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COMPARATIVE STUDY OF FORMULATIONS OF FAST DISINTEGRATING TABLET OF AMLODIPINE BESYLATE BY DIRECT COMPRESSION AND SUBLIMATION METHODS

Nawa Raj Khadka[*1], Junu Khatri Silwal[2], Anil Prasad Shah[3], Rajendra Ayer[4], Emi Maharjan[5] and Srijan Maharjan[6]

[1,2,3,4,5,6]National Model College for Advance Learning, Kathmandu, Nepal.

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***Correspondence for Author**
Nawa Raj Khadka
National Model College for Advance Learning, Kathmandu, Nepal.

ABSTRACT

The aim of present study was to formulate and evaluate fast disintegrating tablets of Amlodipine Besylate for faster action. The comparative study was carried out for selecting best super disintegrant and methods used for preparing fast disintegrating tablets. The superdisintegrants used in this study were Croscarmellose Sodium (CCS), Sodium Starch Glycolate (SSG) and Crospovidone (CP) in varying concentrations (4%, 6% and 8%). The methods used were direct compression method and sublimation method. Menthol was used as sublimating agents. The pre-compression parameters such as bulk density, tapped density, angle of repose, carr's index and hausner's ratio were evaluated. The post compression parameters such as weight variation, thickness, hardness, friability and assay were also evaluated. The major parameters considered for optimization of the formulation were wetting time, disintegration time and *in –vitro* drug release. The pre-compression and post compression parameters were found within limit range as specified. Among various formulations containing different superdisintegrants prepared by direct compression method and sublimation method, the formulation SBC3 prepared using 8% Croscarmellose Sodium by sublimation method showed least wetting time of 9 seconds, disintegration time of 10 seconds and faster dissolution rate of about 95% in 4 minutes and 99.2% in 10 minutes. Formulation SBC3 has been chosen as optimized formulation for preparation of fast disintegrating tablet of Amlodipine Besylate. Thus, Fast disintegrating tablet of Amlodipine Besylate can be best prepared using Croscarmellose sodium as super disintegrant by sublimation method for faster action of drug.

KEYWORDS: Fast disintegrating tablets, Amlodipine Besylate, Superdisintegrants, direct compression, sublimation method.

INTRODUCTION

Despite of tremendous advancements in drug delivery, the oral route still remains the perfect route for the administration of therapeutic agents. Among various oral dosage forms tablet is the most preferred one. Fast disintegrating drug delivery system are Novel Drug Delivery techniques aim for designing dosage forms, convenient to be manufacture and administer without water, free of side effects, offering immediate release, so as to achieve better patient compliance. Such types of formulation is specially designed for pediatric, geriatric, bedridden, psychotic patients who are unable to swallow or refuse to swallow conventional oral formulation and also for active patients who are busy and traveling and may not have access to water.[1] Fast disintegrating drug delivery systems have also been introduced to overcome the drawback of low bioavailability problems associated with conventional oral dosage forms.[2] The medication can 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 gastrointestinal tract.[3] Challenges in Formulating Fast disintegrating tablet (FDT) are Palatability, Mechanical strength, Hygroscopicity, Amount of drug, Aqueous solubility and Size of tablet.[4] Ingredients Mostly Used in FDT are Super Disintegrants, Sugar Based Excipients, Anti-adherents, Binders, Disintegrants Fillers or diluents, Flavours, Colours, Lubricants, Glidants, Preservatives, Sweeteners and Sublimating Agents.[5] Mechanism of Action of Super Disintegrants includes Capillary Action, Swelling, Heat of Wetting (Air Expansion), Release of Gases, Enzymatic Reaction, Disintegrating Particle/Particle Repulsive Forces and deformation.[1,6] Different Technologies for Formulation of FDT are Direct Compression.[7] Freeze-Drying or Lyophilisation, Spray Drying, Mass extrusion, Molding, Cotton Candy Process, Nanonization[1,8] and Sublimation.[6] Important Patented Technologies includes Durasolv Technology,[6] Zydis Technology, Wow Tab Technology, Orasolv Technology and Flash tab Technology.[1,8] To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without need of water. In the present study, an attempt has been made to develop fast disintegrating tablets of Amlodipine besylate.

