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Formulation and evaluation of Amlodipine Besylate orodispersible tablet for the treatment of hypertension

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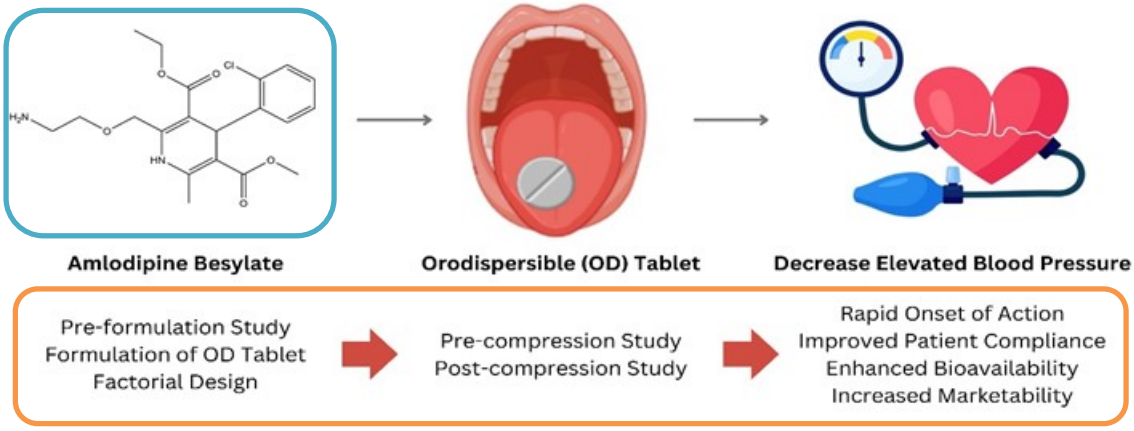
Research Article

ABSTRACT



The primary aim of this research was to develop and assess orodispersible tablets of Amlodipine besylate for hypertension management. The tablets were formulated using the direct compression technique, incorporating croscarmellose sodium as a superdisintegrant. Various parameters, including friability, hardness, disintegration, wetting time, *in vitro* drug release, and drug content were evaluated for the tablets. The results for all formulations fell within acceptable limits. Calibration curves of the pure drug were plotted using different solvents such as phosphate buffer pH 6.8 and methanol. Among the formulations F1-F9, this contained varying concentrations of croscarmellose sodium, F7 demonstrated the shortest disintegration time of 37 ± 3 seconds, attributed to the higher superdisintegrant concentration. The *in vitro* drug release study was conducted in phosphate buffer pH 6.8 at intervals of 5, 10, 15, 20, 25, and 30 minutes revealed that F7 achieved a 98.91% drug release. The findings from this study indicate that orodispersible tablets with an optimal ratio of croscarmellose sodium as a superdisintegrant hold significant potential for the effective treatment of hypertension.

Keywords: Orodispersible tablet, Amlodipine besylate, Bioavailability, Superdisintegrants, Calcium channel blocker

INTRODUCTION

Hypertension is commonly known as high blood pressure and which remains a major global health concern due to its prevalence and associated risks of cardiovascular diseases, stroke, and renal complications.[1-3] Among the pharmacological agents used for its management, Amlodipine Besylate stands out as a widely prescribed calcium channel blocker known for its efficacy and tolerability.[4-7] However, conventional oral dosage forms of Amlodipine Besylate may pose challenges, especially for patients with dysphagia or those who have difficulty swallowing tablets.[8-11] The development of Orodispersible Tablets (ODTs) offers a promising solution to such challenges. ODTs disintegrate rapidly in the mouth, making them suitable for patients having difficulty in swallowing conventional tablets.[12-17] Moreover, they offer the advantages of enhanced patient compliance, rapid onset of action, and higher bioavailability due to their ability to bypass the hepatic first-pass metabolism.[18-22] This research aims to formulate and evaluate Amlodipine BesylateOrodispersible Tablets for the treatment of hypertension. The formulation will focus on optimizing the drug's bioavailability, disintegration time, and taste masking while ensuring dose uniformity and stability. Various pharmaceutical excipients will be explored to achieve the desired

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characteristics of the ODTs. The evaluation of the formulated ODTs will encompass physicochemical characterization, including tests for weight variation, friability, disintegration time, and hardness. *In vitro* dissolution studies will be conducted to assess the drug release profile of ODTs compared to conventional tablets. Furthermore, sensory evaluation will be performed to ascertain the palatability and acceptability of the formulated ODTs.The outcomes of this research are expected to contribute to the development of a patient-friendly dosage form of Amlodipine Besylate, enhancing its efficacy and convenience in the management of hypertension. By addressing the limitations of conventional tablets and catering to the needs of patients with swallowing difficulties, Amlodipine BesylateOrodispersible Tablets have the potential to improve medication adherence and ultimately optimize blood pressure control, leading to better clinical outcomes and quality of life for hypertensive patients.

MATERIALS AND METHODS

Materials

Amlodipine besylate was obtained from Blue Cross Pvt. Ltd., Nashik. While all other chemicals and reagents utilized in the study were of analytical grade.

Method

Drug Characterization

To evaluate the physical characteristics of Amlodipine besylate, several tests were conducted. A small amount of Amlodipine besylate was placed on butter paper and examined under a well-lighted area to assess its color. The odor of the sample was determined by smelling a small amount of Amlodipine besylate. Additionally, the appearance of the substance was observed by taking a pinch of Amlodipine besylate between two fingers and examining its texture and form.

Determination of melting point

The melting point of amlodipine besylate was determined using the open capillary method. The sample was placed in a sealed glass capillary tube, inserted into a melting point apparatus, and the melting point was recorded.[23]

Solubility study

The solubility of amlodipine besylate was assessed in various solvents including methanol, ethanol, dimethyl sulfoxide, and water. For this test, 10 ml of each solvent was placed in separate test tubes, and 20 mg of amlodipine besylate was added to each solvent. The mixtures were sonicated for 10 minutes, after which they were observed for any remaining undissolved particles.

Determination of λ max of amlodipine besylate

The UV spectrum of amlodipine besylate was recorded using a UV-visible spectrometer (Jasco Corporation, Japan V 550). A 10 mg sample was dissolved in methanol and diluted with phosphate buffer (pH 6.8) to make a 1000 µg/ml stock solution. A 0.2 ml aliquot was further diluted to 10 ml with phosphate buffer to prepare a 20 µg/ml solution. The spectrum was recorded to determine the maximum wavelength.

Calibration curve in Phosphate buffer 6.8 pH

From the stock solution, 1 ml was diluted to 10 ml with phosphate buffer (pH 6.8) to obtain a 100 µg/ml concentration. Then, 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml of this solution were each diluted to 10 ml with phosphate buffer, resulting in concentrations of 5 ppm, 10 ppm, 15 ppm, 20 ppm, and 25 ppm. The absorbance of these solutions was measured at 238 nm.[24]

FT-IR of Amlodipine besylate

The IR spectrum of amlodipine besylate was recorded using a Shimadzu IR Affinity-1 spectrometer with potassium bromide (KBr) as a blank. The spectrum was obtained at a resolution of 4 cm^{-1} over a range of 400-4000 cm^{-1}, and the peaks were compared with the principal peaks in the monograph for identification.[25]

Drug excipient compatibility study

The API was mixed with excipients in various ratios (Table 1), sieved, filled into glass vials, and stored in a stability chamber at 40 ± 2°C and 75 ± 5% RH.

