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CURRENT APPROACHES AND FUTURE TRENDS IN BILAYER TABLETS FOR OBESITY TREATMENT

M. Anusha, Archana S. Patil * and Vinayak Halasagi

Department of Pharmaceutics, KLE College of Pharmacy, KLE Academy of Higher Education and Research, Belagavi - 590010, Karnataka, India.

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Correspondence to Author:
Dr. Archana S. Patil

Associate Professor,
Department of Pharmaceutics,
KLE College of Pharmacy, KLE Academy of Higher Education and Research, Belagavi - 590010,
Karnataka, India.

E-mail: archanapatil@klepharm.edu

ABSTRACT: Obesity is a complicated global health issue that necessitates novel therapeutic methods, as traditional treatments frequently fail to fulfill the different patient needs. Bilayer tablets, an advanced oral drug delivery technology, combine immediate-release and sustained-release layers in a single dosage form, allowing for quick symptom relief while maintaining stable plasma drug concentrations. This dual-action method improves therapeutic efficacy, lowers side effects, and increases patient adherence. Manufacturing advances, such as 3D printing and hot-melt extrusion, have improved the solubility, stability, and bioavailability of anti-obesity medications, underlining the promise of bilayer tablets to solve obesity-related issues. Additionally, adding artificial intelligence and precision medicine into bilayer tablet manufacturing allows for tailored drug combinations, optimal release profiles, and precise excipient selection. Emerging advances, such as biodegradable polymers and sensor-enabled systems, improve patient compliance, treatment monitoring, and sustainability. Despite its promise, difficulties like as manufacturing complexity, regulatory barriers, and high costs remain, necessitating additional research and innovation. Addressing these difficulties has the potential to unlock the full potential of bilayer tablets, revolutionizing obesity medicine and contributing to the management of the worldwide health epidemic.

INTRODUCTION: Obesity, defined as excessive fat buildup that poses a health risk, has emerged as a global health concern, with alarming prevalence and huge associated costs. Obesity prevalence has nearly tripled worldwide since 1975, with over 1 billion people affected by 2023, including 650 million adults, 340 million adolescents, and 39 million children [1].

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Over half of the world's population is projected to be overweight or obese by 2030, with obesity rates topping 40% in some countries [2, 3]. Obesity is a significant risk factor for various non-communicable diseases (NCDs): Cardiovascular Diseases: Obesity is closely linked to hypertension, coronary artery disease, and heart failure, contributing to a significant proportion of global mortality [4].

The World Health Organization (WHO) emphasizes preventative interventions such as public health campaigns, policy rules (for example, sugar taxes), and diet and physical activity guidelines. However, more strong and multidisciplinary techniques are required to combat

this escalating epidemic [5]. Drug delivery methods have advanced greatly to address the problems of delivering optimal therapeutic outcomes, particularly in chronic illnesses such as obesity. Traditional pharmacological formulations frequently fail to satisfy patient needs due to low compliance, inconsistent drug release, and insufficient therapeutic efficacy. Advanced drug delivery methods, such as bilayer tablets, provide novel answers to these restrictions, making them an appealing option for obesity therapy [6].

Key Advantages of Bilayer tablets are a type of sophisticated drug delivery device that consists of two layers, each optimized for a distinct drug release profile, such as immediate or controlled release [6]. Other applications like Chronomodulated drug delivery in bilayer tablets enable time-specific medication delivery, guaranteeing that the drug is delivered at the optimal moment based on the body's circadian cycle. For example, bilayer pills of propranolol hydrochloride are manufactured for hypertension treatment, releasing the medicine during the early morning hours, when blood pressure usually jumps [7, 8]. This dual-layer architecture provides significant benefits over standard formulations. Enhanced therapeutic outcomes, improved patient compliance, reduced drug interactions, Customizable for personalized therapy [9, 10, 11, 12].

Obesity management necessitates new drug delivery systems that can overcome the constraints of traditional medicines, such as poor compliance, inferior therapeutic efficacy, and side effects. Bilayer tablets provide a novel platform for delivering anti-obesity medications by allowing for dual-layer formulations that allow for immediate and sustained drug release in a single dosage form. The review assesses the present use of bilayer tablets to administer obesity therapies, focusing on their pharmacokinetics, effectiveness, and effect on patient adherence. Examples include the combination of appetite suppressants and metabolic boosters, and multi-mechanistic therapy tailored to the multifactorial character of obesity [13, 14, 15, 16, 17, 18].

