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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF AMLODIPINE BESYLATE AND ATORVASTATIN CALCIUM

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ABSTRACT

The main aim of this study is to develop a fast-dissolving tablet containing both amlodipine besylate and atorvastatin calcium using superdisintegrants—Croscarmellose Sodium (CCS), and Sodium Starch Glycolate (SSG) at varying concentrations. Thirteen formulations were designed by central composite design (CCD) using Minitab software, in which the concentration of SSG was varied from 0.757% to 9.242% w/w and that of CCS from 0.171% to 5.828% w/w. The preparation process involves geometric mixing of the APIs along with the excipients, followed by direct compression. The UV-visible spectrophotometric method used for the estimation of both the drugs was validated for linearity, limit of detection, limit of quantitation, accuracy and precision. The powder blends were evaluated for pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The formulated tablets were investigated for thickness, appearance, organoleptic properties, weight variation, hardness, friability, wetting time, dispersion test, disintegration time, drug content and in vitro dissolution. FT-IR studies were carried out to determine possible drug–excipient interactions. IR spectra of pure drug Amlodipine and Atorvastatin and its mixture with excipients were analyzed and interpreted. Specturm obtained from FT-IR concluded no interaction occurred between drug and excipients. With addition of super disintegrating agents like Croscarmellose Sodium (CCS), Sodium Starch

Glycolate (SSG) Improved disintegration and dissolution parameters were obtained. Drug content on the optimized formulation for Amlodipine and Atorvastatin was found to be 96.14% and 100.15% and dissolution study for Amlodipine and Atorvastatin was found to be 95.17% and 95.55%. The disintegration time for the optimized formulation was 10 seconds. Fast dissolving tablet of Amlodipine Besylate and Atorvastatin Calcium using super disintegrants was successfully prepared and evaluated. Hence, fast dissolving tablet of Amlodipine and Atorvastatin can be used commercially for the better patient compliance which saves time as well as low cost.

KEYWORDS: Fast Dissolving Tablets, Amlodipine besylate, Atorvastatin Calcium, Superdisintegrants, Direct compression method.

INTRODUCTION

Fast dissolving tablets (FDTs) have emerged as an innovative solution to address these limitations, offering advantages such as ease of administration, enhanced patient compliance, and rapid drug dissolution. These are novel tablets that disintegrate, dissolve, or disperse in saliva. Their unique benefits—like the ability to administer them anytime, anywhere, and without the need for water—make them appropriate for both pediatric and elderly patients. Additionally, people who are immobile, mentally ill, or do not have easy access to water might use them. Due to their advantages over other dosage forms, such as patient compliance, quick start of action, higher bioavailability, and good stability, these tablets are currently very popular.[1]

Patients with swallowing difficulties, Fast Dissolving Tablets (FDTs) are the most commonly accepted and widely used drug delivery method i.e. mainly pediatric's and geriatric's. There is a high prevalence of dysphagia among all age groups, but it is more prevalent in pediatric and geriatric patients. The presence of FDTs with good taste and flavor contributes to the acceptance of bitter drugs. Currently one third of the population find it difficult to swallow tablet because of the medical issue and comorbid condition.[2]

Hypertension and hypercholesterolemia are the two major risk factors for cardiovascular diseases, which remain the leading cause of death worldwide.[3] The treatment of cardiovascular diseases frequently involves the use of two widely prescribed drugs, amlodipine besylate and atorvastatin calcium. Many symptoms in hypertensive and hyperlipidemic patients may be reduced using combination formulations of

antihyperlipidemic and antihypertensive agents. Combined dosage forms of two or more drugs have been proven useful in multiple therapies as they offer better patient compliance than a single drug.[4]

The well-known lipid-lowering and antihypertensive medications, atorvastatin and amlodipine are effective in treating these illnesses. Amlodipine besylate is a dihydropyridine calcium channel blocker, effectively lowers blood pressure by inhibiting calcium influx into vascular smooth muscle cells, thereby dilating coronary and peripheral arteries.[5] Similarly, Atorvastatin calcium, a member of the statin class, exerts its cholesterol-lowering effects by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis.[6]

Despite the availability of amlodipine and atorvastatin many individuals struggles to adhere to their medication regimen due to the fear of choking or confusion over too pills that needs to be taken which can lead to negative health outcome so FDTs are preferred over conventional dosage form.[6] Formulation of Atorvastatin Calcium and Amlodipine Besylate in FDTs is essential as it comes handy for the patient who may be suffering from hypertension and hyperlipidemia at the same time. It is preferred in fast dissolving tablet form rather than in liquid dosage form because of it's accuracy of dosing and stability for longer duration of time since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.[2]

However, the conventional oral dosage forms of these medications often face challenges related to patient compliance and onset of action. Fast dissolving drug technology is one of the best and ideal methods to improve patient compliance and bioavailability.[7] This work's primary goal was to create fast-dissolving tablets made of two distinct pharmacological classes employing a straightforward, simple and easily scalable formulation technique. As binders and fillers, many drug-compatible excipients were tested. Super disintegrating agents such as croscarmellose sodium (CCS), sodium starch glycolate (SSG) were employed to achieve rapid disintegration.[8]

MATERIALS AND METHODS

Materials

The main APIs used in the research (Amlodipine Besylate and Atorvastatin Calcium) were received as samples from Vega Pharmaceuticals, Lalitpur, Nepal. Sodium Starch Glycolate, Croscarmellose Sodium, Magnesium stearate, Microcrystalline cellulose, Starch, Colloidal silica were obtained from commercial sources. All other chemicals and reagents were of analytical grade. Direct compression machine (Accura), Monsanto hardness tester, friability tester, disintegration apparatus and dissolution apparatus (Optics Technology) and UV-Visible spectrophotometer (Shimadzu corporation) were used.