Table 1. Drug-excipient compatibility study ratio.

S. No.	Sample	Ratio
1	Amlodipine besylate: Croscarmellose sodium	1:1
2	Amlodipine besylate: Avicel 102	1:1
3	Amlodipine besylate: Mannitol	1:1
4	Amlodipine besylate: Aspartame	1:1
5	Amlodipine besylate: Lactose	1:1
6	Amlodipine besylate: Magnesium stearate	1:1
7	Amlodipine besylate: Talc	1:1

Formulation of Orodispersible tablets

Pharmaceutical-grade amlodipine besylate, croscarmellose sodium, Avicel 102, mannitol, aspartame, lactose, magnesium stearate, and talc were sourced from certified suppliers. All ingredients were sieved through a 60-mesh sieve. Amlodipine besylate, mannitol, and lactose were weighed and mixed in a mortar and pestle, followed by the addition of croscarmellose sodium, Avicel 102, and aspartame. The blend was granulated in a Rapid Mixer Granulator (RMG) at 150 rpm for 30 minutes. Magnesium stearate and talc were added, and blending continued for 5 minutes. The final blend was compressed into 200 mg tablets using a 7.7 mm punch on a rotary tablet machine. Pre-compression parameters, including angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio, were assessed to ensure optimal flow and compression characteristics.

Table 2. Composition of Orodispersible tablets Amlodipine besylate.

S. No.	Ingredients	Quantity (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Amlodipine besylate	10	10	10	10	10	10	10	10	10
2	Croscarmellose sodium	10	10	10	15	15	15	20	20	20
3	Avicel 102	30	35	40	30	35	40	30	35	40
4	Mannitol	50	50	50	50	50	50	50	50	50
5	Aspartame	10	10	10	10	10	10	10	10	10
6	Lactose	80	75	70	75	70	65	70	65	60
7	Magnesium stearate	5	5	5	5	5	5	5	5	5
8	Talc	5	5	5	5	5	5	5	5	5
Total weight of tablet		**200 mg**								

Factorial design model

A 3^2 full factorial design was used to formulate stable orodispersible tablets, evaluating the effects of varying concentrations of croscarmellose sodium (X1) and Avicel 102 (X2) on disintegration time and hardness. The factor levels were selected based on prior studies. Table 3 summarizes the experimental runs, factor combinations, and the correspondence between coded levels and experimental units.

Table 3. Factorial design model parameters.

S. No.	Independent variables	Name	Unit	Levels	
				Low (-1)	High (+1)
1	X1	Croscarmellose sodium	%	5	10
2	X2	Avicel 102	%	15	20

Evaluation

Pre-compression Parameter

Bulk density

The powder blend was weighed and sieved (#80) before being poured into a 100 ml graduated cylinder. The bulk volume was recorded, and bulk density (ρb) was calculated using the formula:

$$\rho b = m / Vb$$

Where, ρb = Bulk density, m = Mass of powder, and Vb = Bulk volume of powder.

Tapped density

After measuring the bulk volume, the cylinder with the powder blend was placed in a tap density apparatus and tapped 500 times with a fixed drop of 14 ± 2 mm to allow the powder to settle. The tapped volume (Vt) was recorded, and tapped density (ρt) was calculated using the formula:

$$\rho t = m/Vt$$

Where, ρt = Tapped density, m = Mass of powder, and Vt= Tapped volume of powder.

Flow properties

The flow assessment of the API and excipients was conducted to ensure adequate powder flow through processing equipment like compactors, hoppers, and tablet presses. Poor flowability can lead to tablet weight variation due to inconsistent powder feeding into the die.

Compressibility index (C.I.)

It measures the tendency of a powder to consolidate and reflects the inter-particulate interactions present in free-flowing powders, where these interactions are generally minimal, resulting in bulk density and tapped density values that are similar. In poorly flowing materials, increased interparticle interactions can lead to particle bridging, resulting in lower bulk density and a greater difference between bulk and tapped density. This difference is indicative of the compressibility index. The packing ability of the powder was assessed based on volume changes due to rearrangement during tapping. Carr's compressibility index can be calculated as follows:

$$C.I.\ (\%) = (\rho t - \rho b)/\ \rho t * 100$$

Where, ρt = Tapped density, and ρb = Bulk density.

Hausner's ratio

Hausner's ratio is a measurement used to describe the compressibility of powder, defined as the ratio of tapped density to bulk density. It is calculated using the following formula:

$$\text{Hausner's Ratio} = \rho t/\rho b$$

Where, ρt = Tapped density, and ρb = Bulk density

Angle of repose

The angle of repose was determined using the funnel method by forming a cone of powder on a fixed base. The funnel was held 2 cm above the powder surface to avoid vibrations. The height of the powder cone was measured, and the angle of repose was calculated using the following equation:

Angle of repose (Tan θ) = height/radius

Post Compression Parameters

Physical appearance

The appearance of the core tablet was assessed, focusing on surface texture, as well as any chipping or cracks present.

Thickness and diameter

The thickness and diameter of the tablets were measured using vernier calipers during the compression process.

Hardness

Hardness, or crushing strength, is used to evaluate whether the tablet machine requires pressure adjustments. If a tablet is too hard, it may not disintegrate within the required time, while if it is too soft, it may not withstand packaging and shipping procedures.

Friability

Tablet friability was assessed using a Roche Friabilator. Twenty pre-weighed tablets were subjected to rolling and shocks for 4 minutes or 100 revolutions. After reweighing, the weight loss due to abrasion was calculated to determine friability, expressed as a percentage. Acceptable friability is ≤1%. Broken or smashed tablets were excluded from the analysis. The percentage friability was calculated using the formula:

% Friability = (w1-w2) / w1*100

Where, W1 = Weight of tablets before test, and W2 = Weight of tablets after test.

Drug content

Twenty tablets were weighed to determine average weight, ground to a uniform powder, and 10 mg of amlodipine besylate was weighed and transferred to a 10 ml volumetric flask. The flask was filled with methanol, sonicated for 15 minutes, and filtered through a 0.45 µm nylon filter. The filtered solution was diluted with phosphate buffer (pH 6.8) to a final concentration of 10 µg/ml. The drug content was analyzed by measuring the absorbance at 238 nm using UV spectroscopy.

Weight Variation

Weight variation was assessed by weighing 20 tablets from each formulation using an electronic balance. According to Indian Pharmacopoeia (IP) and United States Pharmacopeia (USP) guidelines, no more than two tablets should deviate from the average weight by more than the specified percentage, and no single tablet should vary by more than twice the relevant percentage.

Disintegration test

Tablet disintegration was evaluated using a USP disintegration apparatus. Six tablets were placed in each tube of the basket rack, submerged in water at 37 ± 2°C, and the basket was moved up and down until the tablets completely disintegrated, leaving no residue. The time for complete disintegration was recorded.

