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Review Article

FORMULATION APPROACHES AND EVALUATION OUTCOMES OF BILAYERED TABLETS FOR ANTIHYPERTENSIVE DRUGS: A REVIEW

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ABSTRACT

Bilayered tablets represent an advanced oral dosage form that enables the delivery of two drugs simultaneously or allows sequential release profiles for a single active pharmaceutical ingredient (API). This approach is particularly useful for antihypertensive therapy, where combination therapy is often required to achieve optimal blood pressure control. This review highlights recent advancements in the formulation strategies, characterization, and evaluation of bilayered tablets containing antihypertensive drugs such as Amlodipine, Perindopril, Valsartan, and others. Various formulation approaches, including immediate-release (IR) and sustained-release (SR) layers, use of superdisintegrants, hydrophilic polymers, and gastro-retentive strategies, are summarized. Evaluation outcomes such as disintegration time, *in vitro* dissolution, drug release kinetics, stability, and bioavailability are discussed. The review demonstrates that bilayer tablet technology offers improved patient compliance, optimized therapeutic efficacy, and enhanced pharmacokinetic profiles.

Keywords: Bilayer tablets; Antihypertensive drugs; Amlodipine; Perindopril; Controlled release; Immediate release; Sustained release; Formulation strategies

INTRODUCTION

Hypertension is a chronic medical condition that often requires long-term therapy and multiple drugs for effective management. Conventional single-layer tablets have limitations such as inability to combine multiple APIs, limited control over drug release, and patient compliance challenges. Bilayered tablets overcome these limitations by providing either dual-drug delivery or biphasic release from a single dosage form (Banu and Sahariar, 2011). One layer may provide immediate release (IR) for rapid onset, while the second layer provides sustained release (SR) for prolonged therapeutic effect (Solanki, 2012). This strategy is particularly beneficial in antihypertensive therapy where combination drugs or sequential release are required (Sadhana and Vidya, 2014).

Bilayer tablets also allow physical separation of incompatible drugs, prevent chemical interactions, and enable customization of pharmacokinetic profiles (Ali and Reddy, 2014). Recent research has explored a variety of polymers, superdisintegrants, and manufacturing techniques to optimize bilayer tablet performance (Balaji *et al.*, 2013). This review summarizes key studies on the formulation, characterization, and evaluation outcomes of bilayered tablets for antihypertensive drugs.

Formulation Strategies and Approaches

Bilayer tablets for antihypertensive drugs can be designed using various formulation approaches depending on the desired release profile and therapeutic objectives. One of the most common strategies is the combination of an Immediate-Release (IR) layer with a Sustained-Release (SR) layer (Patel *et al.*, 2010). The IR layer provides a rapid onset of action, while the SR layer maintains therapeutic drug levels over an extended period. Polymers such as HPMC (K4M, K15M, K100M), Carbopol, and Guar gum are frequently used to modulate the release from the SR layer (Li *et al.*, 1995). In addition, superdisintegrants like croscarmellose sodium, crospovidone, and sodium starch glycolate are incorporated into the IR layer to improve disintegration and ensure quick drug release (Parmar and Pednekar, 2011).

Gastro-retentive bilayer tablets represent another formulation approach, particularly useful for drugs with a narrow absorption window, such as Amlodipine. These formulations incorporate floating or swelling layers that prolong the tablet's gastric residence time, thereby enhancing drug absorption (Jayaprakash *et al.*, 2011). Gas-generating agents, including sodium bicarbonate and citric acid, are commonly used to increase buoyancy and maintain the tablet's position in the stomach (Musle *et al.*, 2011).

For drugs with an unpleasant taste, such as Perindopril, taste-masked orodispersible bilayer tablets are developed to improve patient compliance and acceptability. Taste masking is achieved using polymethacrylate coatings, natural superdisintegrants, and direct compression methods, which also facilitate rapid disintegration and faster onset of action. Similarly, bilayer floating and controlled-release tablets combine an immediate-release layer with a sustained-release or floating layer to provide both rapid and prolonged therapeutic effects. The design of such tablets often involves the use of factorial designs and Quality by Design (QbD) approaches to optimize polymer concentration and drug release kinetics (Gohel *et al.*, 2010).

