RESEARCH ARTICLE

Batch Scale-Up and Impact of Process Parameters on Blend Homogeneity in Production of Bilayer Film-Coated Tablets Containing Extended-Release Indapamide and Immediate-Release Amlodipine

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ABSTRACT
This study aimed to develop and optimize a manufacturing process for bilayer film-coated tablets containing extended-release indapamide and immediate-release amlodipine besylate. The formulation process included dry mixing, final blending, bilayer compression, film coating, and quality and stability evaluations. Optimization of the dry mixing and final blending times was performed to ensure uniformity and reproducibility. For the 10,000-tablet batch, the indapamide layer was processed using a high-speed mixer for 7 minutes at 500 rpm paddle speed and 1500 rpm chopper speed, followed by 5 minutes of final blending in a cubic blender at 17 rpm. The amlodipine layer underwent both dry mixing and final blending for 5 minutes in the cubic blender. In scale-up to a 100,000-tablet batch, adjustments in mixer parameters were necessary for the indapamide layer, and an extended initial mixing time of 6 minutes was required for the amlodipine layer. The bilayer tablets were successfully compressed and film-coated, exhibiting consistent physical properties and quality attributes. Stability testing confirmed the robustness of the formulation and process. The optimized manufacturing process was found to be scalable, repeatable, and suitable for commercial production, ensuring the consistent quality of the final bilayer film-coated tablets.

Keywords: bilayer film-coated tablets, dry mixing, final blending, scale-up, stability testing
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INTRODUCTION

Tablets are the most common oral dosage form due to their ease of use, manufacturing efficiency, and stability. However, when multiple active pharmaceutical ingredients (APIs) with differing properties are required, single-layer tablets may be inadequate. Bilayer tablets offer a practical solution by incorporating two distinct layers, each with a specific API or release profile. This design enables fixed-dose combinations (FDCs), separation of incompatible drugs, and modification of release kinetics, thereby improving therapeutic efficacy and patient adherence. Despite their advantages, bilayer tablets pose formulation challenges, including interlayer adhesion, content uniformity, and mechanical strength. These issues necessitate careful material selection and process optimization. In hypertension treatment, combining indapamide, a thiazide-like diuretic, with amlodipine besylate, a calcium channel blocker, provides synergistic effects and is clinically effective.[1-3]

Scaling up tablet production from pilot to industrial scale is a critical phase in pharmaceutical development. It aims to maintain product quality, safety, and efficacy while increasing batch size. However, scale-up is not a simple linear process—differences in equipment size, design, and operating conditions can affect key parameters such as mixing time, granulation, compression, and coating. These changes may influence tablet hardness, dissolution, uniformity, and stability. Therefore, robust, well-controlled, and scalable processes are essential to ensure consistent product performance, regulatory compliance, and successful technology transfer to commercial manufacturing.[4-6]

Blend homogeneity is essential in solid dosage form development, especially for multi-component formulations

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Table 1: Formulation of bilayer film-coated tablets for 10,000-tablet and 100,000-tablet batches

Ingredient	Amount per Tablet (mg)	Amount for 10,000 Tablets (g)	Amount for 100,000 Tablets (g)
Extended-Release Layer			
Indapamide	1.50	15.00	150.00
HPMC K15M	61.58	615.80	6150.80
Lactose Monohydrate	116.73	1167.30	11670.30
Povidone K30	8.57	85.70	850.70
Aerosil	0.82	8.20	80.20
Magnesium Stearate	0.80	8.00	80.00
Water*	11.00	110.00	1100.00
Ethanol 96%*	25.00	250.00	2500.00
Total extended-release layer	190	1900	19000
Immediate-release layer			
Amlodipine besylate**	13.88	138.80	1380.80
Sodium croscarmellose	18.36	183.60	1830.60
MCC 112	120.26	1202.60	12020.60
A Tab	57.00	570.00	5700.00
Aerosil	2.00	20.00	200.00
Magnesium stearate	1.50	15.00	150.00
Total ummediate-release layer	213	2130	21300
Total tablet core weight	403	4030	40300
Film Coating Layer			
HPMC 6cps	7.00	70.00	700.00
PEG 6000	0.70	7.00	70.00
Magnesium stearate	1.40	14.00	140.00
Titanium dioxide	2.78	27.80	278.00
Sunset yellow dye	0.10	1.00	10.00
Ponceau red E124 dye	0.02	0.20	2.00
Water*	50.00	500.00	5000.00
Ethanol 96% *	100.00	1000.00	10000.00
Total coated tablet	415	4150	41500

**solvent evaporates during the preparation process*
***13.88 mg of amlodipine besylate is equivalent to 10 mg of amlodipine*

like bilayer tablets. Uniform distribution of APIs and excipients ensures dose accuracy, therapeutic efficacy, and regulatory compliance. Poor blend uniformity can lead to content variability, compromising safety and effectiveness. This challenge becomes more pronounced during scale-up, where changes in batch size and equipment may affect mixing dynamics. Therefore, controlling factors that influence blend homogeneity is critical to maintaining product quality.[7,8]

This study investigates the scale-up of bilayer tablet production from 10,000 to 100,000 units, focusing on the reproducibility of critical quality attributes and the impact of dry and final mixing times on blend homogeneity. By comparing physical properties, dissolution profiles, and stability data across scales, the study aims to establish a robust, scalable, and reproducible manufacturing process for fixed-dose bilayer tablets.