Experimental design

Various concentrations of superdisintegrants SSG (sodium starch glycolate) and CCS (Croscarmellose sodium) were calculated by using software (Minitab). CCD stands for Central Composite Design and it is an experimental design, useful in response surface methodology, for building a second order model for the response variable without needing to use a complete three-level factorial experiment. Formulation table for 13 formulation was designed by minitab using CCD design.

Table 1: CCD Design for CCS and SSG.

SSG (Sodium starch glycolate) (%)	CCS (Croscarmellose sodium) (%)
2.00	1.00
8.00	5.00
5.00	3.00
0.757	3.00
5.00	3.00
5.00	3.00
5.00	3.00
5.00	3.00
2.00	5.00
5.00	5.828
9.242	3.00
5.00	0.171
8.00	1.00

The formulations with different concentration of SSG in range of 0.757%-9.242% w/w and CCS in between the range of 0.171%-5.828% w/w were designed using CCD in minitab.

Formulation of Amlodipine Besylate and Atorvastatin Calcium in FDT

Fast dissolving tablet of atorvastatin calcium were prepared by using direct compression method. Amlodipine besylate (5 mg) and Atorvastatin Calcium were weighed along with all the excipients. After that, all ingredients, including the API and superdisintegrants, were mixed geometrically. Then, the blended mixture was compressed uniformly and consistently by using tablet compression machine. Finally fast dissolving tablet were formed.[9]

Table 2: Formulation table.

FN	Amlo-dipine	Atorva-statine	SSG	CCS	Mg stearate	Colloidal silica	Starch	Sodium Sacharine	MCC	Total CW
1	5	10	4.0	2.0	4	2	6	0.4	166.6	200
2	5	10	16.0	10.0	4	2	6	0.4	146.6	200
3	5	10	10.0	6.0	4	2	6	0.4	156.6	200
4	5	10	1.5	6.0	4	2	6	0.4	165.1	200
5	5	10	10.0	6.0	4	2	6	0.4	156.6	200
6	5	10	10.0	6.0	4	2	6	0.4	156.6	200
7	5	10	10.0	6.0	4	2	6	0.4	156.6	200
8	5	10	10.0	6.0	4	2	6	0.4	156.6	200
9	5	10	4.0	10.0	4	2	6	0.4	158.6	200
10	5	10	10.0	11.7	4	2	6	0.4	150.9	200
11	5	10	18.5	6.0	4	2	6	0.4	148.1	200
12	5	10	10.0	0.3	4	2	6	0.4	162.3	200
13	5	10	16.0	2.0	4	2	6	0.4	154.6	200

Method of Formulation of fast dissolving tablet

The weighing of Amlodipine Besylate (5 mg) and Atorvastatin Calcium (10 mg) along with the appropriate excipients was carried out. All the materials, including the super-disintegrants and the APIs, were blended using the geometric mixing method. After proper blending, the mixture of APIs and excipients was compressed by using single-punch tablet machine to produce round convex-face tablet.[9] The tablet formulations were developed by using superdisintegrants SSG (0.757–9.242%) and CCS (0.171–5.828%).[10]

Pre-formulation study

Solubility study

Methanol was used as the solvent to assess the solubility of Atorvastatin Calcium, and Amlodipine Besylate due to its compatibility with both drugs. This provided a complete evaluation of their dissolution characteristics. Solubility was measured by shake flask method where 1 g of sample was added to methanol and shaken properly.[11]

Angle of repose

Angle of repose is the maximum angle possible between the surface of the pile of powder and the horizontal plane. The lower the angle of repose, better the flow properties. The angle of repose were determined by the poured angle method.[12]

Bulk Density and Tapped Density

The tapped and bulk densities are determined by demarcating a small cuvette with known volumes, then inserting a small mass of powder into the cuvette (bulk density). The required amount of granules was taken in a graduated measuring cylinder and the initial volume was measured.

Bulk density = Weight of the granules / Apparent volume of the granules

Tapped density is measured by tapping vertically against a padded bench top 50 times or Measuring cylinder containing granules was tapped until no further volume changes occur. Tapped density can be calculated by the following equation.[13]

Tapped density = Weight of the granules / Tapped volume of the granules

Compressibility index (Carr's index)

The Carr's index was determined by utilizing the obtained data of tapped density and bulk density. Carr's index was calculated by

Compressibility Index (CI) = $(\rho t - \rho b) / \rho t \times 100$

where, ρt = Tapped density, ρb = Bulk density

Scale of flowability for compressibility index were measured by using Compressibility index table (%).[14]

Hausner's Ratio

Hausner's ratio was determined by utilizing the obtained data of tapped density and bulk density. Hausner's ratio is the ratio of tapped to bulk density and was calculated by using the following equation. Lower Hausner's ratio indicates better flow properties.[4]

Hausner's ratio = Tapped density (ρt) / Bulk density (ρb)

The flow characteristics of the blends were interpreted using the conventional scales given in Table 3.