Wetting time

A piece of tissue paper folded in half was placed in a 6.5 cm Petri dish with 6 ml of water at 37°C. The tablet was placed on the tissue paper, and the time for complete wetting was measured in seconds. The wetting time was defined as the duration required for the tablet to disintegrate while remaining stationary on the Petri dish.

Dissolution time

In vitro dissolution studies of amlodipine besylate orodispersible tablets were performed using a USP apparatus type II at 50 rpm. The dissolution medium was 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5°C. Aliquots of 10 ml were withdrawn at 5, 10, 15, 20, 25, and 30 minutes, filtered through Whatman filter paper, and analyzed for amlodipine besylate content by measuring absorbance at 238 nm using a UV-visible spectrophotometer.[31-34]

RESULTS AND DISCUSSION

Pre-formulation study

The characteristics of the procured drug samples, including color, odor, and appearance, were evaluated and the findings are presented in Table 4.

Table 4. Drug characterization parameters.

S. No.	Parameters	Features
1	Colour	White
2	Odour	Characteristic
3	Appearance	Fine powder

Melting point

The melting point of Amlodipine besylate was found to be in the range of 196-198ºC which comply with reported melting point of Amlodipine besylate.[35]

Solubility study

The solubility study of amlodipine besylate was conducted using various solvent systems according to the literature. The results of the solubility tests are presented in Table 5.

Table 5. Results for solubility study.

S. No.	Solvent	Observation
1	Methanol	Soluble
2	Ethanol	Soluble
3	Dimethyl sulfoxide (DMSO)	Soluble
4	Water	Insoluble

λ max of amlodipine besylate

The λ max of Amlodipine besylate was found as 238 nm. The spectrum for results was expressed in Figure 1a and 1b.

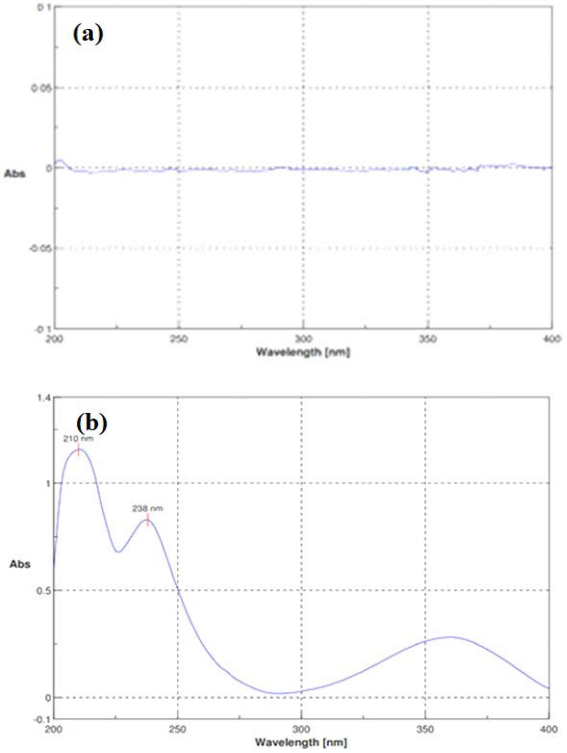


Figure 1. UV-spectrum of **(a)** Blank in Phosphate buffer 6.8 Ph and **(b)** 20 PPM solution of Amlodipine besylate in Phosphate buffer 6.8 pH.

Calibration Curve in Phosphate buffer 6.8 pH

The calibration curve of Amlodipine besylate was drawn by measuring the absorbance of different concentrations in Phosphate buffer 6.8pH at 238nm.[36] The calibration curve obtained was shown in Table 6 and **Figure 2**.

Table 6. Calibration curve for Amlodipine besylate.

S. No.	Concentration (ppm)	Absorbance
1	5	0.2146
2	10	0.4211
3	15	0.6472
4	20	0.8284
5	25	0.9786

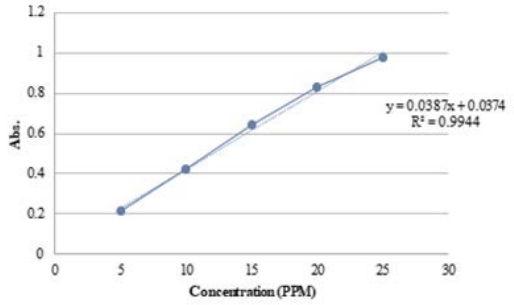


Figure 2. Calibration curve for Amlodipine besylate.

The calibration curves were linear (5-25µg/ml) with a correlation coefficient of 0.9944, indicating excellent linearity.

FT-IR of Amlodipine besylate

The IR spectrum in Figure 3 shows characteristic functional groups, as detailed in Table 7.

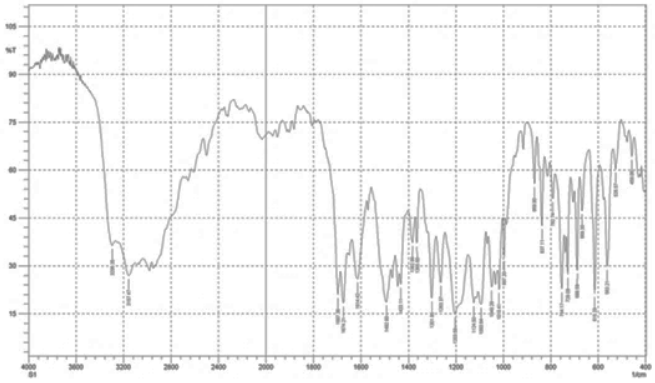


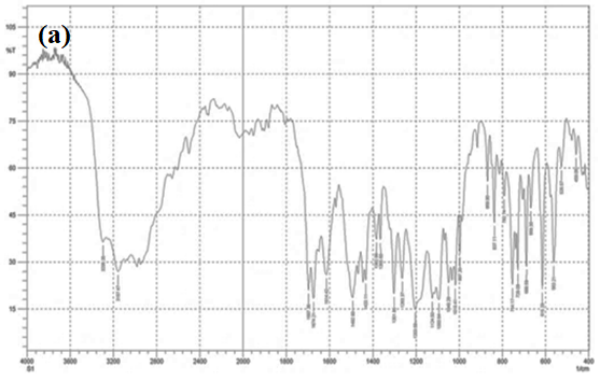
Figure 3. IR of Amlodipine besylate.

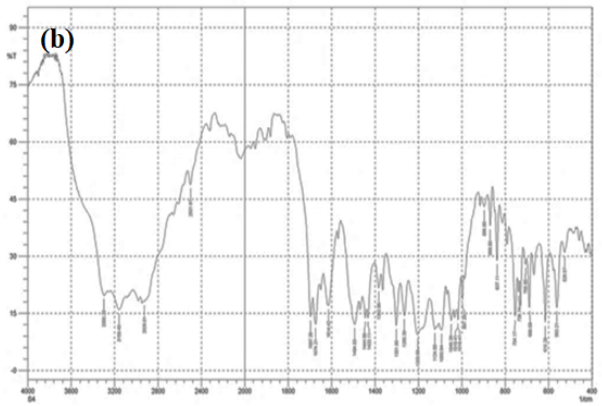
Table 7. IR frequencies of Amlodipine besylate functional group.