MATERIAL AND METHOD

Materials

Amlodipine Besylate was received as gift sample from the Lomus Pharmaceuticals Pvt. Ltd. Gothatar, Kathmandu, Nepal. Other ingredients such as Crospovidone, Microcrystalline cellulose, Sodium Starch Glycolate, Mannitol, Magnesium Stearate, Talc, Aspartame were obtained from research laboratory of National Model College of Advance Learning (NMCAL). All the chemicals and reagents used were of analytical grade.

Methods

Determination of λ max of Amlodipine Besylate in 0.01 N HCL

Weighed amount of Amlodipine Besylate was dissolved in 0.01N HCL to obtain a 1000mcg/ml solution. This solution was subjected to scanning between 200-400 nm and absorption maximum was determined.

Analytical method validation

Analytical method validation was done in terms of linearity, Accuracy, precision, Specificity, Detection limit, Quantitation limit and Range.[9]

Fabrication of tablet

Tablets were prepared by both direct compression and sublimation method. In totality 18 batches were prepared among which 9 batches by direct compression method and 9 batches by sublimation method. Batch size of each formulation was 100 tablets and weight of each tablet was 150 mg.

Direct compression method

All ingredients were weighted as per requirement and stored separately. For uniformity in particle size each material is passed through sieve no. 60 before mixing. First MCC PH101 was mixed with Mannitol. Then the API was mixed geometrically with the previous mixture manually. After that, disintegrants along with lubricant were added to the mixture then tumbled in poly bag for about 5 minutes. The Compression was performed using 10 station compression machines. The punching tool was round, biconvex, 8mm in plain diameter. The total weight of the formulation was maintained at 150mg.

Table 1: Composition of formulations prepared by direct compression method.

Ingredients (mg)	Formulation Code								
	DCC1	DCC2	DCC3	DCS1	DCS2	DCS3	DCP1	DCP2	DCP3
Amlodipine Besylate	10	10	10	10	10	10	10	10	10
MCC	80	80	80	80	80	80	80	80	80
Mannitol	42	39	36	42	39	36	42	39	36
CCS	6 (4%)	9 (6%)	12 (8%)	-	-	-	-	-	-
SSG	-	-	-	6 (4%)	9 (6%)	12 (8%)	-	-	-
CP	-	-	-	-	-	-	6 (4%)	9 (6%)	12 (8%)
Aspartame	10	10	10	10	10	10	10	10	10
Talc	1	1	1	1	1	1	1	1	1
Magnesium Sterate	1	1	1	1	1	1	1	1	1
Total Weight	150	150	150	150	150	150	150	150	150

Sublimation method

The basic principle involved in preparing fast disintegrating tablets by sublimation technique is addition of inert solid ingredient to other tablet excipients. Sublimating agent (menthol) used was triturated prior to use and was then passed through sieve no.60. Prepare power was then compressed. After compression the compressed tablets were collected and vacuum dried at 70°C until a constant weight was obtained to ensure that the complete removal of sublimable components to make the tablet porous. End point of the process is indicated by the complete removal of the menthol by sublimation. The removal of the menthol after sublimation was confirmed by weighing the tablets before and after sublimation.

Table 2: Composition of formulation prepared by sublimation method.