Recent advancements also include the incorporation of liposomal or nanocarrier-based layers, such as ultradeformable liposomes (PE-UDLs) or nanoparticles, which enhance drug permeability and bioavailability. Additionally, sequential and targeted release strategies are applied using pH-sensitive or enteric coatings, allowing the drug to be released at specific sites in the gastrointestinal tract (Hiremath *et al.*, 2010). This approach avoids degradation in the stomach and improves absorption in the intestine.

The evaluation and characterization of bilayer tablets involve comprehensive pre- and post-compression testing (Ramesh, 2010). Pre-compression parameters include angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio, which assess powder flow and compressibility. Post-compression parameters such as hardness, friability, thickness, weight variation, and drug content uniformity evaluate the quality and consistency of the final tablets (Kumar *et al.*, 2010). *In vitro* dissolution studies are typically conducted in simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8–7.4) to analyze biphasic drug release profiles for IR and SR layers separately. Drug release mechanisms are further investigated using kinetic models such as zero-order, first-order,

Higuchi, and Korsmeyer-Peppas models (Naeem *et al.,* 2010). Optimized formulations are subjected to stability studies under ICH guidelines to ensure performance over time, while in vivo studies including pharmacokinetic and pharmacodynamic evaluations confirm enhanced bioavailability and therapeutic efficacy.

Challenges in Bilayer Tablet Development

The development of bilayer tablets presents several challenges that must be carefully addressed to ensure product quality and therapeutic efficacy (Swamy *et al.,* 2011). One of the primary issues is layer separation during compression**,** which necessitates the optimization of compression force and adequate interfacial bonding between layers to maintain structural integrity. Inaccurate weight control of individual layers can also occur, potentially affecting both drug content and release profiles (Pattanayak and Dinda, 2011). Additionally, cross-contamination between layers may arise if the powders used for each layer have different flow properties, compromising uniformity and performance. Polymer incompatibility is another critical concern, as the selection of inappropriate polymers can alter drug release behavior or impact stability. Finally, scale-up presents practical challenges, as manufacturing bilayer tablets on a large scale often requires specialized or modified tablet presses to ensure consistent quality, reproducibility, and efficient production.

Future Perspectives

Future perspectives in the development of bilayer tablets for antihypertensive therapy focus on innovations that enhance efficacy, safety, and patient compliance (Jain *et al.,* 2011). The use of novel polymers and natural excipients offers the potential to improve drug release profiles while minimizing adverse effects. Incorporation of nanocarriers and liposomal systems into bilayer formulations can further enhance drug bioavailability and therapeutic outcomes. Advances in 3D printing technology open avenues for the development of personalized bilayer tablets, enabling customized dosing and tailored release profiles for individual patient needs (Mohindeen *et al.,* 2011). The integration of Quality by Design (QbD) and Design of Experiments (DoE) approaches allows systematic optimization of formulation and process parameters, ensuring consistent product quality. Additionally, bilayer tablets offer significant advantages in combination therapy for hypertension, reducing pill burden and improving patient adherence while providing controlled and sequential drug release.

Table 1: Summary of formulation strategies for anti hypertensive drugs

Author (Year)	Drug / Formulation Type	Method / Technique	Key Findings / Results
Khan *et al.,* (2024)	Amlodipine besylate, Orodispersible tablets	Evaluated friability, hardness, disintegration, wetting time, in vitro release; calibration curves in phosphate buffer pH 6.8 & methanol	Formulation F7 (highest croscarmellose sodium) showed shortest disintegration time (37 ± 3 s) and 98.91% drug release