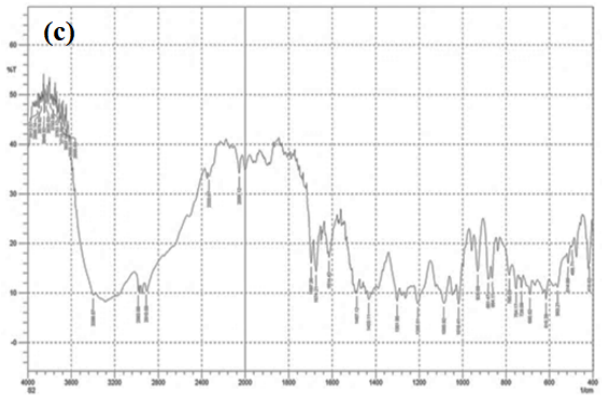
S. No	Functional group	Observed Frequency	Reported Frequency
1	O-H stretching (Hydroxyl group)	3296.35	3300-3500
2	C-H stretching (Alkyl group)	3157.47	3100-3200
3	C=O stretching (Carbonyl group)	1697.36	1710-1700
4	C=C stretching (Conjugated ring)	1614.42	1650-1600
5	C-H bending (Alkyl group)	1433.11	1450-1400
6	C-N stretching (Amine group)	1365.60	1350-1300
7	C-O stretching (Ether group)	1124.50	1150-1100

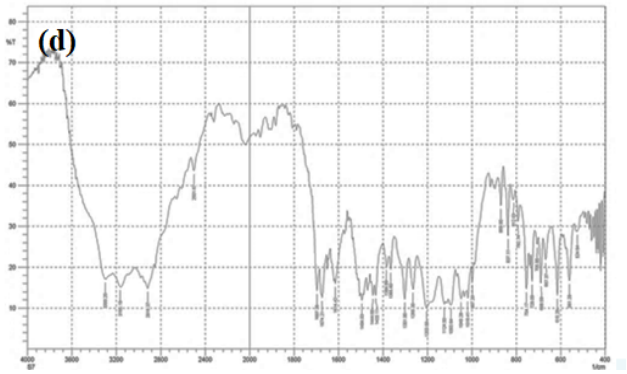
Drug excipient compatibility study

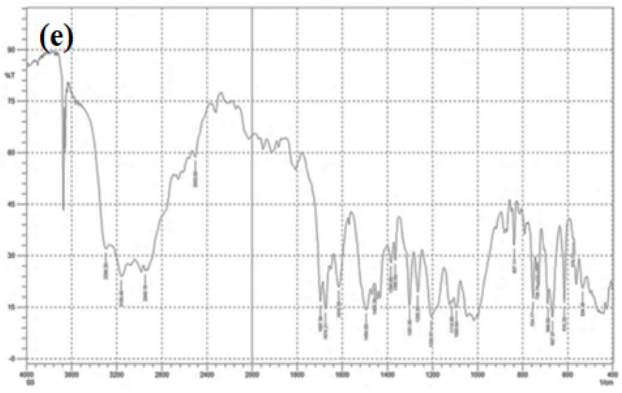
The FTIR spectra of Amlodipine besylate in pure form and its physical mixture showed no interaction with the polymer and excipients. Compatibility data is presented in **Figures 4a-4g** and Table 8.











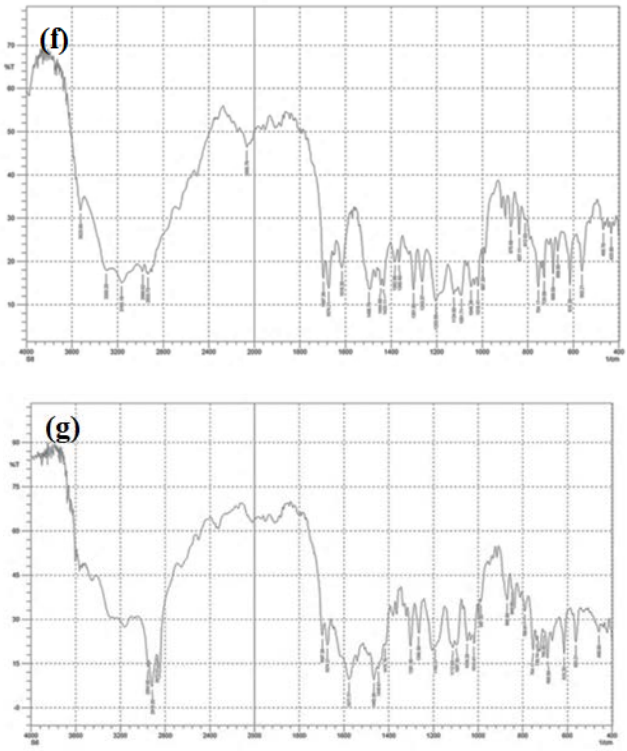


Figure 4. Compatibility IR for **(a)** Amlodipine besylate, Croscarmellose sodium, **(b)** Amlodipine besylate: Avicel 102, **(c)** Amlodipine besylate: Mannitol, **(d)** Amlodipine besylate: Aspartame, **(e)** Amlodipine besylate: Lactose, **(f)** Amlodipine besylate: Talc and (**g**) Amlodipine besylate: Magnesium stearate.

Table 8. Drug excipient compatibility.

Ingredient	Ratio	Initial	Condition 40°C/75% RH (Accelerated) for 1 month
Amlodipine besylate	NA	White	NCC
Amlodipine besylate: Croscarmellose sodium	1:1	White	NCC
Amlodipine besylate: Avicel 102	1:1	White	NCC
Amlodipine besylate: Mannitol	1:1	White	NCC
Amlodipine besylate: Aspartame	1:1	White	NCC
Amlodipine besylate: Lactose	1:1	Off White	NCC
Amlodipine besylate: Talc	1:1	White	NCC
Amlodipine besylate: Magnesium stearate	1:1	White	NCC

*NCC (No conformational change) in physical appearance from initial description.

It can be seen from the above data that Amlodipine besylate combination was stable with all the excipients used for formulation and development.

Formulation of Orodispersible tablet

The formulation of an orodispersible tablet involves the use of various ingredients, each serving a specific purpose to ensure the tablet dissolves quickly in the mouth and delivers the active pharmaceutical ingredient effectively.[37] The common ingredients used in the formulation of an orodispersible tablet along with their roles are mentioned in Table 9.

Table 9. Formulation ingredients and its roles.