Table 3: Scales of flowability used for interpretation of micromeritic data.

Flow character	Angle of repose (°)	Carr's index (%)	Hausner's ratio
Excellent	25–30	≤10	1.00–1.11
Good	31–35	11–15	1.12–1.18
Fair	36–40	16–20	1.19–1.25
Passable	41–45	21–25	1.26–1.34
Poor	46–55	26–31	1.35–1.45
Very poor	56–65	32–37	1.46–1.59
Very, very poor	>66	≥38	>1.60

Post-compression parameters

Weight Variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Hardness

Hardness of the tablet was measured using a tablet hardness tester (Monsanto hardness tester).[15] Three tablets from each formulation batch were tested randomly and the average reading was noted. The strength of the tablet is expressed as tensile strength (kg/cm2).the result is expressed as the crushing in kg/cm².

Friability

Friability of the tablets was determined using Roche Friabilator. Pre-weighed sample of 20 tablets was placed in the friabilator and was subjected to 100 revolutions.[6] Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$F\ (\%) = (1 - W0 / W) \times 100$

Where, W is weight of the tablets before the test, W0 is the weight of the tablets after test.

Wetting Time

A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a Petri dish (Internal Diameter = 9 cm) containing 10 mL of water.[16] A pre weighed tablet was placed on the paper and the time required for water to reach the upper surface of the tablets was noted as the wetting time.

$R = (Wa - Wb / Wb) \times 100$

Wa = Weight of the tablet before wetting, Wb = Weight of tablet after Wetting

Dispersion Test

Dispersion test is performed to evaluate how well a solid substance, such as powder or granules, disperse or dissolve in a liquid medium. In this research dispersion of the tablet is tested as mentioned in the pharmacopeia, where one tablet is placed in beaker with 100 ml of water and the complete dispersed tablet is passed through sieves screen 30. If all parts pass through sieve result is positive otherwise the dispersion test seems negative.[17]

In Vitro Disintegration Time

Six tablets of each batch were placed in each tube of the disintegration apparatus. Water was used for disintegration and temperature was maintained at 37°C ± 2°C. The time required for complete disintegration of the tablets was noted.[18]

In Vitro Drug Release Studies

Dissolution studies were conducted using phosphate buffer (pH - 6.8) using USP type 2 apparatus. At an interval of 30 min, samples were taken and the amount of drug release was determined by using UV-visible spectrometry. After the three trials the average percentage of drug release was calculated.[19]

Simultaneous Determination of Atorvastatin and Amlodipine

Atorvastatin and amlodipine were simultaneously determined by using dual-wavelength absorbance detector at 244 nm and 362 nm, respectively. Accurately weighed tablet powder of 15 mg was dissolved in methanol, sonicated and made up to volume in a volumetric flask. The resulting solution filtered and diluted to 10 and 15 µg/mL and the absorbance was recorded in dual-wavelength absorbance detector.[20]

Analytical Method Validation

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. This validation assay method covers the validation of Amlodipine Besylate and Atorvastatin Calcium tablets which is performed by means of UV-Visible spectroscopy method. Accuracy, precision, linearity, limit of detection (LOD) and limit of quantitation (LOQ) were carried out.[21]

The linearity of an analytical procedure is it's ability to obtain results which are directly proportional to the concentration of analyte in the sample.[22] In order to demonstrate linearity various concentration of Amlodipine Besylate 3 ppm, 4.5 ppm, 6 ppm, 7.5 ppm, 9 ppm and

10.5 ppm & Atorvastatin Calcium in 6 ppm, 9 ppm, 12 ppm, 15 ppm, 18 ppm and 21 ppm was prepared in mixture of 50% Methanol & 50% Distilled water.

LOD means the lowest concentration or amount of analyte that can be identified, measured and reported with confidence that the concentration is not a false positive value. LOQ means the lowest concentration at which the analyte cannot only be reliably detected but at which some predefined goals for bias and imprecision are met. These were calculated as LOD = 3.3 × S.D/S and LOQ = 10 × S.D/S, where S.D = Standard Deviation and S = Slope.

Accuracy is the closeness of agreement between the actual value which is accepted either as conventional true value or an accepted reference value of a component and the measured value. Accuracy is expressed as percent recovery by assay of known added amount of analyte in the sample. Precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision test is carried out in Inter day and Intraday.

RESULT AND DISCUSSION

Using Minitab central composite design of various concentrations of SSG and CCG with all API and excipients were calculated. Different batches were formed by varying the concentration of the super disintegrants. To make sure that every parameter was within the limit, pre-compression evaluations were carried out. After performing the angle of repose, Hausner's ratio, tapped density index, and other tests, it appears to be suitable for the next step. FDTs were prepared using the direct compression method, using SSG and CCS as superdisintegrants, with amlodipine besylate and atorvastatin dosed at 5 mg and 10 mg, respectively.

