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Bilayer Tablets: An Emerging Platform for Fixed Dose Combination Therapy for Hypertension

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ABSTRACT:

Fixed-dose combinations (FDCs) are cornerstone therapies in hypertension management. Bilayer tablets allow physical separation of two active pharmaceutical ingredients (APIs) while providing different release profiles in a single dosage form — typically an immediate-release (IR) layer for rapid onset and a sustained-release (SR) layer for prolonged action. This review focuses on bilayer formulations combining atenolol (a β-blocker) and amlodipine (a calcium channel blocker), summarizing rationale, formulation strategies, manufacturing considerations, evaluation tests, stability issues, case studies and regulatory aspects. Evidence from formulation studies shows successful IR release of atenolol within 30–60 min and prolonged release of amlodipine up to 24 h using hydrophilic matrix polymers; bilayer format often improves stability versus monolayer mixes. Practical recommendations and potential pitfalls for scale-up and regulatory submission are provided.

Keywords: bilayer tablet, atenolol, amlodipine, fixed-dose combination, immediate release, sustained release, formulation, stability.

1.INTRODUCTION:

Hypertension frequently requires combination therapy to reach target blood pressure. Combining agents with complementary mechanisms (e.g., a β-blocker and a calcium channel blocker) improves BP control and reduces adverse effects by allowing lower doses of each drug. Bilayer tablets provide an attractive pharmaceutical platform for FDC antihypertensive therapy because they: (1) physically separate chemically or physically incompatible APIs, (2) enable different release kinetics per layer (IR + SR), and (3) reduce pill burden to improve adherence. Several formulation and stability studies specifically addressing atenolol + amlodipine bilayer tablets have been reported, indicating feasibility and therapeutic promise.

2. Rationale:

Complementary pharmacology: Atenolol (hydrophilic, β1-selective blocker) lowers heart rate and cardiac output, while amlodipine (lipophilic dihydropyridine CCB) reduces peripheral resistance. Together they provide additive BP lowering.

Different PK requirements: Atenolol typically requires an early plasma concentration for symptomatic control; amlodipine has long half-life and benefits from sustained exposure for 24-hour control. Designing atenolol as IR and amlodipine as SR within a bilayer tablet supports optimal PK/PD.

Stability & compatibility: Physical separation in bilayer format reduces direct API–API or API–excipient interactions that may accelerate degradation compared with monolithic blends. Studies show bilayer tablets can improve amlodipine stability versus single-layer blends.

3. Formulation Strategies

3.1 Layer design choices

Immediate-release (IR) layer — Atenolol: target complete release within 30–60 minutes (typical target in literature is ~90–100% within 45 min). Use super disintegrants (croscarmellose sodium, sodium starch glycolate), water-soluble diluents (lactose, mannitol), and direct compression, when possible, to preserve simplicity.

Sustained-release (SR) layer — Amlodipine: target extended release up to 12–24 h. Hydrophilic matrix polymers (HPMC K15M/K100M) or hydrophobic matrix (ethylcellulose) are commonly used. Matrix tablets, reservoir coatings or multiarticulate SR layers can be used depending on desired release kinetics.

3.2 Common excipients and their roles:

Binders: PVP, PVPP, starch paste (for granulation layers).

Super disintegrants (IR): croscarmellose sodium (CCS), sodium starch glycolate (SSG).

SR polymers: HPMC (various grades), Carbopol (where pH dependence permitted), ethylcellulose for hydrophobic control.

Fillers/diluents: Microcrystalline cellulose (MCC), lactose, mannitol.

Lubricants/glidants: Magnesium stearate, talc — use sparingly in SR layer to avoid retarding matrix hydration.

Film coatings: Enteric or protective coatings may be used to further modulate release or to improve appearance and stability.

3.3 Manufacturing approaches:

Direct compression: Preferred when APIs/excipients have good flow/compressibility. Provides simple, cost-effective route to bilayer tablets but requires precise control to avoid lamination.

Wet granulation for one or both layers: Improves flow and content uniformity, useful when APIs are poorly compressible or have segregation risk.

Dry granulation: For moisture/heat sensitive actives.

Compression sequence: Typically compress the SR layer first (lower density) followed by deposition and compression of the IR layer — but sequence may vary depending on tablet press and formulation. Compression forces and dwell times must be optimized for both interlayer adhesion and overall hardness without compromising release characteristics.

4. Evaluation and In-Vitro Testing

4.1 Pre-compression tests (powders/granules)

Angle of repose, bulk/tapped density, Carr's index, Hausner ratio — ensure acceptable flow for uniform die fill.

4.2 Post-compression tests

Weight variation, thickness, hardness, friability, content uniformity, disintegration (for IR), and assay.

4.3 Dissolution testing

IR layer (atenolol): USP II (paddle) in 0.1 N HCl for initial 2 h; target ~>80–90% released within 30–60 min (literature examples show ~98% by 45 min).

