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Research Article

Formulation Development, Process Optimization, and Quality Assessment of Amlodipine Besylate 5 Mg Tablets for Regulatory Submission

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Abstract

Amlodipine besylate is a long-acting calcium channel blocker widely used for hypertension and angina, for which 5 mg amlodipine base is a standard dose; however, moisture sensitivity and excipient-mediated degradation can complicate development of pharmaceutically equivalent generic tablets intended for regulatory submission. This work aimed to develop, optimize, and quality-characterize an Amlodipine Besylate 5 mg tablet aligned with technical dossier expectations, with explicit excipient justification and stability assurance. To deliver 5 mg amlodipine base, tablets were formulated with 6.93 mg amlodipine besylate and manufactured by direct compression to reduce moisture exposure. The active substance was identified by UV spectrophotometry and open-capillary melting point. A lactose-free formulation strategy was implemented to avoid lactose–magnesium stearate interaction pathways associated with glycosyl degradation products; microcrystalline cellulose and anhydrous dibasic calcium phosphate were used as diluents/binders, sodium starch glycolate as super-disintegrant, and magnesium stearate as lubricant. Process optimization included Co-mill speeds of 1700–1900 RPM (optimized at ~1800 RPM), controlled sifting (#60 for API and sodium starch glycolate; #40 for diluents/lubricant), blending for 15 min, lubrication for 3 min, and compression. Optimized pilot batches met pharmacopoeial quality targets, including weight uniformity within ±7.5%, hardness >3.0 kg/cm^2, friability <1.0%, disintegration <10 min, and dissolution >80% in 30 min (exceeding the ≥75% criterion). Assay by stability-indicating HPLC-UV (C18, 237 nm) showed 98.5–101.3% across three batches, within the 90–110% specification. Forced degradation under acid/alkali hydrolysis and oxidation supported formulation stability without emergence of glycosyl impurities, and process capability evaluations indicated robust, reproducible milling and blending. Overall, the lactose-free direct-compression product provides a compliant quality package suitable for Module 3 dossier compilation and supports stable, equivalent tablet manufacture for approval.

Keywords: Amlodipine besylate, Direct compression, Stability-indicating, Process optimization, Regulatory submission, Dossier

1. INTRODUCTION

Amlodipine besylate is a potent, long-acting calcium channel blocker used primarily as an antihypertensive and antianginal agent. It functions by inhibiting the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, leading to vasodilation and reduced peripheral resistance. [1,2]

A critical aspect of formulation development for this strength is the precise calculation of the drug substance. To achieve a 5 mg dose of amlodipine base, a concentration of 6.93 mg of amlodipine besylate is required. Furthermore, generic developers must navigate the stability challenges of the molecule, which is sensitive to moisture and specific excipient interactions. This study focuses on creating a stable, high-quality 5 mg tablet using direct compression, ensuring the formulation satisfies global regulatory standards for quality and bioequivalence. [3-6]

2. METHODOLOGY

2.1 Active Substance and Excipient Characterization

The drug substance, Amlodipine Besylate, was identified using UV spectrophotometric analysis and melting point determination via the open capillary technique. Based on pre-formulation stability research, the excipient profile was designed to exclude lactose. Studies have shown that the interaction between amlodipine besylate and lactose in the presence of magnesium stearate can lead to the formation of amlodipine besylate glycosyl, a significant degradation product. [7-11]

2.2 Study Design

A document-based regulatory research combined with experimental formulation development was undertaken. The study integrated literature review, formulation development, analytical evaluation, stability

studies, and regulatory documentation focusing on CTD Module 3 (Quality).

2.3 Formulation Components

The tablets were formulated using the following components:

- **Active Ingredient:** Amlodipine Besylate (6.93 mg).
- **Diluents/Binders:** Microcrystalline Cellulose and anhydrous dibasic calcium phosphate.
- **Super-disintegrant:** Sodium starch glycolate.
- **Lubricant:** Magnesium stearate. [12,13]

2.4 Preformulation Studies

- Organoleptic properties, solubility, moisture content, and compatibility with excipients were evaluated.
- Compatibility studies conducted under stressed conditions (60°C for 6 hours, 80°C for 30 minutes) confirmed no adverse interactions. [14-16]

2.5 Formulation Development

- Solid oral uncoated tablets developed with API content of 5 mg.
- Optimization of excipient ratios and flow properties through trial batches.
- Objective: Achieve bioequivalence with marketed formulation and ensure uniformity and stability. [17-19]

2.6 Manufacturing Process

The direct compression method was employed to minimize moisture exposure.