MATERIALS AND METHODS

Materials and instruments

The active pharmaceutical ingredients (APIs) used were amlodipine (99.5%, Cadila Healthcare, India) and indapamide (99.7%, Suzhou Lixin Pharmaceutical, China). Excipients included HPMC K15M and HPMC 6 cps (Colorcon, USA), PVP K30 (Germany), aerosil (Evonik, Germany), sodium croscarmellose (Mingtai, Taiwan), sodium starch glycolate (Roquette, France), dicalcium phosphate and maltodextrin (Innophos, USA), microcrystalline cellulose (China), lactose monohydrate (Kemphasol, India), magnesium stearate and PEG 6000 (Evolutics, India), titanium dioxide, Sunset Yellow, and Ponceau 4R (India). Distilled water and 96% ethanol (Vietnam) were also used. All materials complied with USP-NF standards. Indapamide (97.7%) and amlodipine besylate (103%) internal standards were provided by the Institute of Drug Quality Control, Ho Chi Minh City, Vietnam. HPLC-grade solvents included acetonitrile (Fisher Scientific, USA), methanol (Sigma-Aldrich, USA), triethylamine (Merck, Germany), and phosphoric acid (Xilong, China).

Equipments included electronic and analytical balances (Shimadzu and AND, Japan), drying oven (Yihder, Taiwan), moisture analyzer (AND, Japan), bulk density tester (Copley, UK), flowability tester, dissolution tester, hardness tester, and friability tester (ERWEKA, Germany). Manufacturing equipment included a high-shear mixer, cube mixer, film coater (Tien Tuan, Vietnam), oscillating granulator (ERWEKA, Germany), tablet press (Clit, India), and magnetic stirrer (Labtech, Korea).

Manufacturing Process of Granules

Formulation Design and Scale-Up Preparation of Bilayer Tablets: The formulation of the bilayer film-coated tablets containing immediate-release amlodipine and extended-release indapamide at the 10,000-unit and 100,000-unit scales was developed based on results obtained from the pilot-scale batch (500 tablets), which met all required specifications. The composition per tablet is summarized in Table 1. The extended-release indapamide layer was prepared using the wet granulation method.[9] Indapamide, lactose monohydrate, and HPMC K15M were passed through a 0.5 mm sieve and dry-mixed in a high-shear mixer. The povidone K30/alcohol–water solution (0.44:1, w/w) was then added, and wet granulation was performed using a 1.6 mm sieve. The resulting granules were dried in

Table 2: Processing parameters for indapamide and amlodipine besylate layers at the 10,000-tablet and 100,000-tablet scales

Stage	10,000-tablet batch		100,000-tablet batch	
	Indapamide	Amlodipine	Indapamide	Amlodipine
Dry mixing stage	Equipment: high-shear mixer (5 kg)	Equipment: cube mixer (5 kg)	Equipment: high-shear mixer (70 kg)	Equipment: cube mixer (50 kg)
	Impeller speed: 500 rpm Chopper speed: 1500 rpm	Mixing speed: 17 rpm	Impeller speed: 120 rpm Chopper speed: 2800 rpm	Mixing speed: 10 rpm
	Sampling locations: 6 different spots Sample amount: 2 g/time/spot × 3 times			
	Sampling time points: 1, 3, 5, 7, 9 min	Sampling time: 3, 4, 5, 6, 7 min	Sampling time: 1, 3, 5, 7, 9 min	Sampling time: 3, 4, 5, 6, 7 min
Final blending	Equipment: cube mixer (5 kg)		Equipment: cube mixer (50 kg)	
	Mixing speed: 17 rpm Sampling locations: 10 different spots Sample amount: 2 g/time/spot × 3 times Sampling time points: 4, 5, 6 min		Mixing speed: 10 rpm	

Table 3: Dissolution test conditions

Buffer solution	pH = 1.2	pH = 4.5	pH = 6.8
Temperature (°c)	37 ± 0.5°C		
Stirring speed (rpm)	75	75	100
Sampling time	10, 15, 30, 45, 60 min	10, 15, 30, 45, 60 min	2, 4, 8, 12, 16 h

a hot air oven at 60 °C until the moisture content was ≤ 2%. The dried granules were then passed through a 0.5 mm sieve. Magnesium stearate and aerosil, previously sieved through a 0.5 mm mesh, were weighed and blended with the granules using a cubic mixer.