Analytical Method Validation

Table 4: LOD and LOQ of Amlodipine and Atorvastatin.

	LOD in 50% Methanol + 50% Water	LOQ in 50% Methanol + 50% Water	LOD in Buffer	LOQ in Buffer
Amlodipine at 362 nm	0.337712	1.023371	1.026939	3.111937
Amlodipine at 244 nm	0.251537	0.762234	0.803108	2.433659
Atorvastatin at 244 nm	1.050846	3.184381	0.751813	2.278222

Table 5: Accuracy of Amlodipine and Atorvastatin.

	% Amlodipine (n=3)	% Atorvastatin (n=3)
Less than 100% i.e. 75%	98.24±2.6754	99.72±1.1136
100% (300 mg)	97.43±2.2145	102.49±2.3817
More than 100% i.e. 125%	99.27±1.5197	98.97±1.2294
SD	0.9233	1.8548
Mean	98.32	100.39
RSD	0.9391	1.8475

Table 6: Intraday and Interday Precision test of Amlodipine and Atorvastatin.

Time / Day	Amlodipine % (n=3)	Atorvastatin % (n=3)
12:00 P.M	97.43±1.053	102.49±0.987
2:00 P.M	91.78±2.565	101.40±1.023
4:00 P.M	93.07±1.639	103.60±0.896
Day 1	97.43±1.235	102.49±1.265
Day 2	96.95±1.679	95.24±1.385
Day 3	93.07±2.003	94.41±1.227

Both the drugs obeyed Beer's law over the concentration ranges studied and the method was found suitable for the simultaneous estimation of Amlodipine and Atorvastatin.

Pre-compression Parameter

Table 7: Angle of repose, bulk density, tapped density, Carr's Index and Hausner's Ratio of different formulations.

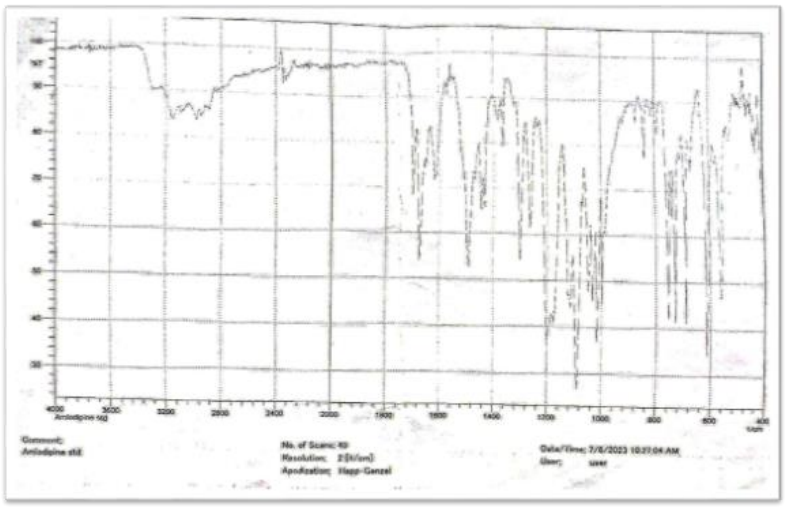
Formulation	Angle of repose (n=3)	Bulk density	Tapped density	Carr's index	Hausner's ratio	Result
F1	42.62±0.798	0.538	0.556	3.23	1.03	Excellent
F2	37.042±1.337	0.433	0.557	22.26	1.28	Passable
F3	42.3±0.72	0.455	0.538	15.42	1.18	Fair
F4	35.29±1.464	0.464	0.578	19.72	1.24	Fair
F5	42.3±0.72	0.455	0.538	15.42	1.18	Fair
F6	42.3±0.72	0.455	0.538	15.42	1.18	Fair
F7	42.3±0.72	0.455	0.538	15.42	1.18	Fair
F8	42.3±0.72	0.455	0.538	15.42	1.18	Fair
F9	43.37±0.861	0.544	0.568	1.36	1.04	Excellent
F10	41.25±1.102	0.541	0.565	4.24	1.04	Excellent
F11	28.91±0.545	0.443	0.575	22.95	1.29	Passable
F12	40.76±0.851	0.429	0.576	25.52	1.34	Passable
F13	27.37±1.323	0.444	0.582	23.71	1.31	Passable
F (optimized)	27.37±1.323	0.439	0.564	3.23	1.03	Excellent

Precompression study of powders (API+Excipients) were done. From the above table, it was found that the angle of repose of formulation 1,3,5,6,7,8,9,10 and optimized formulation were passable whereas, the angle of repose of formulation 2,4 and 12 was fair. Similarly, the angle

of repose of formulation 11 and 13 was excellent. Likewise the Carr's index and Hausner's ratio for formulation 1, 9 and 10 were excellent and for formulation 2,11,12,13 and opt the Carr's index and Hausner's ratio was passable whereas for formulation 3,4,5,6,7 and 8 Carr's index and Hausner's ratio was fair.