SR layer (amlodipine): dissolution in 0.1 N HCl (2 h) followed by phosphate buffer pH 6.8 up to 24 h; target release profile matching desired T50/T90 for once-daily dosing. Use similarity factor (f2) when comparing to reference formulations.

4.4 Interaction/compatibility studies

DSC, FTIR, XRD to detect possible incompatibilities or polymorphic changes — especially important because amlodipine is more prone to degradation under some conditions.

5. Stability Considerations:

Bilayer architecture often improves the chemical stability of labile components compared to simple mixtures — studies with atenolol/amlodipine showed better amlodipine retention in bilayer versus monolayer tablets and improved outcomes with aluminium strip packaging vs. PVC blister. Monitor assay loss and degradation products per ICH stability protocol (accelerated and long-term).

Moisture and heat sensitivity: Amlodipine besylate can be sensitive to humidity; choose desiccant-friendly packaging (aluminium/aluminium blisters or strip) and include moisture scavengers if required.

6. Case Studies & Reported Formulations

Sikdar et al. (2019) formulated bilayer tablets with atenolol in the IR layer and amlodipine in SR layer. Reported ~99% atenolol release at 45 min (0.1 N HCl) and ~98% amlodipine release after 24 h (phosphate buffer) after optimization of excipients and compression parameters. This study is a concrete example of feasibility for this FDC in bilayer form.

Patents describe compound bilayer formulations of atenolol + amlodipine with specific excipient ratios and manufacturing methods — indicative of industrial interest and prior art to consider during development.

Stability analyses showed that bilayer tablets retained amlodipine content far better than monolayer mixes and that aluminium packaging improved stability versus blister packs. These findings demonstrate practical considerations for packaging and shelf life.

7. Regulatory & Intellectual Property Considerations

For registration, follow local regulatory guidance (e.g., FDA/EMA/ CDSCO) for fixed-dose combination and modified release products: submit CMC (chemistry, manufacturing and controls), dissolution specifications, bioequivalence data (if required), stability data (ICH long-term and accelerated), impurity profiling, and manufacturing scale-up information. Review patents covering atenolol + amlodipine bilayer compositions to avoid infringement or to plan licensing.

8. Scale-up and Manufacturing Challenges

Interlayer adhesion / delamination: Ensure optimal surface roughness and compatible compression forces; use intermediate binder formulations if needed.

Weight variability & layer weight control: Precision feeders and frequent in-process check to maintain content uniformity.

Segregation risk during die fill: Control granule size and density; use compatible excipients.

Analytical method validation: Stability-indicating HPLC methods for simultaneous assay of atenolol and amlodipine must be validated (specificity, linearity, accuracy, precision). Some recent studies and method papers provide HPLC methods for such combinations.

9. Clinical & Therapeutic Considerations

Bilayer FDCs should match clinical dosing needs and be flexible to allow dose titration (manufacturer may create multiple strength variants, e.g., atenolol 25/50 mg + amlodipine 2.5/5/10 mg).

WHO and national formularies often recommend combination therapy for stage II HTN or when monotherapy fails; having a stable, once-daily bilayer tablet can improve adherence and outcomes.

10. Recommendations & Practical Formulation Example

Example target product profile (TPP): Atenolol 50 mg (IR) + Amlodipine 5 mg (SR), once daily, immediate atenolol onset (90% in 45 min), sustained amlodipine release over 24 h, low dose dumping risk, shelf life ≥24 months under standard ICH conditions.

Atenolol (IR layer): Atenolol API, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium (4–8%), PVP K30 (binder if granulating), magnesium stearate (0.5–1%).

Amlodipine (SR layer): Amlodipine besylate API, HPMC K15M/K100M (10–30% depending on target release), MCC or lactose as filler, PVP (if wet granulation), magnesium stearate (0.5%) — test hydrophobic polymer blends (ethylcellulose) if further retardation needed.

Compression: Optimize pre-compression and main compression forces, compress SR layer first (light to medium) then IR layer to final hardness while monitoring interfacial adhesion.

Packaging: Aluminium-aluminium strips strongly recommended for improved amlodipine shelf life.

11. Future Directions

Multiparticulate SR approaches (pellets layered into bilayer tablets) to further improve GI variability and reduce food effects.

3D printing for precise spatial control of IR vs SR compartments and customized dosing.

Stability enhancement using co-processed excipients and advanced packaging technologies. Recent work in bilayer technology and polymer science (2020–2025) is expanding options for robust once-daily antihypertensive FDCs.

12. Conclusion

Bilayer tablets of atenolol and amlodipine are a feasible and clinically useful fixed-dose platform for hypertension. Literature and preclinical formulation studies demonstrate that careful excipient selection, layered design (IR atenolol + SR amlodipine), controlled compression, and suitable packaging yield acceptable dissolution profiles and improved stability versus monolithic mixtures. Attention to interlayer adhesion, validated analytical methods and ICH stability testing will smooth pathway to regulatory submission and market success.

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