The immediate-release amlodipine besylate layer was prepared by direct compression.[10] Amlodipine, microcrystalline cellulose 112, A-Tab, and sodium croscarmellose were passed through a 0.5 mm sieve and uniformly blended in a cubic mixer. Aerosil and magnesium stearate were then added to the mixture and mixed thoroughly. Detailed process parameters for the preparation of both layers are presented in Table 2.

Optimization of dry mixing and final blending time: Pilot-scale batches of 10,000 and 100,000 tablets were prepared to optimize key process parameters, with a focus on evaluating dry mixing and final blending time durations (Table 2). Blend homogeneity was assessed by quantifying the content of indapamide and amlodipine besylate in samples collected at various time points during both dry mixing and final blending stages. The coefficient of variation (CV%) was calculated, with a target threshold of ≤ 2% to indicate acceptable uniformity. The mixing time that yielded the lowest CV% was selected as the optimal mixing duration.

Assessment of Final Granule Physical Properties

The granules were evaluated for moisture content, bulk density, tapped density, compressibility index (Carr's Index, CI), Hausner ratio, and angle of repose.[11]

The compressibility index (CI) and Hausner ratio were calculated using the following formulas:

Compressibility index (CI, %) = (Tapped density − Bulk density)/Tapped density × 100

Hausner ratio = Tapped density/Bulk density

These parameters are commonly used to assess the flow properties of granules prior to compression.

Bilayer Tablet Compression and Film Coating Process

Bilayer Tablet Compression Process: Tablet compression was performed using a 45-station rotary tablet press operating at a speed of 12 revolutions per minute, equipped with round-headed punches (9 × 12 mm). The indapamide layer was compressed first with an average tablet weight of 190 mg ± 5%, using an initial compression force of 5–6 kN. The final bilayer tablet had an average weight of 403 mg ± 5%.

To monitor tablet weight during bilayer compression, a Shewhart control chart was applied.[12] For the 10,000-tablet batch (compressed over approximately 0.5 hours), samples were collected every 3 minutes (sampling interval k = 10). Each sample consisted of 20 tablets, used to calculate the mean weight and define the control range. For the 100,000-tablet batch (5 hours of compression), samples were taken every 15 minutes (k = 20). Tablet hardness and friability were also assessed during compression. Ten tablets were tested at each sampling point. Samples were collected every 15 minutes for the 10,000-tablet batch and every 30 minutes for the 100,000-tablet batch. The target hardness was 250 ± 10 N, and friability was required to be less than 1%

Film Coating Process: The bilayer tablets were film-coated using a coating suspension prepared according to the formulation described in Table 1. The coating ingredients were gradually added into a container containing a hydroalcoholic solution and stirred for approximately 15 minutes. The resulting suspension was then passed through a 0.4 mm sieve to obtain a homogeneous coating dispersion. The suspension was continuously stirred throughout the coating process. Film coating parameters included an inlet air temperature of 55–60°C, outlet air temperature of 50–

Table 4: Mixing time during the dry mixing stage at different positions (P) in batch 1

Batch	Layer	Time (min)	P1	P2	P3	P4	P5	P6	Mean	CV%
10,000 tablets	Inda	1	83.13	73.49	113.25	115.66	101.20	93.98	96.79	17.19
		3	96.39	86.75	90.36	102.41	98.80	96.39	95.18	5.99
		5	104.82	98.80	104.82	106.02	97.59	102.41	102.41	3.41
		7	100.00	100.00	100.00	101.20	98.80	98.80	99.80	0.91
		9	98.80	98.80	102.41	97.59	100.00	98.80	99.40	1.67
	Amlo	3	97.89	97.74	90.51	104.67	101.66	101.81	99.05	4.99
		4	99.85	99.55	100.60	99.10	101.66	97.44	99.70	1.43
		5	101.20	101.36	100.00	101.20	99.85	100.75	100.73	0.65
		6	100.60	95.18	96.69	103.31	101.36	102.11	99.87	3.22
		7	102.56	99.40	96.84	101.05	103.31	102.26	100.90	2.40
100,000 tablets	Inda	1	85.54	83.13	93.98	107.23	109.64	86.75	94.38	12.18
		3	96.39	95.18	102.41	103.61	100.00	98.80	99.40	3.32
		5	102.41	97.59	101.20	102.41	101.20	101.20	101.00	1.76
		7	101.20	101.20	102.41	100.00	100.00	100.00	100.80	0.98
		9	100.00	97.59	103.61	100.00	101.20	100.00	100.40	1.96
	Amlo	3	96.84	97.44	90.51	104.67	101.66	101.81	98.82	5.08
		4	100.15	98.04	100.60	99.25	101.66	97.44	99.52	1.60
		5	100.00	100.60	100.00	100.75	99.55	99.55	100.08	0.51
		6	100.45	100.00	100.00	100.30	100.00	100.15	100.15	0.19
		7	102.56	99.55	99.85	101.05	100.30	100.75	100.68	1.07

55°C, pan speed of 14–16 rpm, peristaltic pump speed of 28–30 rpm, atomizing air pressure of 1–3 bar, and a spray gun-to-tablet bed distance of 15 cm. After coating, the tablets were dried at 55–60°C for approximately 60 minutes.