S. No.	Ingredients	Role
1	Amlodipine besylate	Anti-Hypertensive
2	Croscarmellose sodium	Super disintegrant
3	Avicel 102	Direct compression binder, Flow property enhancer
4	Mannitol	Sweetener, Cool taste and diluent property
5	Aspartame	Artificial sweetener
6	Lactose	Diluents
7	Magnesium stearate	Lubricant
8	Talc	Glidant

Formulation strategy

The formulation strategy for orodispersible tablets was carefully designed to achieve rapid disintegration and dissolution, ensuring quick onset of action and improved patient compliance.[38] The strategy involved the systematic selection and optimization of various excipients to balance the mechanical strength, disintegration time, and overall acceptability of the tablets. Table 10 summarizes the key aspects of the formulation strategy adopted in this study.

Table 10. Formulation strategy.

S. No.	Ingredients	Quantity (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Amlodipine besylate	10	10	10	10	10	10	10	10	10
2	Croscarmellose sodium	10	10	10	15	15	15	20	20	20
3	Avicel 102	30	35	40	30	35	40	30	35	40
4	Mannitol	50	50	50	50	50	50	50	50	50
5	Aspartame	10	10	10	10	10	10	10	10	10
6	Lactose	80	75	70	75	70	65	70	65	60
7	Magnesium stearate	5	5	5	5	5	5	5	5	5
8	Talc	5	5	5	5	5	5	5	5	5
Total weight of tablet		**200 mg**								

Evaluation of formulated batches

Pre-compression parameters

The powder blend from all batches was evaluated for density and flow property parameters, including Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio, and Angle of Repose.[39] The results are presented in Table 11.

The pre-compression parameters for the batches (F1-F9) demonstrate favorable flowability and compressibility, essential for consistent and high-quality tablet production. Bulk density (0.513 to 0.545 g/mL) and tapped density (0.605 to 0.645 g/mL) values indicate uniform particle size distribution and packing ability. The compressibility index, ranging from 13.96% to 17.41%, and Hausner's ratio (1.16 to 1.21) suggest good flow properties, with values well within acceptable limits (below 20% for

compressibility index and below 1.25 for Hausner's ratio). The angle of repose, between 23.15° and 26.24°, further confirms satisfactory flowability, typically considered excellent if below 30°. These results collectively indicate that the powder blends for all batches exhibit excellent pre-compression characteristics, supporting efficient manufacturing and uniformity of the final orodispersible tablets.

Table 11. Pre-compression parameters.

Batches	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose
F1	0.545	0.635	14.17	1.17	24.2
F2	0.535	0.635	15.75	1.19	26.24
F3	0.533	0.645	17.36	1.21	25.36
F4	0.534	0.641	16.69	1.20	24.74
F5	0.522	0.632	17.41	1.21	23.34
F6	0.513	0.605	15.21	1.18	24.45
F7	0.524	0.609	13.96	1.16	24.98
F8	0.521	0.615	15.28	1.18	23.34
F9	0.531	0.625	15.04	1.18	23.15

Post compression parameters

Physical appearance: The tablets from all trial batches were White round convex shaped beveled edge with having plane upper and lower side.

Thickness and diameter: The thickness and diameter of the tablets were measured using a Vernier caliper, with tablets picked randomly. The mean values are shown in Table 9. The measurements were nearly uniform across all formulations. The thickness ranged from 4.40 ± 0.02 mm to 4.80 ± 0.05 mm, and the diameter ranged from 6.90 mm to 7.20 mm. The uniformity of these values indicates that the formulations were compressed effectively, without sticking to the dies and punches.

Hardness: The Monsanto hardness tester was used to determine the hardness of all batches, with results provided in Table 9. The hardness values ranged from 3.5 kg/cm² to 5 kg/cm². All formulated batches exhibited uniform hardness, demonstrating good mechanical strength and adequate hardness.

Friability: Tablets from all batches were evaluated using a Roche Friabilator. The friability of the tablets was observed to be within the acceptable range of 0.33% to 0.76% (less than 1%). The results are provided in Table 12.

Drug content: The drug content uniformity test was conducted for all formulated batches, with results detailed in Table 10. The drug content ranged from 98% to 102%, which is within the specified limits.

Table 12. Post compression parameters.

Batches	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Friability (%)
F1	4.60±0.01	7.10±0.01	3.5	0.47
F2	4.80±0.05	7.15±0.03	4	0.42
F3	4.70±0.05	7.15±0.02	4	0.67
F4	4.60±0.02	6.90±0.02	3.5	0.49
F5	4.50±0.01	7.0±0.02	4.5	0.33
F6	4.40±0.05	7.0±0.02	4.5	0.47
F7	4.70±0.05	6.90±0.02	4	0.62
F8	4.60±0.02	7.15±0.02	4.5	0.59
F9	4.50±0.01	7.20±0.02	5	0.72

Weight Variation: Tablets were prepared using the direct compression technique. Due to the free-flowing nature of the material, the tablets achieved uniform weight, resulting from consistent die fill. The tablets from all prepared batches fell within the acceptable weight variation range as specified by pharmacopoeia standards, with variations of less than 7.5%. The results are presented in Table 13.

Table 13. Weight variation, drug content, disintegrating time and wetting time results.

Batches	Weight variation		Drug content (%)	Disintegration time (Sec)	Wetting time (Sec)
	Weight (mg) ± S. D.	Weight variation (5%)			
F1	205 ± 2	Passes	98.21	52 ± 2	26 ± 5
F2	195 ± 5	Passes	99.84	55 ± 3	31 ± 4
F3	200 ± 7	Passes	100.55	62 ± 4	36 ± 5
F4	198 ± 3	Passes	101.28	42 ± 2	23 ± 3
F5	205 ± 6	Passes	100.41	50 ± 2	28 ± 4
F6	205 ± 5	Passes	99.99	54 ± 4	33 ± 4
F7	195 ± 8	Passes	101.65	37 ± 3	23 ± 3
F8	190 ± 4	Passes	100.45	40 ± 4	26 ± 4
F9	195 ± 6	Passes	100.5	42 ± 3	29 ± 3

Disintegration test

Disintegration times for all batches are shown in Table 13, ranging from 35 to 60 seconds. Times decreased with higher superdisintegrant concentrations and increased with more binder.

Wetting time: Wetting times for all batches, detailed in Table 10, ranged from 23 to 36 seconds.

In vitro dissolution test

In vitro evaluations of all batches were conducted for 30 minutes using a phosphate buffer (pH 6.8) as the dissolution medium. The percentage of cumulative drug release (% CDR) was calculated using the corresponding equation. Results are presented in Table 14 and Figure 5.

Table 14. *In vitro* dissolution.

Time (min)	Cumulative Drug Release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	22.25	18.48	19.36	25.39	25.35	21.06	27.35	25.37	23.15
10	41.26	36.36	36.17	40.06	41.93	39.55	45.06	44.48	42.48
15	60.68	56.52	54.69	63.48	56.45	52.07	65.69	62.55	62.26
20	79.11	75.65	69.68	79.58	74.92	73.91	79.02	78.39	75.59
25	91.85	89.56	86.35	91.36	88.48	86.99	89.45	88.35	85.16
30	96.14	95.69	95.18	96.96	97.05	96.47	98.91	98.64	97.95

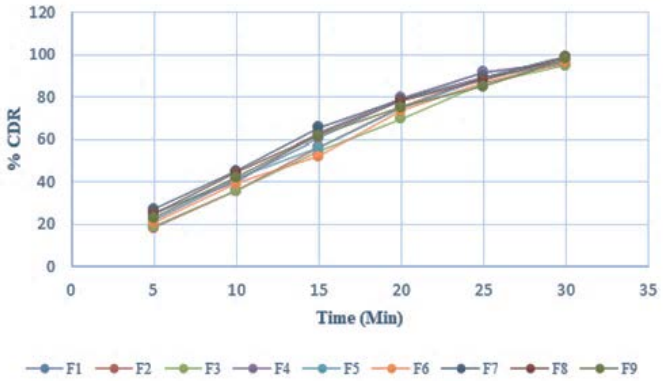


Figure 5. % drug release of F1-F9 batches.