1. **Milling:** Raw materials were milled using a Co-mill at 1700–1900 RPM to ensure uniform particle size distribution.
2. **Sifting:** The API and sodium starch glycolate were sifted through a #60 mesh, while diluents and lubricants passed through a #40 mesh.
3. **Blending:** An initial 15-minute blend was conducted in an octagonal blender for content uniformity, followed by a strictly timed 3-minute lubrication phase.
4. **Compression:** The final blend was compressed into 5 mg tablets with targeted physical specifications. [20-22]

2.7 Analytical Methodology

- Tests performed as per USP specifications for drug substance and finished product: identification (IR, HPLC, UV), assay, uniformity, and impurity characterization.
- Analytical methods validated as per USP guidelines. [23-25]

2.8 Process Validation

- Conducted on three consecutive batches evaluating critical process parameters and quality attributes to ensure consistency. [26-28]

2.9 Stability Studies

- Conducted under ICH guidelines:
- Accelerated: 40°C ± 2°C / 75% RH ± 5% for 6 months
- Long-term: 30°C ± 2°C / 65% RH ± 5% for 36-60 months
- Parameters evaluated: appearance, assay, dissolution, moisture content. [29,30]

2.10 Regulatory Dossier Preparation

- Compilation of CTD Module 3 covering drug substance and drug product sections, including manufacturing processes, specifications, analytical methods, validation, and stability data. [31-34]

3. RESULTS AND DISCUSSION

3.1 Preformulation and Compatibility

- Amlodipine Besylate was a white or almost white powder, slightly soluble in water, freely soluble in methanol.
- Compatibility studies showed no physical changes with excipients under stress conditions, confirming formulation feasibility.

Table 1: Analytical Evaluation of Drug Substance

Parameter	Specification	Batch Result
Appearance	White or almost white powder	Complies
Solubility	Slightly soluble in water	Complies
Identification	IR Spectroscopy	Complies
Optical Rotation	-0.10° to +0.10° at 20°C	+0.02°
Water Content	NMT 0.5%	0.03%
Residue on Ignition	NMT 0.2%	0.09%
Assay	97.0 - 102.0%	99.56%

3.2 Formulation Characteristics

- Average tablet weight: ~134–135 mg
- Assay: ~98.7%
- Dissolution: >95% within 30 minutes (specification NLT 75%)
- Uniformity of dosage units complied with USP <905>.

3.3 Discussion on Stability and Excipient Justification

Table 2: Accelerated Stability (40°C/75% RH) - 6 months

Parameter	Initial	6th Month	Specification Range
Appearance	Complies	Complies	White to off-white, uniform
Assay (%)	99.4	97.8	90–110%
Dissolution (%)	96.2	93.9	NLT 75%

Table 3: Long-term Stability (30°C/65% RH) - 36 months

Parameter	Initial	36th Month	Specification Range
Appearance	Complies	Complies	White to off-white, uniform
Assay (%)	99.4	94.3	90–110%
Dissolution (%)	96.2	90.2	NLT 75%

Stability data indicated minor but acceptable decreases in assay and dissolution over time, confirming product shelf life.

3.4 Process Validation

Three consecutive batches showed consistent critical parameters and quality attributes, confirming reproducibility of manufacturing process.

3.5 Regulatory Dossier

Complete CTD Module 3 dossier prepared, meeting regulatory requirements for drug substance and product quality documentation.

4. CONCLUSION

In conclusion, the present study successfully achieved the development and regulatory dossier preparation of Amlodipine Besylate tablets (5 mg), resulting in a stable, effective, and pharmacopeially compliant generic formulation. Systematic preformulation and compatibility studies confirmed the suitability of selected excipients, ensuring the physical and chemical stability of the final product.

The analytical evaluation of the drug substance demonstrated excellent quality, complying with USP standards, as evidenced by a high assay value, low moisture content, and minimal residue on ignition. The finished product consistently met all critical quality attributes, including uniform tablet weight, satisfactory assay values, and rapid dissolution exceeding pharmacopeial limits, along with compliance to content uniformity requirements.

Stability studies conducted under both accelerated and long-term conditions indicated only minor and acceptable variations in assay and dissolution profiles, confirming the robustness and stability of the formulation throughout its shelf life. Furthermore, process validation across multiple batches established the reproducibility and reliability of the manufacturing process, with all in-process and finished product parameters meeting predefined specifications.

The successful preparation of a comprehensive CTD Module 3 dossier, incorporating detailed information on formulation development, manufacturing, analytical validation, and stability data, demonstrates alignment with global regulatory requirements.

Overall, the developed Amlodipine Besylate tablets are of high quality, stable, and therapeutically effective, with a validated manufacturing process and complete regulatory documentation. These findings support the product's suitability for regulatory approval and commercialization as a reliable generic option for the management of hypertension.

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