Ingredients (mg)	Formulation Code								
	SBC1	SBC2	SBC3	SBS1	SBS2	SBS3	SBP1	SBP2	SBP3
Amlodipine Besylate	10	10	10	10	10	10	10	10	10
MCC	80	80	80	80	80	80	80	80	80
Mannitol	32	29	26	32	29	26	32	29	26
CCS	6 (4%)	9 (6%)	12 (8%)	-	-	-	-	-	-
SSG	-	-	-	6 (4%)	9 (6%)	12 (8%)	-	-	-
CP	-	-	-	-	-	-	6 (4%)	9 (6%)	12 (8%)
Menthol	10	10	10	10	10	10	10	10	10
Aspartame	10	10	10	10	10	10	10	10	10
Talc	1	1	1	1	1	1	1	1	1
Magnesium Sterate	1	1	1	1	1	1	1	1	1
Total Weight	150	150	150	150	150	150	150	150	150

Evaluation of pre compression parameters

Pre compression parameters were evaluated in terms of Bulk Density, Tapped Density, Angle of repose,[10] Carr's Index and Hausner's Ratio.[11]

Evaluation of post compression parameters

The post compression parameters were evaluated in terms of Weight variation, Thickness, Hardness, Friability[12] and Assay.[13]

Assay

Twenty tablets from each formulation was taken, weighed and crushed in mortar to make powder. A quantity of powder weighing equivalent to 10 mg of Amlodipine Besylate was taken in 100 ml volumetric flask. Initially, 10 ml of 0.01 N HCL was added and it was sonicated for 15 minutes. Then, the volume was made up to 100ml with same solution and it was filtered. 10 ml of the resulting solution was diluted to 100 ml with 0.01 N HCL. The absorbance of the resulting solution was analyzed spectrophotometrically at 239 nm using 0.01 N HCL as blank and the amount of drug present was determined.[13]

The drug content was calculated using the following equation.

$$\text{Drug content per tablet} = \frac{spl\ abs}{std\ abs} \times \frac{std\ weight}{spl\ weight} \times \frac{spl\ dil}{std\ dil} \times \frac{\text{std potency}}{100} \times Avg.Wt\ of\ tab \ldots\ldots 1$$

$$\%\ \text{of label claimed} = \frac{Quantity\ found\ per\ tablet}{Label\ claim} \times 100 \ldots\ldots\ldots\ldots 2$$

Optimization of the formulation

Wetting time[14]

To measure wetting time, five circular tissue papers of 10 cm diameter are placed in a petri dish with a 10 cm diameter. 10 ml of distilled water was taken in a petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

In-vitro disintegration time[15]

In-vitro disintegration test was determined by using disintegrating apparatus. Six tablets from each formulation were taken and tablets were kept in each tube of disintegration test apparatus (USP) containing 900 ml of distilled water. Temperature was maintained at 37± 2°C. The result was expressed as disintegration time± standard deviation.

In-vitro Dissolution test[16]

In vitro release of Amlodipine Besylate tablets were carried out in USP dissolution testing apparatus type II by paddle method. The dissolution medium was 900 ml phosphate buffer pH 7.4 at 50 rpm and 37 ± 0.5ºC. A 10 ml of sample was periodically withdrawn at 2, 4, 6, 8, 10, 15, 20 and 30 minutes and volume replaced with equivalent amounts of same dissolution medium to maintained sink condition. The samples were analyzed spectrometrically at 239 nm by using Phosphate buffer pH 7.4 as a blank and drug content in dissolution sample were determined.

$$\%\ \text{drug release per tab} = \frac{spl\ abs}{std\ abs} \times \frac{spl\ dil}{std\ dil} \times \frac{900}{10} \times \frac{\text{std potency}}{100} \times 100\% \quad \text{.....3}$$

RESULT AND DISCUSSION

Determination of λ max of Amlodipine Besylate in 0.01 N HCL

The λ max of amlodipine besylate in 0.01 N HCL was found to be 239nm.

Analytical Method Validation

The method was found accurate with % recovery of 98.6%, 99.5% and 101.5% respectively for three different concentrations (7.5 µg/ml, 10 µg/ml and 12.5 µg/ml) which were within the range (98-102)%. The method was also Precise with mean RSD value of 0.153 which was less than 2%. The method was specific for Amlodipine Besylate. The limit of detection of Amlodipine Besylate is 0.338µg/ml. The limit of quantification of Amlodipine Besylate is 1.176µg/ml. The range of concentration detected was found to be 0.338µg/ml to 25µg/ml. The value of correlation coefficient (R^2) was determined to be 0.9998.