OPTIMIZATION OF ORODISPERSIBLE TABLET

To examine the impact of independent variables on the responses, Design Expert 7.0 software was employed. An experimental design layout was created for 9 potential batches of Amlodipine besylate orodispersible tablets, as shown in Table 15. Among the various models—Linear, 2FI, Quadratic, and Cubic—the software suggested the best-fitting model, which was then tested using analysis of variance (ANOVA). Regression polynomials were calculated for each dependent variable, followed by the generation of one-factor and perturbation graphs for each dependent variable. Mathematical models were developed for each dependent variable or response (R) and expressed as Equations 1-2. In these equations, X1 and X2 represent the main effects, indicating the average result of changing one factor at a time from its low to high value. The interaction terms, X1 and X2, show how the response changes when two factors are altered simultaneously.[41,42]

Table 15. The layout of the Actual Design of DOE.

Runs	Factor 1	Factor 2	Response 1	Response 2
	A: % Croscarmellose sodium	B: % Avicel 102	Disintegration time (sec)	Hardness (kg/cm2)
1	7.5	15	42	3.5
2	10	15	37	4
3	10	20	42	5
4	10	17.5	40	4.5
5	5	17.5	55	4
6	5	20	62	4
7	7.5	17.5	50	4.5
8	7.5	20	54	4.5
9	5	15	52	3.5

RESULTS FOR THE DISINTEGRATION TIME OF DOE:

A. Fit Summary: After entering the data in Design-Expert software, fit summary applied to the data after which the "Linear vs Mean" was suggested by the software (Table 16).

B. ANOVA for Disintegration time of DOE: The analysis of variance (ANOVA) was conducted to determine the significant and insignificant factors. The ANOVA results for the disintegration time in the DOE are presented in Table 17.

Table 16. Fit summary table for Disintegration time of DOE.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	Result
Mean vs Total	20928.44	1	20928.44			
Linear vs Mean	538.17	2	269.08	83.27	< 0.0001	Suggested
2FI vs Linear	6.25	1	6.25	2.38	0.1837	
Quadratic vs 2FI	0.94	2	0.47	0.12	0.8941	
Cubic vs Quadratic	8.83	2	4.42	1.31	0.5250	Aliased
Residual	3.36	1	3.36			
Total	21486.00	9	2387.33			

Table 17. ANOVA table for a disintegration time of DOE.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	Result
Model	538.17	2	269.08	83.26934	< 0.0001	Signi-ficant
A-Croscarmellose sodium	416.67	1	416.67	128.94	< 0.0001	
B-Avicel 102	121.50	1	121.50	37.60	0.0009	
Residual	19.39	6	3.23			
Cor Total	557.56	8				

The Model F-value of 83.27 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob> F" less than 0.0500 indicate model terms are significant.

In this case A and B are significant model terms.

Fit Statistics for disintegration time of DOE

The "Pred R-Squared" of 0.9152 is in reasonable agreement with the "Adj R-Squared" of 0.9536, indicating a good fit of the model. "Adeq Precision," which measures the signal-to-noise ratio, shows a ratio of 24.730, well above the desirable threshold of 4. This suggests that the model has an adequate signal and can be used effectively to navigate the design space (Table 18).

Table 18. Fit statistics for disintegration time of DOE.

S. No	Parameters	Value
1	Std. Dev.	1.80
2	Mean	48.22
3	C.V. %	3.73
4	PRESS	47.28
5	R-Squared	0.9652
6	Adj R-Squared	0.9536
7	Pred R-Squared	0.9152
8	Adeq Precision	24.730

Final Equation in Terms of coded Factors for disintegration time of DOE:

The equation in terms of coded factors can be used to predict the response based on specific levels of each factor in the model (Table 19).

Table 19. Final equation in terms of coded factors.

S. No.	Disintegration time	Coded Factor
1	+48.22	
2	-8.33	* A
3	+4.50	* B

Diagnostics of disintegration time for DOE

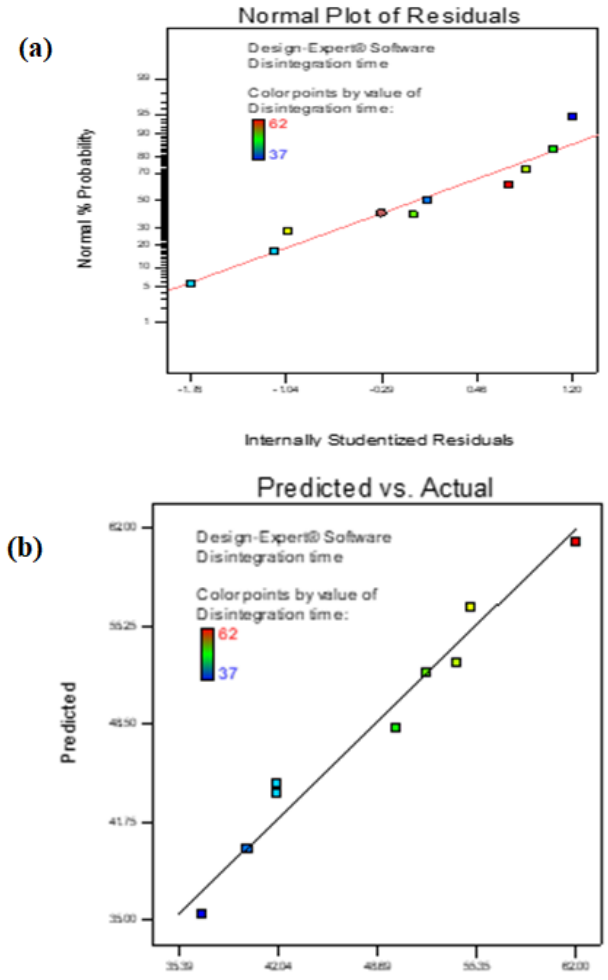


Figure 6. (a) Normal % Probability for DOE of disintegration time for DOE and **(b)** Predicted Vs Actual for DOE of disintegration time for DOE.