Quality Evaluation of Film-Coated Tablets

The film-coated tablets were evaluated for uniformity of weight, content uniformity, hardness, friability, assay, and *in vitro* dissolution. Hardness and friability were tested on 20 tablets. The acceptance criteria were a hardness of 250 ± 10 N and friability less than 1%. In vitro dissolution was conducted using 6 tablets in dissolution media at pH 1.2, pH 4.5, and pH 6.8. The tests were performed in 1000 mL of buffer solution maintained at 37 ± 0.5°C under specific conditions. At each sampling time point, 10 mL of dissolution medium was withdrawn, filtered through a 0.45 µm membrane filter, and analyzed using HPLC–DAD under previously optimized chromatographic conditions. The relative standard deviation (RSD) was calculated from six replicates. According to regulatory requirements, the RSD must be ≤ 10% for active pharmaceutical ingredients (APIs) with a dissolution level below 85%, and ≤ 5% for those with a dissolution level above 85%. For assay, twenty tablets were crushed and analyzed by HPLC to determine the concentrations of indapamide and amlodipine. The acceptance criteria for assay were 90–110% of the labeled amount.

Stability Evaluation of Film-Coated Tablets

The long-term and accelerated stability of the bilayer film-coated tablets were evaluated according to ASEAN guidelines under Zone IVB conditions.[13] Storage conditions were set at 30 ± 2°C/75 ± 5% RH (long-term) and 40 ± 2°C/75 ± 5% RH (accelerated), with assessments at 0, 6, and 12 months. Parameters evaluated included

Table 5. Processing time during the final blending stage at different sampling positions (P') in Batch 1

Batch	10.000 tablets						100.000 tablets					
Layer	Indapamide			Amlodipine			Indapamide			Amlodipine		
Time (min)	4	5	6	4	5	6	4	5	6	4	5	6
P1'	102.53	100	101.27	106.75	100.15	99.69	103.80	98.73	100.00	103.37	99.85	100.15
P2'	101.27	98.73	101.27	97.39	100.02	101.23	102.53	100.00	100.00	98.47	100.31	102.61
P3'	98.73	98.73	97.47	105.67	101.23	100.31	97.47	98.73	98.73	102.3	101.38	100.61
P4'	102.53	101.27	98.73	101.69	100.31	99.69	105.06	98.73	98.73	100.92	100.15	100.46
P5'	106.33	100.00	100.00	100.31	99.69	101.23	107.59	98.73	98.73	97.24	101.07	100.61
P6'	105.06	100.00	100.00	102.91	101.23	101.23	102.53	98.73	96.20	100.61	100.77	101.69
P7'	103.03	100.00	100.95	103.22	100.15	101.38	102.21	101.23	101.34	103.07	100.00	100.92
P8'	102.01	99.98	100.34	101.84	100.46	102.3	102.01	100.17	100.42	101.38	99.85	101.38
P9'	101.24	100.23	101.72	103.99	100.15	100.61	101.24	100.21	101.77	103.53	100.31	101.07
P10'	102.24	99.46	99.45	98.93	100.00	100.31	102.24	100.34	101.23	100.61	100.46	100.92
TB	102.5	99.84	100.12	102.27	100.43	100.8	102.67	99.56	99.72	101.15	100.41	101.04
CV (%)	2.03	0.74	1.30	2.83	0.52	0.82	2.61	0.93	1.67	2.05	0.51	0.70

Table 6: Evaluation of in-process parameters of intermediate products in three batches of 10,000 and 100,000 tablets

Batch Size	Active Ingre-dient	Batch No.	Moisture Content (%)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (CI)	Hausner Ratio	Angle of Repose (°)
10.000 tablets	Inda	1	1.76±0.11	0.606±0.001	0.635±0.005	4.649±0.643	1.049±0.007	23.465±0.273
		2	1.82±0.12	0.607±0.002	0.638±0.003	4.981±0.248	1.052±0.003	22.916±0.432
		3	1.67±0.09	0.606±0.001	0.634±0.009	4.421±1.332	1.046±0.014	23.538±0.141
	Amlo	1	1.23±0.08	0.494±0.005	0.517±0.007	4.372+1.880	1.046±0.021	24.053±0.465
		2	1.46±0.23	0.498±0.003	0.519±0.007	4.042±0.797	1.042±0.009	24.357±0.325
		3	1.54±0.21	0.501±0.006	0.523±0.002	4.202±1.182	1.044±0.013	23.895±0.670
100.000 tablets	Inda	1	1.56±0.43	0.607±0.001	0.646±0.007	6.147±0.868	1.066±0.010	22.065±0.587
		2	1.72±0.82	0.607±0.001	0.641±0.002	5.251±0.460	1.055±0.005	23.105±0.472
		3	1.61±0.25	0.605±0.001	0.644±0.006	6.114±0.997	1.065±0.011	22.981±0.364
	Amlo	1	1.34±0.28	0.496±0.005	0.528±0.006	5.926±1.845	1.063±0.021	24.253±0.107
		2	1.66±0.12	0.508±0.003	0.539±0.004	5.749±1.262	1.061±0.014	24.345±0.397
		3	1.56±0.11	0.503±0.004	0.535±0.008	5.975±0.658	1.064±0.007	24.187±0.284