Drug-Excipient Interaction study by using FT IR

IR spectroscopic studies were conducted to determine possible drug–excipient interactions. The IR spectra of pure drug amlodipine and atorvastatin and their mixtures with the excipients are shown in Figures 1 and 2.



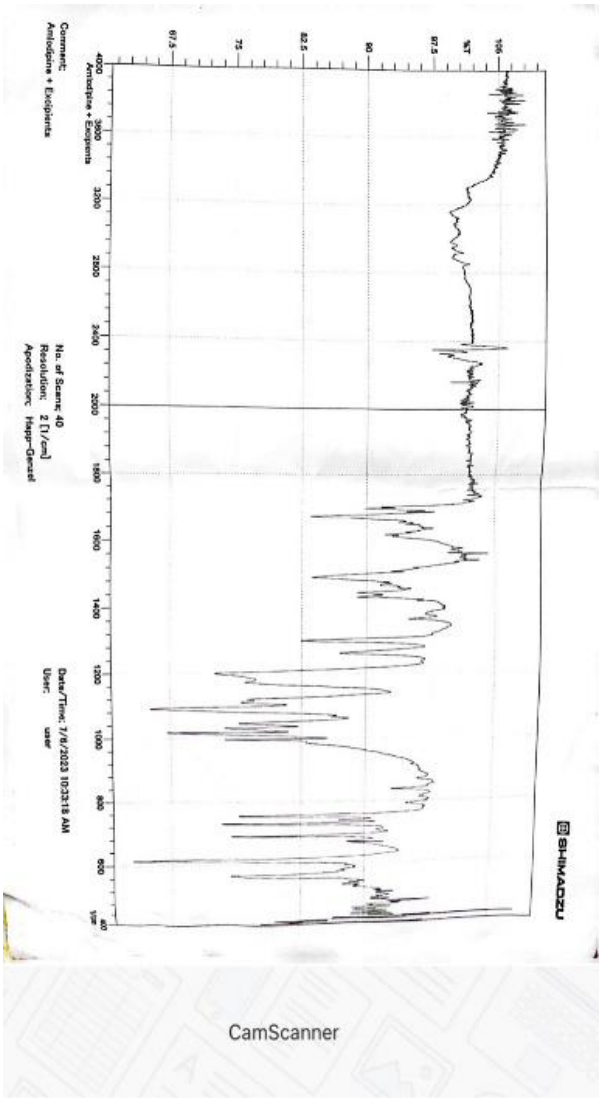


Figure 1: FT-IR spectra of amlodipine standard and of amlodipine with excipients.

IR spectroscopy has been used to investigate the interaction of Amlodipine and Atorvastatin and its mixture with excipients and ensure their safety. Figure no 1 and 2 shows that there is No significant intraction was observed between the API and the mixture.

Table 8: Interpretation of IR spectra of Amlodipine standard and Amlodipine-Excipients.

Frequency(cm^{-1})	Functional group in Amlodipine	Functional group in Amlodipine+Excipients
3297	Amine (N-H) Stretches	Amine (N-H) Stretches
3158	Aromatic (C-H) Stretch	Aromatic (C-H) Stretch
2982	Aliphatic (C-H) Stretch	Aliphatic (C-H) Stretch
1698, 1676	Ester carbonyl (C=O) Stretches	Ester carbonyl (C=O) Stretches
1614, 1493	Aromatic Skeletal Stretch	Aromatic Skeletal Stretch
1445, 1432	CH3, CH2 bending	CH3, CH2 bending
1207, 1196, 1095	Ester (C-O) asymmetric and	Ester (C-O) asymmetric and symmetric

	symmetric stretches, Ether (C-O-C) asymmetric stretch	stretches, Ether (C-O-C) asymmetric stretch
1207	Sulfonate (S=O) asymmetric stretch	Sulfonate (S=O) asymmetric stretch
1095	Sulfonate (S=O) symmetric stretch	Sulfonate (S=O) symmetric stretch
1095	Aromatic (C-Cl) Stretch	Aromatic (C-Cl) Stretch
1034, 1018	Ether (C-O-C) symmetric stretch	Ether (C-O-C) symmetric stretch
755, 730, 615	Aromatic (C-H) bending	Aromatic (C-H) bending

From the above table and the spectrum presented, it was found that there was no interaction between the drug and the excipients.