Model Graphs of disintegration time: One-factor Graphs of disintegration time for DOE:

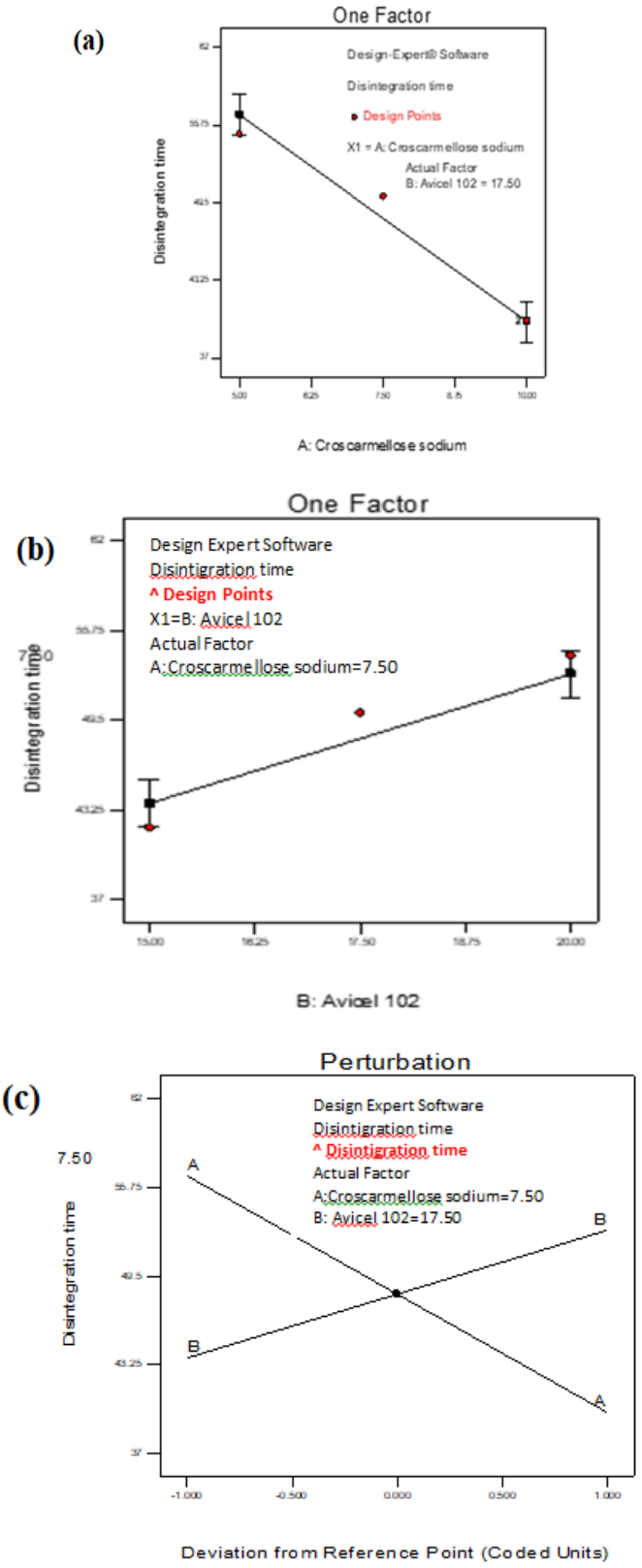


Figure 7. Effect of **(a)** % Croscarmellose sodium on disintegration time, **(b)** % Avicel 102 on disintegration time and **(c)** All 2 factors on disintegration time.

The percentage of Croscarmellose sodium and Avicel 102 in a formulation affects the drug's disintegration time. As the percentage of Croscarmellose sodium increases, the disintegration time decreases (Figure 7a, & 7b & 7c). Conversely, an increase in the percentage of Avicel 102 leads to a longer disintegration time. Croscarmellose sodium has a more significant impact on disintegration time compared to Avicel 102, as indicated by its much lower P value.

RESULTS FOR THE HARDNESS OF DOE:

1. Fit Summary: After entering the data into Design-Expert software and applying the fit summary, the software recommended the "Linear vs Mean" model (Table 20).

Table 20. Fit summary table for Hardness of DOE.

Source	Sum of Squares	df	Square Mean	F Value	p-value Prob> F	Result
Mean vs Total	156.25	1	156.25			
Linear vs Mean	1.71	2	0.85	17.57	0.0031	Suggested
2FI vs Linear	0.06	1	0.06	1.36	0.2956	
Quadratic vs 2FI	0.13	2	0.06	1.80	0.3065	
Cubic vs Quadratic	0.04	2	0.02	0.33	0.7746	Aliased
Residual	0.06	1	0.06			
Total	158.25	9	17.58			

2. ANOVA for Hardness of DOE: The analysis of variance (ANOVA) was performed to identify significant and insignificant factors. The results of ANOVA for the hardness factor of DOE are as following Table 21.

Table 21. ANOVA table for hardness of DOE as such.

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	Result
Model	1.708	2	0.8542	17.57142857	0.0031	Significant
A-Croscarmellos sodium	0.667	1	0.6667	13.7142857 1	0.010 0	
B-Avicel 102	1.042	1	1.0417	21.42857143	0.0036	
Residual	0.292	6	0.0486			
Cor Total	2	8				

The Model F-value of 17.57 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A and B are significant model terms.

Fit Statistics for hardness for DOE

Table 22. Fit statistics for hardness for DOE.

S. No.	Parameters	Value
1	Std. Dev.	0.22
2	Mean	4.17
3	C.V. %	5.29
4	PRESS	0.60
5	R-Squared	0.8542
6	Adj R-Squared	0.8056
7	Pred R-Squared	0.7015
8	Adeq Precision	11.784

The “Pred R-Squared” of 0.7015 is in reasonable agreement with the “Adj R-Squared” of 0.0.8056

“Adeq Precision” measures the signal to noise ratio (Table 22). A ratio greater than 4 is desirable. Ratio of 11.784 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors of hardness for DOE:

Table 23. Final equation in terms of coded factor of hardness.

S. No.	Hardness	Coded Factor
1	**+4.17**	
2	**+0.33**	*** A**
3	**+0.42**	*** B**

Diagnostics of hardness for DOE:

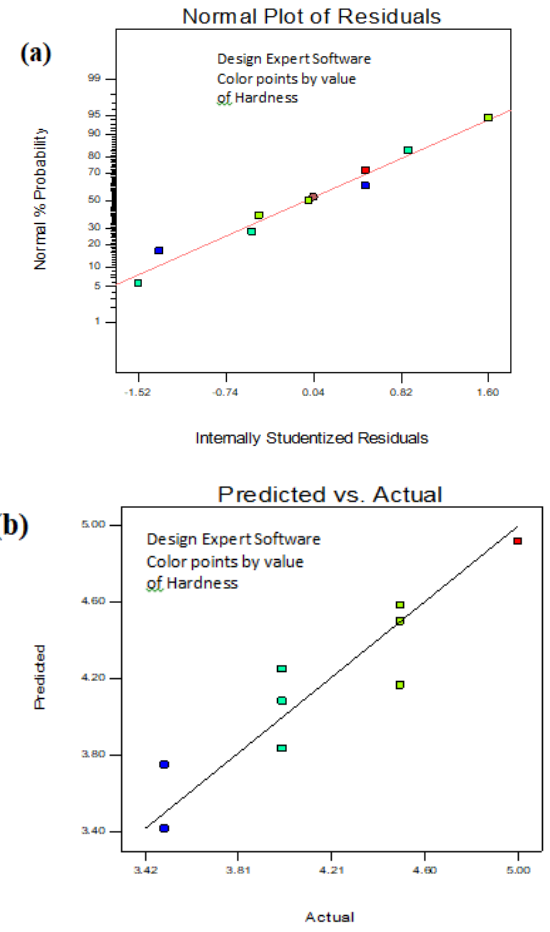


Figure 8. (a) Normal % Probability for DOE of hardness for DOE and **(b)** Predicted Vs Actual of hardness for DOE.