The results are presented as mean ± standard deviation (SD)

Table 7: Evaluation results of film-coated tablets from three batches of 10,000 tablets

Batch	Uniformity of Mass	Content Uniformity		Hardness (kp) (n=10)	Friability (%) (n=10)	Active Ingredient Content (%)	
		Inda (n=10)	Amlo (n=10)			Inda (n=20)	Amlo (n-20)
1	415±0.58	1.5±0.01	10.02±0.03	25.11±0.57	0.17±0.22	97.63±0.23	99.63±0.32
2	414±0.84	1.5±0.02	10.01±0.02	25.23±0.53	0.18±0.13	98.72±0.76	99.93±0.16
3	416±1.02	1.5±0.01	10.01±0.03	25.43±0.21	0.17±0.17	98.11±1.02	98.98±0.11

Appearance: The tablets are round, film-coated, with a smooth and glossy surface, uniform pinkish-red color, and free from cracks
The results are expressed as mean ± standard deviation (SD)

Table 8: Evaluation results of film-coated tablets from three batches of 100,000 tablets

Batch	Uniformity of Mass	Content Uniformity		Hardness (kp) (n=10)	Friability (%) (n=10)	Active Ingredient Content (%)	
		Inda (n=10)	Amlo (n=10)			Inda (n=20)	Amlo (n-20)
1	416±0.63	1.5±0.02	10.01±0.03	25.21±0.32	0.18±0.12	97.92±1.13	99.97±0.09
2	415±0.72	1.5±0.01	10.02±0.01	25.33±0.47	0.17±0.23	99.67±0.24	100.01±0.26
3	416±1.27	1.5±0.03	10.02±0.02	25.13±0.46	0.17±0.09	98.23±0.42	99.72±0.41

Appearance: The tablets are round, film-coated, with a smooth and glossy surface, uniform pinkish-red color, and free from cracks
The results are expressed as mean ± standard deviation (SD)

appearance, assay, weight variation, content uniformity, hardness, friability, and in vitro dissolution.

RESULTS AND DISCUSSION

Optimization of Dry Mixing and Final Blending Times

The uniformity of the dry mixing and final blending stages of batch 1 was evaluated based on the content uniformity results for indapamide and amlodipine besylate, as summarized in Tables 4 and 5.

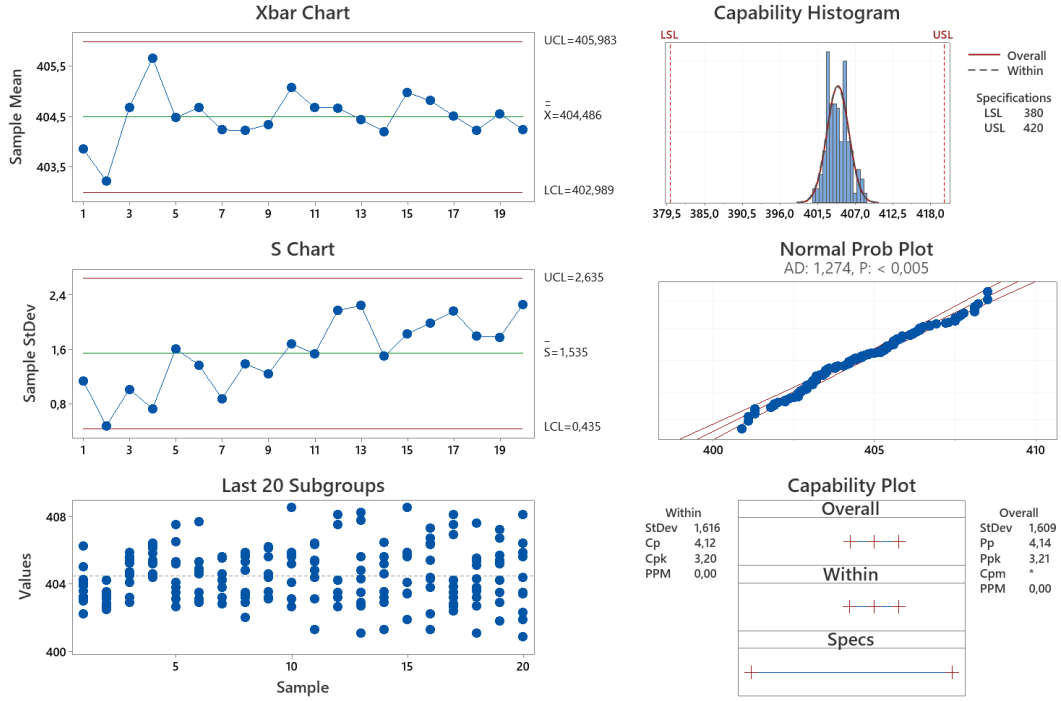
Based on the evaluation results, the optimal dry mixing time for the indapamide layer was 7 minutes, and the optimal final blending time was 5 minutes for both 10,000-tablet and 100,000-tablet batches, yielding the lowest coefficient of variation (CV%). In contrast, the amlodipine layer exhibited a difference in optimal dry mixing time, with 5 minutes for the 10,000-tablet batch and 6 minutes for the 100,000-tablet batch, while the final blending time remained optimal at 5 minutes for both scales. Using these optimized parameters, each batch size was manufactured in triplicate. All three batches at both scales achieved CV% values below 2%, demonstrating the reproducibility and scalability of the process. There was no significant difference in the optimal dry mixing time for indapamide between the 10,000- and 100,000-tablet batches. However, prolonged mixing beyond 7 minutes (up to 9 minutes) led to decreased uniformity and increased CV%, which is consistent with findings reported by Vipin Kukkar et al.[14]