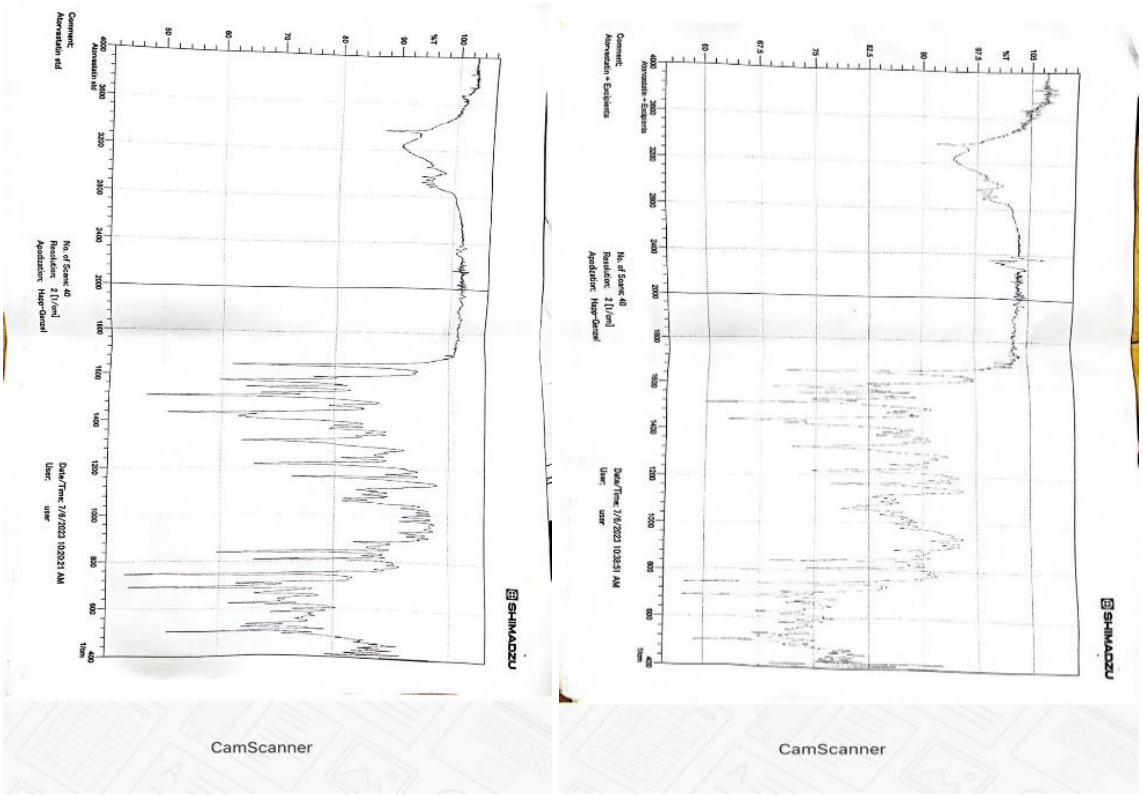


Figure 2: FT-IR spectra of atorvastatin standard and of atorvastatin with excipients.

Table 9: Interpretation of Atorvastatin Calcium standard and Atorvastatin with excipients.

Frequency	Functional group in Atorvastatin	Functional group in Atorvastatin+Excipients
3404.71	Amine (N-H) Stretches	Amine (N-H) Stretches
3060.48	Alkane (C-H) Stretch	Alkane (C-H) Stretch
2961.16	Aromatic (C-H) Stretch	Aromatic (C-H) Stretch
1656.55	Carbonyl (C=O) Stretches	Carbonyl (C=O) Stretches
1562.06	Aromatic Skeletal Stretch	Aromatic Skeletal Stretch
1516.74	Carboxylate	Carboxylate
1314.25	Aromatic in plane bending (C-H) Stretch	Aromatic in plane bending (C-H) Stretch
1227.47	Mono fluorinated benzene Ring	Mono fluorinated benzene Ring

From the above tables and spectrum presented, it was found that there was no interaction between drug and excipients.

Evaluation of Formulated Tablets

Tablets were round and slightly sweeting taste for the acceptability of the patients that FDT dissolve in mouth. Different parameters were evaluated after the formation of the FDT. Thickness was found to be 0.4 mm which almost similar to every batch. Uniform thickness of die indicates that the die fill up was uniform. Tablets of all batches were round, white in color and plain surface on both sides. Hardness is one of the crucial factors for the FDT. The hardness is the indication for the strength of the tablet that handle the mechanical pressure, hardness also affects the disintegration time. Tablet hardness was evaluated using a Monsanto hardness tester. The measured hardness values were approximately 3 kg/cm², which fall within the acceptable range for fast-dissolving tablets. Maintaining hardness at the lower limit is desirable, as it facilitates rapid tablet disintegration in the oral cavity. The obtained results confirm that the prepared tablets possessed suitable mechanical strength while still allowing quick disintegration.

Table 10: Result of weight variation and friability.

Formulation	Weight Variation (mg)	Friability %
F1	201.55±3.28	0.049
F2	198.85±2.98	0.024
F3	194.8±2.52	0.012
F4	197.05±6.74	0.024
F5	194.8±2.52	0.012
F6	194.8±2.52	0.012
F7	194.8±2.52	0.012
F8	194.8±2.52	0.012
F9	204±4.41	0.024
F10	199.6±2.30	0.049
F11	204.5±3.03	0.049
F12	202.45±3.22	0.025
F13	202.9±3.74	0.049
Optimized	200.5±3.57	0.025

Disintegration time

The necessity of a fast dissolving tablet is to disintegrate within 30 seconds in the limited amount of water available in the form of saliva.[23] In the present study rapid disintegration time was observed, and it is shown in Table 24. Based on the in vitro disintegration test of all the formulations, optimization was done. The disintegration time obtained from each

formulation was plotted on a contour plot to find out the optimal concentration which will give the disintegration time of the formulation in between 10–30 seconds. That shows two possible concentrations (higher and lower concentration) of SSG and CCS which show a disintegration time of about 10 seconds. The contour plot and the surface plot are given in Figures 3 and 4.3