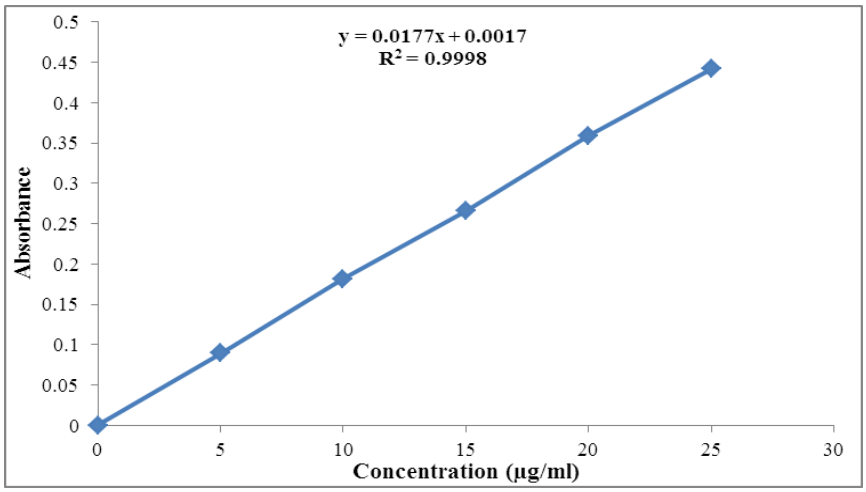

Figure 1: Calibration curve of Amlodipine Besylate reference standard in 0.01 N HCL.

Evaluation of Fast Disintegrating Tablets of Amlodipine Besylate

Pre-compression Parameters

Tablets were evaluated for pre-compression parameters for both direct compression method and sublimation method.

Table 3: Result of pre-compression parameters of Direct Compression method.

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of repose (^{0})	Carr's index (%)	Hausner's Ratio
DCS1	0.5±0.007	0.625±0.02	29.25±1.5	20±1.5	1.25±0.03
DCS2	0.5±0.007	0.606±0.03	28.43±1.48	17.49±1.39	1.21±0.04
DCS3	0.5±0.007	0.645±0.06	30.72±1.22	22.48±1.58	1.29±0.03
DCC1	0.5±0.007	0.606±0.03	29.24±1.35	17.49±1.20	1.21±0.04
DCC2	0.5±0.007	0.645±0.06	30.03±0.87	22.48±1.20	1.29±0.03
DCC3	0.5±0.007	0.625±0.01	30.1±1.70	20±1.58	1.25±0.04
DCP1	0.48±0.007	0.606±0.02	29.86±1.23	20.79±1.43	1.26±0.03
DCP2	0.5±0.007	0.625±0.05	28.04±1.34	20±1.58	1.25±0.04
DCP3	0.5±0.007	0.645±003	26.28±1.47	22.48±1.57	1.29±0.03

Table 4: Result of pre-compression parameters of Sublimation method.

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of repose (^{0})	Carr's index (%)	Hausner's Ratio
SBS1	0.53±0.007	0.64±0.01	29.21±1.52	18±1.62	1.20±0.04
SBS2	0.50±0.007	0.63±0.01	27.23±1.12	20±1.58	1.26±0.03
SBS3	0.54±0.007	0.65±0.02	28.20±1.20	19±1.53	1.20±0.04
SBC1	0.51±0.007	0.65±0.01	29.25±156	17±1	1.27±0.02
SBC2	0.52±0.007	0.62±0.01	28.02±1.20	16±1.51	1.19±0.04
SBC3	0.53±0.007	0.61±0.02	29.11±1.70	13±1.20	1.15±0.03
SBP1	0.52±0.007	0.63±0.38	30.10±0.87	17±2.51	1.20±0.04
SBP2	0.51±0.007	0.62±0.02	29.04±1.34	16±1.51	1.21±0.04
SBP3	0.53±0.007	0.63±0.01	30.28±1.26	16±1.55	1.18±0.03

Post-compression Parameters

Table 5: Post-compression parameters for Direct Compression method.