This can be explained by the fact that indapamide, being present in very small amounts in the formulation, may accumulate electrostatic charges during prolonged mixing, causing it to separate from the mixture and adhere to the equipment surfaces, resulting in a loss of uniformity.[15]

Therefore, dry mixing should be performed in a high-shear mixer with appropriate speed and duration. For the amlodipine layer, the mixing time increased in the 100,000-tablet batch due to changes in equipment and a lower

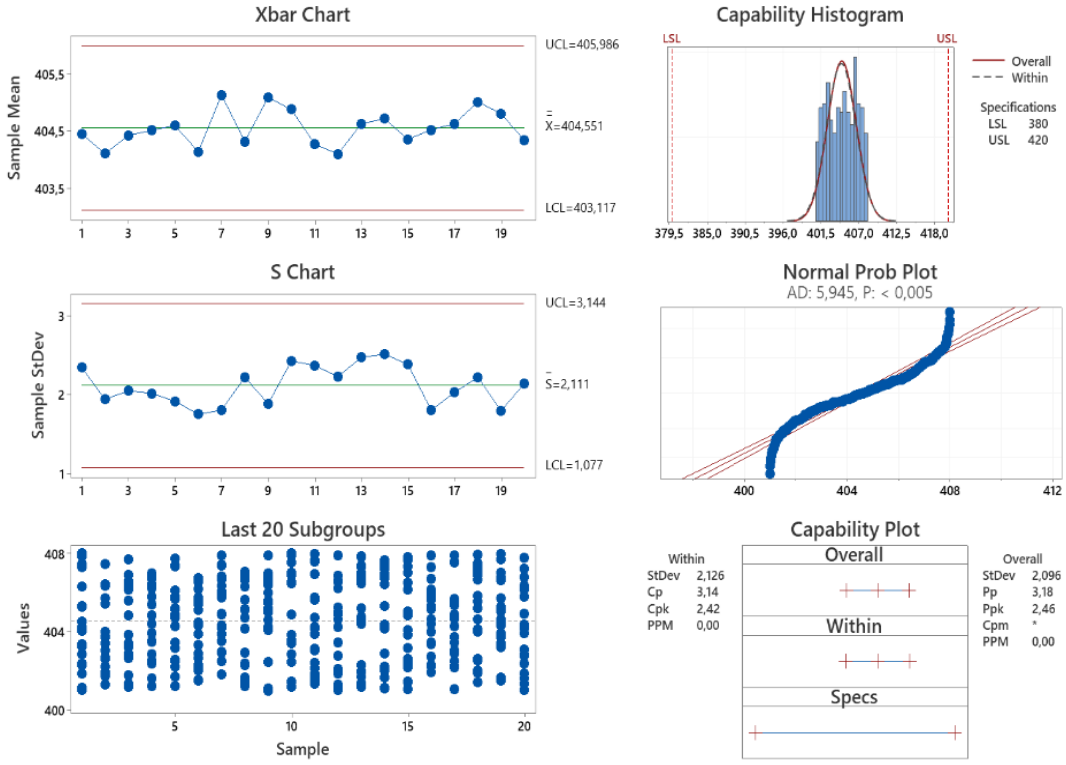
number of rotations (17 rotations for the 10,000-tablet batch versus 10 rotations for the 100,000-tablet batch), which resulted in a longer mixing duration. In the final blending stage, for both layers, an increase in blending time beyond the optimal point led to higher CV% values. According to several studies,[16, 17] this phenomenon can be explained by the difference in density between the granules and the lubricants (magnesium stearate and aerosil) added during final blending.

Since indapamide is present in granulated form at this stage, its higher density causes it to separate more quickly from the mixture, resulting in content non-uniformity, as



The actual process spread is represented by 6 sigma.