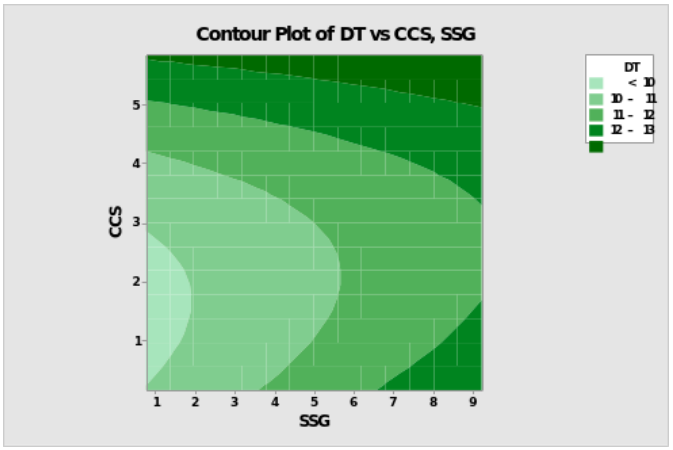


Figure 3: Contour plot of disintegration test vs CCS, SSG.

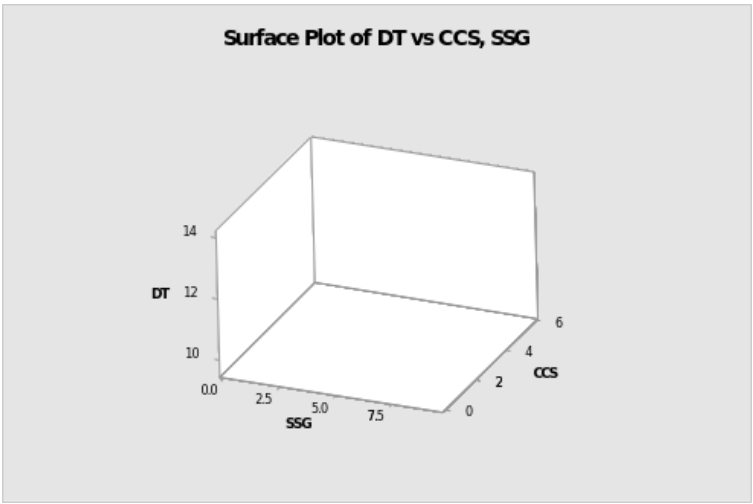


Figure 4: Surface plot of DT vs CCS, SSG.

The regression equation obtained in uncoded units for the disintegration time is given below, where SSG is x and CCS is y

DT = 9.88 + 0.343x − 0.552y + 0.0000 x*x* + *0.1875 y*y − 0.0417 x*y

Negative coefficients of the regression value of SSG and CCS suggest that they decrease the disintegration time, whereas positive coefficients of SSG and CCS increase the disintegration time.

The weight variation of the tablets ranged from 190.47 to 210 mg, indicating uniformity of tablet weight and compliance with pharmacopeial limits of ±5% of the average weight. Friability is closely associated with tablet hardness.[24] Despite the tablets exhibiting lower hardness values, the friability remained below 1% as shown in above table no. 9, indicating adequate resistance to mechanical stress. These results confirm that the tablets possessed satisfactory mechanical strength and were suitable for handling and transportation.

Table 11: Result of Wetting time, dispersion test, Disintegration Time and dissolution test.

Formulation no	Wetting time (n=3)	Dispersion test	Disintegration Time	Amlodipine Dissolution % (n=3)	Atorvastatin Dissolution % (n=3)
F1	21±1.414	Complied	10±0.05	98.61±1.106	97.67±1.990
F2	44±1.414	Complied	12±0.04	95.48±1.106	95.88±2.714
F3	22±1.414	Complied	11±0.08	81.39±2.213	88.46±1.628
F4	33±1.414	Complied	10±0.09	95.48±0.553	104.32±2.714
F5	22±1.414	Complied	11±0.08	82.39±2.151	87.46±1.628
F6	22±1.414	Complied	11±0.08	81.69±1.913	88.56±1.628
F7	22±1.414	Complied	11±0.08	82.49±2.061	89.46±1.628
F8	22±1.414	Complied	11±0.08	83.39±1.867	88.96±1.628
F9	20±0	Complied	12±0.04	95.48±0.675	96.65±2.545
F10	31.5±1.414	Complied	14±0.12	79.83±2.545	82.57±2.981
F11	27±1.414	Complied	13±0.09	86.09±2.213	94.09±2.171
F12	15.5±0.707	Complied	12±0.13	81.98±2.213	84.11±2.352
F13	31.5±2.121	Complied	11±0.08	92.35±1.992	98.95±2.091
Optimized	22±0	Complied	10±0.11	95.17±0.885	95.99±0.996

The wetting time of all formulated tablets was found to be within the acceptable range. Wetting time significantly influences the disintegration behavior of fast-dissolving tablets; shorter wetting time results in faster disintegration.[25] SSG and CCS induce swelling and generate capillary action, which leads to moisture absorption which helps in the disintegration of the tablet. Wetting time has the linear relationship with the disintegration time. The wetting time and time of dispersion shows that the all formulated batch complied with pharmacopeia standards. It was determined that the disintegration time 9–14 second, which shows the clear data about the tablet can rapid disintegrate within the mouth. The data of the disintegration time and hardness shows that the tablet having higher value of hardness have more disintegration. Tablet having higher concentration of the CCS and SSG shows the lower disintegration time i.e. 10 sec whereas tablet having relatively low concentration of SSG and CCS shows the higher disintegration time about 14 sec.