Formulation Code	Average Weight (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)
DCC1	152±0.82	3.79±0.04	3.5±0.12	0.53	97.4±1.83
DCC2	152±0.83	3.76±0.05	3.6±0.11	0.66	98.7±1.07
DCC3	152±0.73	3.65±0.03	3.7±0.12	0.68	99.6±1.06
DCS1	150±0.56	3.89±0.05	3.7±0.15	0.52	97.5±0.73
DCS2	151±0.74	3.72±0.04	3.8±0.18	0.66	98.4±0.65
DCS3	151±0.64	3.64±0.04	3.6±0.12	0.70	99.7±0.45
DCP1	151±0.84	3.70±0.03	3.6±0.21	0.69	98.6±0.67
DCP2	153±0.73	3.76±0.05	3.8±0.10	0.78	98.6±0.39
DCP3	152±0.46	3.65±0.06	3.6±0.13	0.87	99.3±0.39

Table 6: Post-compression parameters for Sublimation method.

Formulation Code	Average Weight (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)
SBC1	149±1.78	3.59±0.03	3.1±0.12	0.62	99±0.83
SBC2	149±1.32	3.66±0.05	3.2±0.11	0.70	98±1.58
SBC3	150±1.97	3.45±0.02	3.7±0.10	0.84	98±0.36
SBS1	148±0.65	3.69±0.06	3.4±0.15	0.62	98±0.83
SBS2	147±1.74	3.62±0.03	3.5±0.21	0.67	97±0.65
SBS3	148±1.23	3.34±0.03	3.6±0.12	0.78	98±1.23
SBP1	150±1.50	3.65±0.02	3.5±0.21	0.79	98±1.67
SBP2	147±1.43	3.26±0.03	3.3±0.15	0.80	99±0.29
SBP3	149±0.16	3.53±0.05	3.2±0.13	0.93	98±0.39

The assay was found 98.4% - 99.02% for the formulation prepared by direct compression and 98.09% - 99.6% for the formulation prepared by sublimation method. The results which complies with the IP specification which states that Amlodipine Besylate tablet contains not less than 97.0 percent and not more than 100.2 percent of labeled amount of $C_{20}H_{25}CIN_2O_5C_6H_6O_3S$.[17]

The percentage of drug content was found in the range of 97.4% - 99.7% for the formulation prepared by direct compression and the percentage of drug content was found in the range of 98.0% - 99% for the formulation prepared by sublimation approach. The results complies with the IP specification which states that tablets must contain not less than 85% and not more than 115% of lebelled amount of drug.

Comparison between disintegration time and wetting time of direct compression method.