Uday *et al.,* (2024)	Amlodipine besylate, Buccal films	Solvent casting method	Fast-dissolving buccal films improved patient compliance, bypassed first-pass metabolism, allowed rapid systemic absorption
Choi *et al.,* (2024)	Perindopril erbumine, Ultradeformable liposomes	Thin-film hydration & extrusion; EPC + Tween 80 / sodium deoxycholate	Optimized formulation: particle size 75 nm, deformability 54.2, EE 35.7%; enhanced permeation & ameliorated LPS-induced sarcopenia in mice
Ansari *et al*., (2024)	Vildagliptin, Immediate-release layer of bilayer tablets	Varying superdisintegrant & polymer concentrations (HPMC K15M, Eudragit RSPO)	Formulation F8 achieved controlled release up to 12 h with maximum release
Taimoor *et al.,* (2024)	Lornoxicam, Bilayer tablets (IR + SR)	Direct compression; polymers: guar gum, Carbopol 940P, HPMC K4M	IR layer released drug within 15 min; SR layer maintained release up to 24 h; F9 chosen as optimized batch, zero-order kinetics
Suryawanshi *et al.,* (2023)	Bilayer tablets, Review	Overview of production techniques	Discussed challenges, presses (single/double), advantages & limitations of bilayer tablets
Saxena *et al.,* (2020)	Bilayer tablets, Review	Overview	Highlighted uses in patent extension, therapeutic efficacy, modified presses to overcome layer separation & weight control issues
Patil *et al.,* (2019)	Amlodipine besylate + Valsartan, Oral tablets	Different granulation techniques	Optimized tablets showed stable physicochemical parameters and in vitro release over 3 months
Annapurna & Priyanka, (2019)	Bilayer tablets, Review	Delayed release formulation	Delayed release achieved by pH-sensitive coating; dissolution tested in 0.1N HCl & phosphate buffer
Kiran *et al.,* (2015)	Bilayer tablets, Review	Controlled release & sequential drug release	Enabled separation of APIs and sequential/combined release profiles
Buddhade *et al.,* (2015)	Glipizide + Lisinopril, Bilayer floating tablets	Direct compression; HPMC K4M & K100M; sodium bicarbonate + citric acid	Optimized FT4: immediate release of Lisinopril within 30 min; sustained Glipizide release 98.86% at 20 h; first-order & Korsmeyer-Peppas kinetics

Momin *et al.*, (2015)	Venlafaxine HCl, Bilayer tablets	Polymers: HPMC, Carbopol, Xanthan gum; 3^2 factorial design	Good bioadhesion & drug release; dissolution followed Higuchi model, non-Fickian diffusion
Dey *et al.*, (2014)	Atorvastatin + Atenolol, Bilayer tablets	Fast-release layer: atorvastatin + β-cyclodextrin; SR layer: xanthan & guar gum	Fast release of atorvastatin (>60% in 2 h); sustained atenolol for 12 h; improved bioavailability
Dholariya *et al.*, (2014)	Hydrochlorothiazide, Bilayer tablets	QbD approach; croscarmellose sodium + hydrophilic polymers	Optimized formulation: DT ~70 s; T95% ~720 min; erosion predominant in drug release
Ramasubramaniyan *et al.*, (2013)	Amlodipine, Gastro-floating drug delivery system	HPMC K100M & K4M; sodium bicarbonate	F3 showed controlled release 67.6% at 12 h; floating duration maximized by polymer selection
Patil *et al.*, (2013)	Perindopril erbumine, Mouth dissolving tablets	Natural superdisintegrant: Ocimum basilicum; direct compression	Optimized F2: good hardness, friability, wetting & disintegration time
Ratnaparkhi *et al.*, (2012)	Perindopril erbumine, Orodispersible tablets	Taste masking: polymethacrylate; superdisintegrants (Ac-Di-Sol, Primogel, Tulsion)	Batch A2: best disintegration time; complete drug release within 5 min

CONCLUSION

Bilayer tablets provide a versatile and effective dosage form for antihypertensive therapy, combining immediate and sustained release profiles in a single unit. The formulation strategies, including polymer selection, superdisintegrant optimization, and layering techniques, have shown improved patient compliance, enhanced drug release profiles, and better therapeutic outcomes. Future research should focus on novel excipients, targeted delivery, and further optimization of bilayer tablets to maximize efficacy and patient adherence.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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