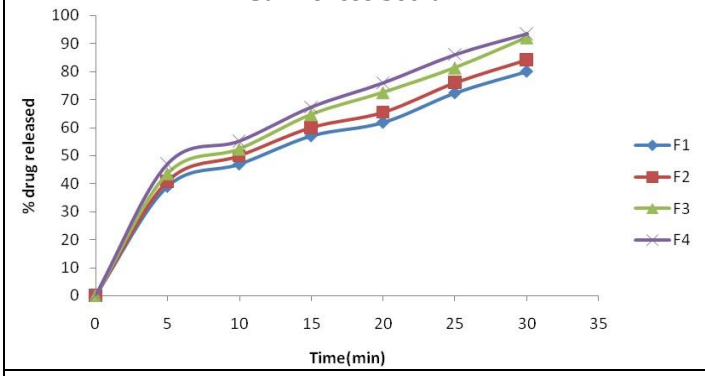


Fig 6. First order plots of Amlodipine Besylate tablets containing various concentrations of Cross Carmellose Sodium prepared by steam granulation method

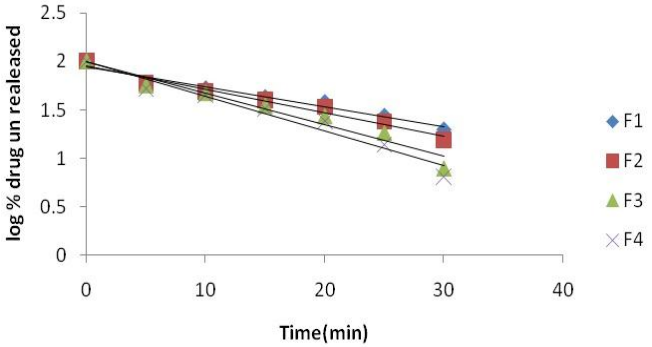


Fig 7. In vitro release profiles of Amlodipine Besylate tablets containing various concentrations Sodium Starch Glycolate

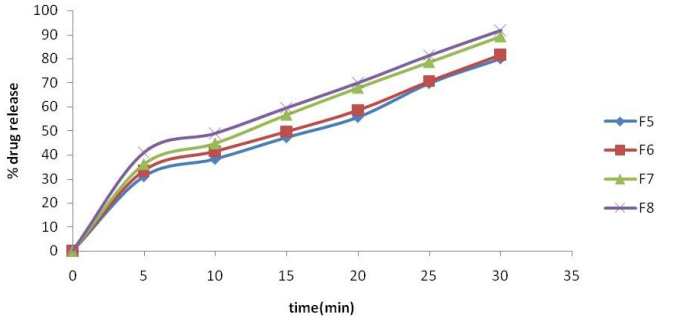


Fig 8. First order plots of Amlodipine Besylate tablets containing various concentrations of Sodium Starch Glycolate prepared by direct compression method

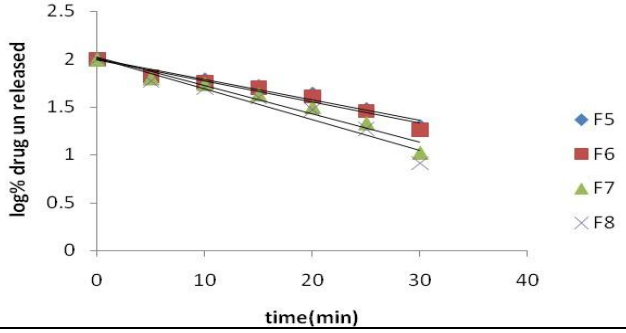


Fig 9. In vitro release profiles of Amlodipine Besylate tablets containing various concentrations of Cross Povidone.

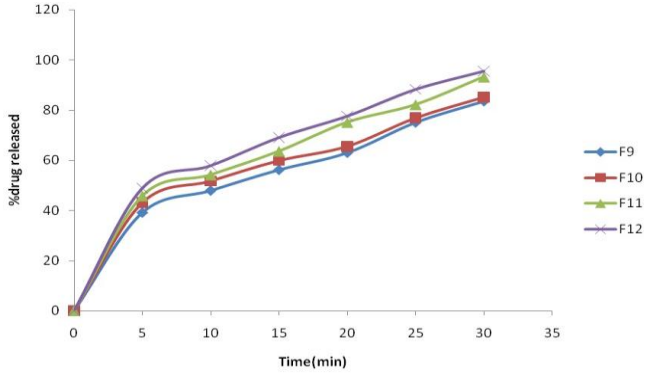
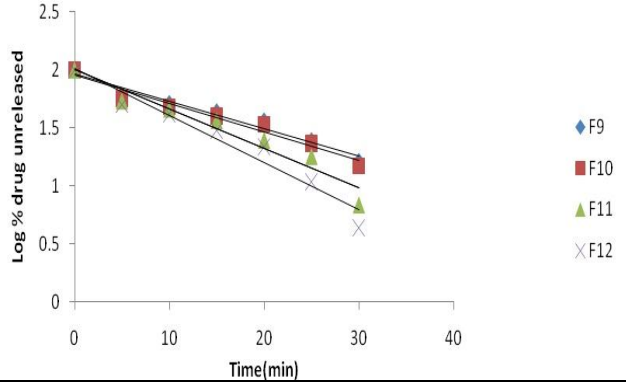


Fig 11. First order plots of Amlodipine Besylate tablets containing Cross Povidone prepared by steam granulation method.



SUMMARY AND CONCLUSION

The formulations F1, F2, F3 and F4 having Cross Carmellose Sodium as superdisintegrant at a concentration of 2, 4, 6, 8% respectively. The formulations F5, F6, F7and F8 having Sodium Starch Glycolate as superdisintegrant at a concentration of 2, 4, 6, 8% respectively. The formulations F9, F10, F11and F12 having Cross Povidone as superdisintegrant at a concentration of 2, 4, 6, 8% respectively.

The formulation of F12having less disintegration time compare to all formulations. The maximum increase in the dissolution rate was observed with Cross Povidone amongst the three superdisintegrants. So, formulation F12 producued better drug release compare to all formulations.

- Drug excipient compatability studies were investigated by FT-IR spectroscopy studies, that results indicated that the Amlodipine Besylate was compatible with all the excipients i.e Cross Carmellose Sodium, Sodium Starch Glycolate and Cross Povidone.
- Precompression parameters (angle of repose, bulk density, tapped density, Hausner's ratio and car'sindex) of Amlodipine Besylate tablets were found to be within limits.
- Postcompressional parameters (hardness, friability,

thickness and drug content) of Amlodipine Besylate tablets werefound to be within the acceptable limits.

- The % drug release for the formulations F1, F2, F3 and F4 were 79.05± 0.05, 86.29 ±0.06, 90.07± 0.01 and 91.41± 0.09 observed at the end of 30 mins.
- The % drug release for the formulations F5, F6, F7 and F8 were 80.88±0.01, 82.48±0.02, 88.22± 0.07 and 90.56± 0.05 observed at the end of 30 mins.
- The % drug release for the formulations F9, F10, F11 and F12 were 81.46±0.07, 86.28 ± 0.09, 95.41± 0.08 and 98.51± 0.07 observed at the end of 30 mins.

Finally, it was concluded that the formulation F12 was optimized as better formulation hence it shows fast release amongst all the formulations. The best release of the formulation F12 due to the disintegrating agents of Cross Povidone and shape of the tablet.

ACKNOWLEDGEMENT
Nil

CONFLICT OF INTEREST
None.

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