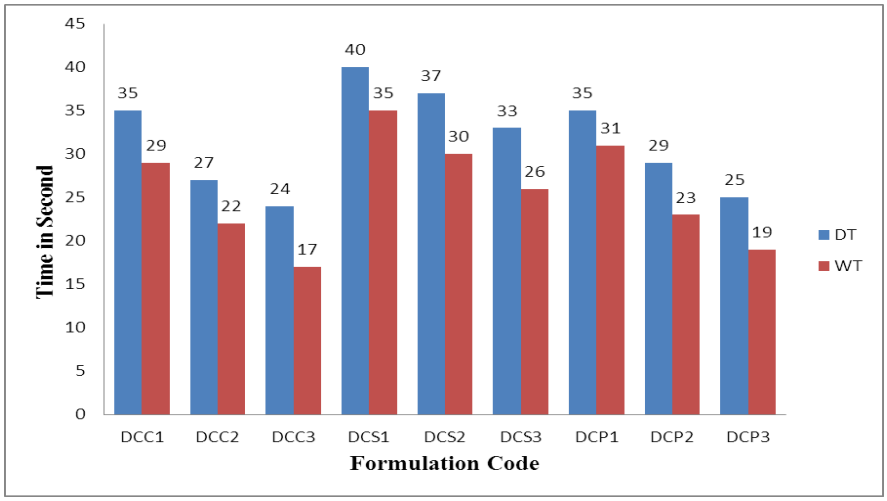

Figure 2: Comparison of disintegration and wetting time of direct compression method.

Among the different formulation prepared by direct compression with different concentration of superdisintegrants (CCS, SSG and CP; 4%, 6% and 8%), Formulation DCC3 containing CCS 8% shows disintegration time at 24 seconds and wetting time at 17 seconds which shows best result among all other formulations. The result shows decrease in wetting time consequently decrease the disintegration time.

Comparison between disintegration time and wetting time of sublimation method.

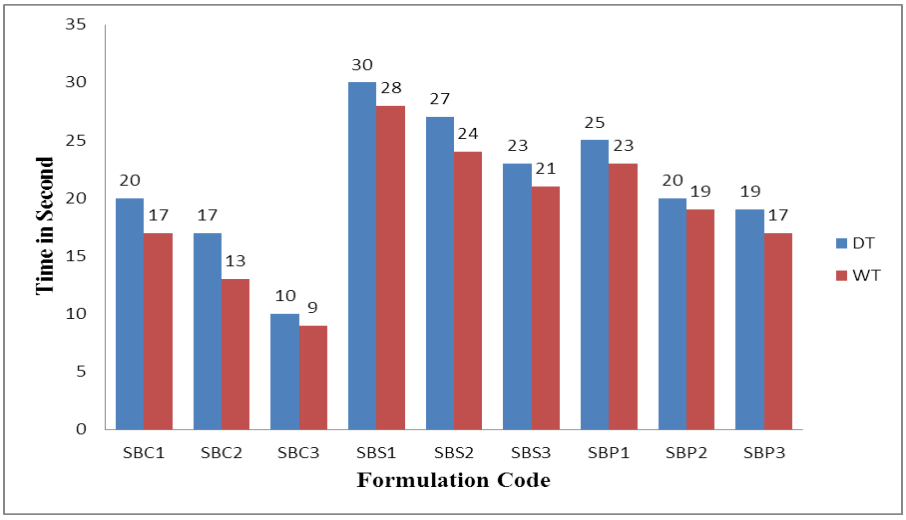

Figure 3: Comparison of disintegration and wetting time by sublimation method.

Among the different formulation prepared by sublimation with different concentration of superdisintegrants (CCS 4%, SSG 6%, CP 8%) along with sublimating agent menthol (6.6%), Formulation SBC3 containing 8% Croscarmellose sodium and 6.6% menthol shows disintegration time at 10 second and wetting time at 9 seconds which shows best result among all other formulations. The result of the formulation SBC3 shows that presence of menthol also enhanced disintegration and wetting time of the tablets. This may be due to the porous structure formed by menthol in the tablets which facilitates disintegration action of the superdisintegrants.

The disintegration time and wetting time of formulation prepared by direct compression and sublimation method with different concentration of Croscarmellose sodium (4%, 6%, 8%) were compared. Between two methods, formulations (SBC3) prepared by sublimation method shows minimum disintegration time and wetting time than direct compression method at the same concentration of Croscarmellose sodium used. This may be due to the porous structure formed by menthol in the tablets prepared by sublimation method which facilitates disintegration action and wetting time of the superdisintegrants.

Comparison of disintegration time of formulated batch with marketed products.