Dissolution of different formulation including optimized formulation have found within the range of Amlodipine 81.68%-98.61% and Atorvastatin in the range of 87.46%-104.32%. All the formulations met the IP dissolution criteria, showing greater than 80% drug release. Drug release was rapid for batch NP-F1, which contained a relatively higher amount of superdisintegrant, indicating that disintegration significantly influenced the dissolution rate.[26]

Table 12: Drug Content of Amlodipine and Atorvastatin of all the formulations.

Formulation	Amlodipine % (n=3)	Atorvastatin % (n=3)
F1	92.79±1.566	97.78±1.672
F2	99.34±1.251	103.11±1.456
F3	95.00±2.013	100.69±1.543
F4	96.51±1.679	96.23±2.017
F5	95.00±2.013	100.69±1.543
F6	95.00±2.013	100.69±1.543
F7	95.00±2.013	100.69±1.543
F8	95.00±2.013	100.69±1.543
F9	94.34±1.761	101.50±0.981
F10	90.42±1.856	99.61±1.432
F11	96.51±2.015	102.30±1.328
F12	92.17±1.987	106.06±1.596
F13	94.34±1.765	95.48±2.447
Optimized	96.14±2.017	100.15±2.598

The drug content for all the formulation batches was found to be uniform and within the range of 90.42%-99.34% for Amlodipine Besylate and 95.48%-106.06% for Atorvastatin Calcium observed by the help of UV-spectrometry at the wavelength of 244 nm and 362 nm.

Optimization

Fig. 3: Response optimizer curve of disintegration

Above plot optimized curve of disintegration and concentration of SSG and CCS shows that the concentration of SSG and CCS should be within 1.2532 and 0.6287 to obtain the 10 second disintegration which as shown in the figure no 3. Disintegration eventually influences the dissolution rate. When FDC is introduced into the mouth, it dissolved rapidly because the disintegration time is low.

As the optimizing parameter is disintegration, the targeted value of disintegration was set as 10 seconds to optimize the formulation using response optimizer in minitab. The intersection

point in the curve represents the 10 seconds disintegration time. Hence, optimized formulation was formulated accordingly.

Table 13: Optimized Formulation for one tablet.

S.no	Formulation	Optimized (mg)
1	Amlodipine Besylate	5
2	Atorvastatin Calcium	10
3	Sodium Starch Glycolate	2.5
4	Croscarmellose Sodium	1.3
5	Magnessium Stearate	4
6	Colloidal Silica	2
7	Starch	6
8	Sodium Saccharin	0.4
9	Microcrystalline cellulose	168.8

Response surface regression for % Amlodipine release versus SSG and CCS gave the equation:

% Amlod Release = 107.3 − 9.80 SSG + 0.19 CCS + 0.821 SSG×SSG − 0.110 CCS×CCS + 0.261 SSG×CCS

The response optimization for % Ator release, % Amlod Release and DT gave the solution SSG = 1.25316 and CCS = 0.628692, with fitted values of 99.99% atorvastatin release, 96.57% amlodipine release and a disintegration time of 10.002 seconds, at a composite desirability of 0.959540.

CONCLUSION

Fast-dissolving tablets containing amlodipine besylate and atorvastatin calcium were successfully developed and tested in this study, which addressed the requirement for enhanced patient compliance, especially for populations with swallowing difficulties, i.e., elderly and pediatric patients. Disintegration and dissolving properties of the combination drug formulation were considerably enhanced by the addition of superdisintegrants such as Sodium Starch Glycolate and Croscarmellose Sodium. In this study, it was concluded that the concentration of SSG should be 1.2532% and CCS should be 0.6287% to achieve a disintegration time of 10 seconds. The optimized formulation achieved a disintegration time of 10 seconds with uniform drug content and dissolution efficiency above 95%, ensuring rapid onset of action and high bioavailability. The drug content was consistent across all formulation batches, ranging from 90.42% to 99.34% for amlodipine besylate and 95.48% to 106.06% for atorvastatin calcium. FT-IR studies confirmed no significant drug–excipient interactions, ensuring the stability of the formulation.

The findings of our investigation show that treating hypertension and hypercholesterolemia concurrently with amlodipine besylate and atorvastatin calcium in an FDT format is not only feasible but also advantageous. The direct compression method employed for tablet preparation is simple, scalable, and offers a reliable approach for mass production. More development or modification of this formulation for use with different medication combinations or in more extensive clinical settings may be investigated in future studies.

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AUTHOR'S CONTRIBUTIONS

All the authors have contributed equally to the design of the study, the formulation and evaluation work, the analysis of the data, and the preparation of the manuscript. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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