Figure 1**:** Shewhart chart of tablet weight for batch 1 at the 10,000-tablet scale



The actual process spread is represented by 6 sigma.

Figure 2: Shewhart chart of tablet weight for batch 1 at the 100,000-tablet scale

Table 9: Dissolution test results of three batches (scale: 10,000 tablets)

	Amlo	Inda	Amlo	Inda	Amlo	Inda	Amlo	Inda	Amlo	Inda
pH = 1.2										
Time (mins)	10		15		30		45		60	
Ave. (%)	92.63	-	93.72	-	94.45	-	95.23	-	97.84	-
SD (%)	0.63	-	1.13	-	0.67	-	2.01	-	1.02	-
pH = 4.5										
Time (hours)	2		4		8		12		16	
Ave. (%)	98.72	13,16	98.72	20.11	98.54	41.73	98.75	65.12	98.50	86.12
SD (%)	0.66	0.85	0.21	1.82	0,17	2.85	1.01	1.28	0.23	1.67
pH = 6.8										
Time (hours)	2		4		8		12		16	
TB (%)	98.68	14.67	98.42	18.18	98.76	45.35	98.38	63.02	98,55	85.67
SD (%)	0.56	1.32	0.45	1.23	1.13	1.76	0.24	1.54	0.97	2.05

All results are presented as the mean ± standard deviation (SD) for each batch, with n = 6.

Table 10: Dissolution test results of three batches (scale: 100,000 tablets)

	Amlo	Inda	Amlo	Inda	Amlo	Inda	Amlo	Inda	Amlo	Inda
pH = 1.2										
Time (mins)	10		15		30		45		60	
Ave. (%)	93.54	-	93.97	-	94.57	-	95.63	-	97.81	-
RSD (%)	0.72	-	1.13	-	1.47	-	0.68	-	1.24	-
pH = 4.5										
Time (mins)	2		4		8		12		16	
Ave. (%)	99.42	13.97	99.71	16.78	99.47	53.02	99.67	68.72	99.63	85.11
RSD (%)	0.23	0.92	0.13	1.23	0.78	2.56	1.23	1.78	0.89	1.56
pH = 6.8										
Time (mins)	2		4		8		12		16	
Ave. (%)	99.97	13.67	100.32	19.36	100.42	40.24	100.01	65.78	100.13	84.23
RSD (%)	0.56	2.26	0.34	2.11	0.38	2.56	0.34	1.75	0.43	1.56

All results are presented as the mean ± standard deviation (SD) for each batch, with n = 6.

reflected by the difference in CV% values at 5 and 6 minutes (0.53% for the 10,000-tablet batch and 0.59% for the 100,000-tablet batch). In contrast, for the amlodipine layer, the deviation was less significant because the excipients were used in their original powder forms, resulting in smaller density differences and slower separation.

Evaluation of the Physical Properties of Final Granules

The evaluation results of intermediate parameters for indapamide and amlodipine besylate from three production batches are presented in Table 6. The assessed parameters included moisture content, bulk density, tapped density, compressibility index (CI), Hausner ratio, and angle of repose. The moisture content of both indapamide and amlodipine granules in both batch sizes was below 2%, meeting the quality requirements for intermediate products. According to USP 38 standards, a compressibility index (CI) of less than 10, a Hausner ratio below 1.1, and an angle of repose below 25º indicate excellent flowability of both types of granules. When scaling up from 10,000 to 100,000 tablets, the intermediate products maintained consistent and repeatable quality across batches, indicating a robust manufacturing process unaffected by changes in equipment type, parameters, or batch size.

All flow properties met the required specifications, confirming that the bilayer tablet formulation containing indapamide and amlodipine is suitable for large-scale

Figure 3: Bilayer film-coated tablet containing indapamide and amlodipine besylate

Table 11: Drug stability after 12 months of film-coated tablets

Active Ingredient	Initial	6 months		12 months	
	Content (%)	40°C/75% RH	30°C/75% RH	40°C/75% RH	30°C/75% RH
Indapamide	99.51 ± 0.52	99.01 ± 0.08	99.13 ±0.24	97.73 ± 0.45	98.81 ± 0.63
Amlodipine	100.32 ± 0.23	99.63 ± 0.14	99.87 ±0.17	98.49 ± 0.45	99.52 ± 0.45

production. However, a slight increase in moisture content, CI, and Hausner ratio was observed in the immediate-release amlodipine layer, suggesting that tighter control during production is necessary for this component.