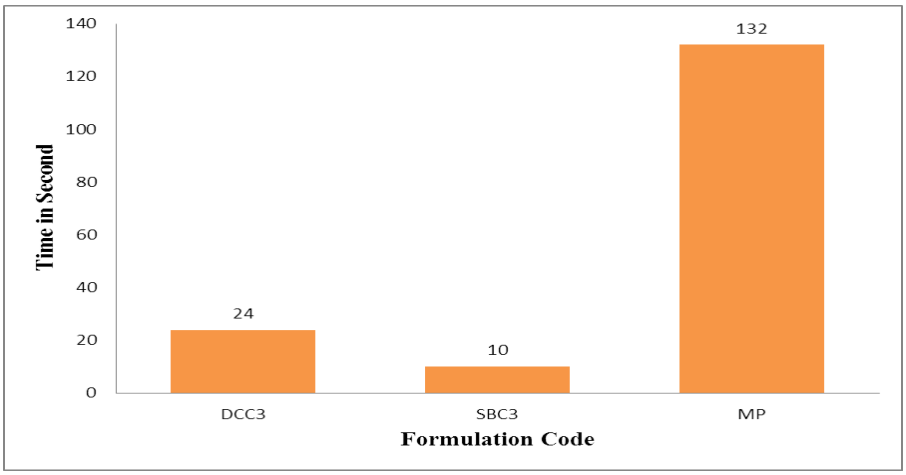

Figure 4: Comparison of disintegration time of formulated batch with market products.

The result shows that the disintegration time of formulations prepared by direct compression (DCC3; which contain Croscarmellose sodium 8%) at 24 seconds, sublimation method (SBC3; which contain Croscarmellose sodium 8% and menthol 0.66%) at 10 seconds which is least as compare to market products (MP).

Table 7: Drug release profile of Amlodipine Besylate prepare by direct compression containing Croscarmellose sodium.

Time (Min)	% Drug release								
	DCC1	DCC2	DCC3	DCS1	DCS2	DCS3	DCP1	DCP2	DCP3
2	37.22	38.17	39.36	30.14	32.63	35.11	35.06	36.41	38.21
4	46.24	48.35	49.37	39.02	43.25	43.34	44.11	46.05	47.89
6	61.91	67.90	73.08	51.13	53.42	68.44	50.00	56.68	70.17
8	70.94	75.23	80.16	69.15	74.03	76.82	67.91	70.01	78.11
10	86.13	89.42	93.51	82.07	84.33	87.12	85.45	87.04	91.62
20	93.90	94.36	97.56	90.10	91.94	94.11	92.73	93.35	94.11
30	96.45	97.34	99.66	95.34	96.65	97.34	95.34	96.65	97.34

Table 8: Drug release profile of Amlodipine Besylate prepare by sublimation containing Croscarmellose sodium.

Time (Min)	% Drug Release								
	SBC1	SBC2	SBC3	SBS1	SBS2	SBS3	SBP1	SBP2	SBP3
2	63.33	70.63	84.31	52.98	59.25	67.29	59.94	63.62	69.71
4	77.18	83.86	95.09	70.93	74.04	79.52	73.25	79.39	84.60
6	91.54	94.65	98.24	86.27	90.16	91.04	76.60	81.92	89.78
8	94.41	98.52	98.59	91.71	95.89	96.59	80.29	87.02	91.96
10	97.02	98.42	99.20	93.78	96.09	97.20	85.18	90.30	95.70
20	98.08	99.26	99.67	95.35	97.09	98.17	93.38	96.89	98.02
30	98.76	99.34	99.89	97.32	98.41	98.49	97.72	98.01	99.18

Among the various formulation prepared by direct compression, formulation DCC1, DCC2 and DCC3 which contains superdisintegrants 4%, 6% and 8% shows 86.13%, 89.42% and 93.51% of drug release at 10 min. The formulation DCC3 shows the best drug release profile among all other formulation prepared by direct compression. Whereas in case of sublimation method SBC1, SBC2 and SBC3 which contains superdisintegrants 4%, 6% and 8% along with sublimating agent menthol (6.6%) shows 97.02%, 98.42% and 99.20% of drug release at 10 min. The maximum drug release was observed in SBC3 between two methods which containing higher concentration of superdisintegrnts (CCS 8%) and sublimating agent menthol (6.6%). This shows that with increase in concentration of CCS along with menthol the drug release was also increased. These result showed that the release of drug was directly proportional to the concentration of disintegrant. Fast release of drug may be due to the porous structure formed within the tablets by menthol and which also facilitates the wicking action of Croscarmellose Sodium.