Model Graphs of hardness: One-factor Graphs of hardness for DOE

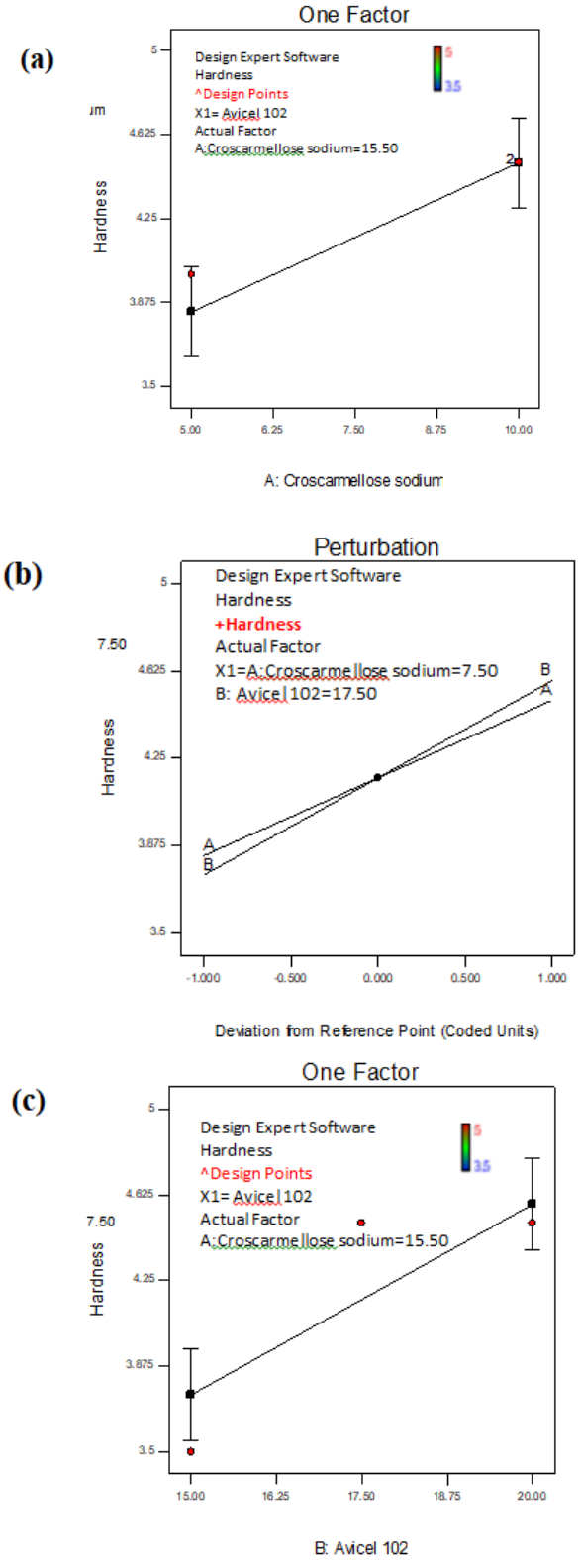


Figure 9. Effect of **(a)** % Croscarmillose sodium on hardness, **(b)** % Avicel 102 on hardness and **(c)** All 2 independent parameters on hardness.

In a formulation, the percentage of Croscarmellose sodium and Avicel 102 both influence tablet hardness (Table 24, Figure 9a to 9c). As the percentage of Croscarmellose sodium increases, there is a corresponding increase in hardness. Similarly, increasing the percentage of Avicel 102 also results in greater hardness. However, Avicel 102 has a significantly stronger impact on hardness compared to Croscarmellose sodium, as indicated by its much lower P value.

Table 24. Summary of effect of independent variable on dependent variables.

Independent variables	Disintegration time	Hardness
% Croscarmellose sodium in formulation	Inversely proportional (As Croscarmellose sodium increases, disintegration time decreases)	Directly proportional (As Croscarmellose sodium increases, hardness also increases)
% Avicel 102 in formulation	Directly proportional (As Avicel 102 increases, disintegration time increases)	Directly proportional (As Avicel 102 increases, hardness also increases)

Based on the data obtained from pre-compression and post-compression evaluations, as well as the factorial design model study, batch F7 was selected as the optimized batch.

Evaluation of optimized batch (F7):

The optimized batch (F7) of the orodispersible tablets was thoroughly evaluated to ensure it met the required quality standards. The results (Table 25) are as follows: The tablet thickness was 4.7 mm and the diameter was 7.10 mm, indicating consistent size. Hardness was measured at 4 kg/cm², ensuring adequate mechanical strength while maintaining rapid disintegration. Friability was low at 0.62%, indicating the tablets are resistant to crumbling. The drug content was found to be 99.53%, reflecting uniformity and precision in the formulation. The disintegration time was rapid at 35 seconds, crucial for orodispersible tablets. The weight variation test was passed, indicating consistency in tablet weight. The wetting time was 25 seconds, further supporting quick disintegration. Finally, the *in vitro* dissolution test showed 99.15% cumulative drug release (CDR), indicating efficient drug release. These results confirm that batch F7 exhibits excellent physical characteristics, rapid disintegration, and effective drug release, making it suitable for patient use.

Table 25. Evaluation of optimized batch (F7).

S. No.	Evaluation parameter	Results
1	Thickness	4.7 mm
2	Diameter	7.10 mm
3	Hardness	4 kg/cm2
4	Friability	0.62 %
5	Drug content	99.53 %
6	Disintegration time	35 sec
7	Weight variation test	Passed
8	Wetting time	25 sec
9	*In vitro* dissolution (%CDR)	99.15 %

CONCLUSION

The research successfully formulated and evaluated orodispersible tablets of amlodipine besylate, aiming to improve the treatment of hypertension through enhanced patient compliance. The tablets were prepared using the direct compression method, incorporating croscarmellose sodium as superdisintegrants in various concentrations. Comprehensive assessment parameters, including friability, hardness, disintegration time, wetting time, *in vitro* drug release, and drug content, demonstrated that all formulations met the prescribed limits. Notably, formulation F7, which contained the highest concentration of superdisintegrants, exhibited the most favorable performance with a disintegration time of 37 ± 3 seconds and an impressive drug release rate of 98.91% within 30 minutes. These findings highlight the efficacy of combining croscarmellose sodium and Avicel 102 in the specified ratios, offering a promising approach for developing orodispersible tablets of amlodipine besylate for hypertension management. The study concludes that the optimized formulation (F7) holds significant potential for enhancing patient adherence and therapeutic outcomes in hypertension treatment.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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