Tablet Compression Process Evaluation

The sustained-release indapamide granules were loaded into Hopper 1, and the immediate-release amlodipine besylate blend was placed in Hopper 2. Bilayer tablet compression was performed using a Cadpress II rotary tablet press (Clit, India) equipped with 45 punches and 9 mm round punches, operating at a speed of approximately 12 rpm. The indapamide layer was compressed first, with an average tablet weight of 190 mg ± 5% (9.5 mg) and a preliminary hardness of 5–6 kN. Once this layer met the required specifications, the immediate-release amlodipine blend from Hopper 2 was added, and the final bilayer tablet was compressed to an average weight of 403 mg ± 5% (20.15 mg), with a final hardness of 24–26 kN and friability of less than 1%. The average tablet weight was monitored using Shewhart R/$\bar{X}$ control charts across three batches at the 10,000-tablet scale and three batches at the 100,000-tablet scale. Figures 1 and 2 illustrate the Shewhart chart values for Batch 1 at both production scales. Based on the evaluation results from Batch 1 at both the 10,000-tablet and 100,000-tablet scales, all tablet samples had weights within the specified limits.

The calculated C_p and C_{pk} values were greater than 1.33, confirming that the compression process was capable of consistently producing tablets with stable average weights, closely aligned with the target value and exhibiting minimal variation beyond the acceptable limits.[18] The results obtained from all three batches at both scales met the requirements according to the Shewhart control charts. Compression force is a critical parameter in the formation of bilayer tablets. As compression force increases, the mechanical strength of the tablet improves, while porosity decreases.[19] Consequently, bilayer tablets become less permeable to water, leading to prolonged disintegration times and a reduction in drug release rates.[20] During tablet compression, a low pre-compression force (5–6 kN) is required to ensure proper bonding between layers. Applying higher compression forces to the second layer may result in delamination and hardness issues during the bilayer compression process. Therefore, the quality of the produced tablets met all product specifications. The average tablet weight was monitored during compression using Shewhart R and $\bar{X}$ control charts. A comparison between the control charts of the 10,000-tablet batch (Figure 1) and the 100,000-tablet batch (Figure 2) showed better weight stability in the 100,000-tablet batch.[21] The results from all three production batches fulfilled the quality control criteria, confirming that the bilayer tablet compression process was robust, stable, and scalable for large-scale manufacturing.

Evaluation of the Quality of Film-Coated Tablets

The pharmaceutical quality assessment results of the film-coated bilayer tablets met the required specifications. The apperance of tablets is showed in Figure 3. The three batches of 10,000 tablets values are presented in Table 7. The three batches of 100,000 tablets values are presented in Table 8. The evaluation results of the film-coated bilayer tablets containing extended-release indapamide and immediate-release amlodipine from the three production batches met all quality requirements. The tablets were visually acceptable, exhibiting a round shape, smooth and glossy pinkish-red film coating, and intact structure without cracks or chipping. Weight uniformity was within the acceptable range of ±5%, and the tablets met specifications for content uniformity, hardness, friability, and active ingredient content. The dissolution profiles of the bilayer tablets in three different media—pH 1.2, 4.5, and 6.8—are presented in Table 9 and Table 10. The repeated dissolution testing results from three 10,000-tablet batches and three 100,000-tablet batches demonstrated that all samples met the dissolution requirements in the three testing media (pH 1.2, 4.5, and 6.8), with RSD values below 5% at all time points. These results indicate that the film-coating process remained stable upon scale-up, yielding tablets of consistent quality in terms of appearance and weight uniformity. Although heat was applied during the coating process, no adverse effects on the active ingredient content or dissolution profile were observed. Therefore, the coating conditions are considered suitable for industrial-scale production of film-coated bilayer tablets.

Stability Evaluation of Film-Coated Tablets

After 12 months of stability testing under both accelerated and long-term conditions, the bilayer film-coated tablets containing indapamide and amlodipine met all quality criteria, including appearance, assay, weight uniformity, content uniformity, hardness, friability, and dissolution (Table 11).

Dissolution results from stability tests showed that both indapamide and amlodipine remained stable over 6 and 12 months under long-term and accelerated conditions, with only minor fluctuations in active ingredient content. No significant degradation occurred across varying temperature and humidity levels, confirming the suitability of the APIs for their pharmacological use and administration route. These findings support the product's stability, storage recommendations, and sustained therapeutic efficacy throughout its shelf life.[22]

The film-coated tablets met the required specifications after 12 months of accelerated stability data, showing minimal changes and compliance with quality standards. The study will continue to monitor the stability for at least 24 months.

CONCLUSION

The study has selected the optimal process for producing film-coated, bilayer tablets containing extended-release

indapamide and immediate-release amlodipine at batch sizes of 10,000 and 100,000 tablets. For the 10,000-tablet batch, the indapamide layer was mixed using a high-speed mixer for 7 minutes at a paddle speed of 500 rpm and a shaper speed of 1500 rpm, with final mixing carried out for 5 minutes using a cubic blender at 17 rpm. For the amlodipine besylate layer, both dry mixing and final mixing were performed in the cubic blender for 5 minutes. When scaling up to a 100,000-tablet batch, changes in high-speed mixer parameters were noted in the indapamide layer preparation, and the amlodipine layer required a longer initial mixing time (6 minutes). The process was shown to be repeatable, stable, and suitable for real-world production.

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