Comparison with market product

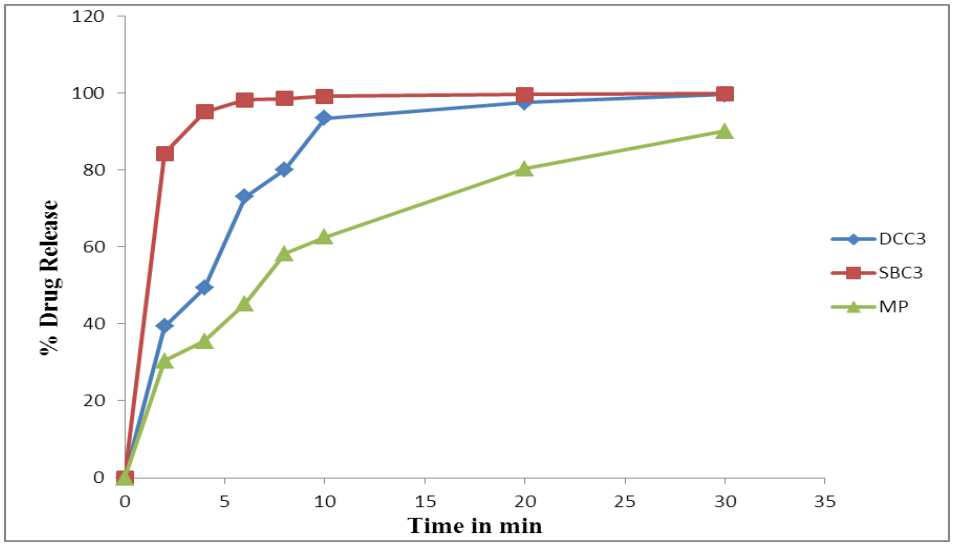

Figure 5: Comparison of market product with formulated product DCC3 and SBC3.

The conventional uncoated market product of Amlodipine Besylate was compared with formulated product DCC3 and SBC3. The *in vitro* release of market product (MP) was 62.56% at 10 min. whereas formulation prepared by direct compression (DCC3) was 93.51% and formulation prepared by sublimation method (SBC3) was 99.20% at 10 min.

CONCLUSION

Fast disintegrating tablets of Amlodipine Besylate can be prepared by using two different approaches; direct compression and sublimation method which could give desired

disintegration time of less than 15 seconds. Amlodipine Besylate was prepared successfully using different ratios of superdisintegrants. Out of 18 formulations formulated using various superdisintegrants like CCS (4%, 6%, 8%) SSG (4%, 6%, 8%) and CP (4%, 6%, 8%) among these formulation SBC3 containing 8% Croscarmellose Sodium (CCS) showed maximum drug release within 10 minutes of dissolution study. These formulations showed disintegration of 10 seconds respectively. Thus based on disintegration time and dissolution profiles, formulation SBC3 is optimized to be the best among all the 18 formulations. The study conclusively demonstrated significant results for Amlodipine Besylate fast disintegrating tablet. The fast disintegrating tablets of Amlodipine was mostly helpful to the patients for the management of cardiac failure, hypertension and angina. In this certain conditions patient leads to discomfort with or unwillingness to swallow the available oral tablet and associated water. Hence, at the end of this investigation it can be concluded that fast dissolving tablet of Amlodipine was successfully prepared by sublimation technique using different superdisintegrants.

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