The paper also looks at improvements in bilayer tablet technology, such as new materials for controlled-release layers, 3D printing processes, and machine-learning-based design approaches. These developments promise to improve medication release precision, patient-specific customisation, and production scalability [6, 7]. Special emphasis is placed on their ability to include novel pharmacological agents such as glucagon-like peptide-1 (GLP-1) receptor agonists and other weight-loss drugs [8, 9]. Emerging trends in regulatory and manufacturing processes that promote the development of sophisticated bilayer tablets are also addressed [19, 20].

Design and Structure of Bilayer Tablets: Bilayer tablets as shown in fig1are the advanced oral drug delivery technology that provides instant and sustained release of active pharmaceutical ingredients (APIs) in a single dosage form. This dual-layer structure solves the disadvantages of standard formulations, such as uneven drug release and unsatisfactory therapeutic effects, especially in chronic disorders like obesity [21].

Immediate Release Layer:

Function: This layer ensures rapid breakdown and medication release for a speedy therapeutic impact, which is typically crucial in diseases that require urgent symptom relief [22].

Components: To speed up drug dispersion and absorption, super disintegrants (such as croscarmellose sodium or sodium starch glycolate) are combined with water-soluble binders and effervescent agents [23].

Applications in Obesity: In obesity therapies, this layer may include medicines like phentermine or naltrexone, which have a quick start of action to decrease appetite or modify cravings [22].

Sustained-Release Layer:

Function: This layer gradually releases the drug over time, resulting in consistent plasma drug levels and reduced dosage frequency. It reduces the adverse effects associated with peak plasma concentrations [19, 20].

Components: Typically comprise hydrophilic or hydrophobic polymers, such as hydroxypropyl methylcellulose (HPMC) or ethyl cellulose, which influence drug dispersion *via* matrix swelling, erosion, or diffusion mechanisms [24].

Applications in Obesity: Sustained-release formulations may contain bupropion or liraglutide analogs to help with appetite control and metabolic regulation throughout the day [13].

Barrier Layer: Some designs use a barrier layer to prevent incompatible APIs from interacting, assuring stability and efficacy [25, 26]. Bilayer tablet design demands accuracy to maintain homogeneity in weight, hardness, and medication distribution between layers. Advanced compression methods, such as multi-stage rotary tablet presses, are frequently used to create these formulations with high precision [27].

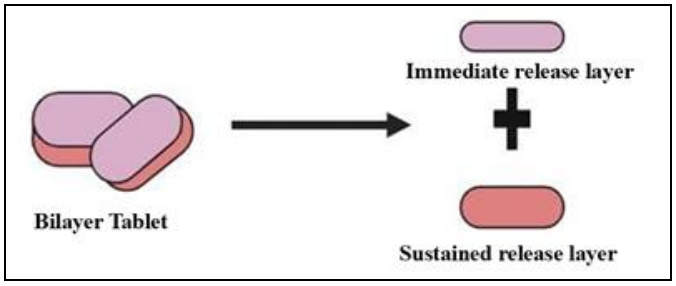

FIG. 1: STRUCTURE OF BILAYER TABLET

Mechanisms of Drug Release in Bilayer Tablets:
Hydrophilic Matrix System: The sustained-release layer uses hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) to generate a gel matrix in the gastrointestinal tract, allowing for progressive drug diffusion [28].

Examples:

Metformin HCl: Used to manage type 2 diabetes, Metformin bilayer tablets with an HPMC-based sustained-release layer efficiently maintain blood glucose levels over 24 hours [29].

Diltiazem HCl: A calcium channel blocker with HPMC in the sustained-release layer to treat hypertension and angina with once-daily dose [30].

Erosion-Controlled Release: In hydrophobic matrix systems, the sustained-release layer erodes over time, regulating medication release. This technique is employed for medicines that are weakly water soluble [26].

Layer-Specific Solubility: The immediate-release layer quickly dissolves in stomach juices, whereas the sustained-release layer resists breakdown and releases the drug over time [31, 32].

Examples:
Ibuprofen: Bilayer pills combine quick pain relief from the immediate-release layer with long-lasting anti-inflammatory benefits [33].

Time-Delayed Release: Some bilayer tablets have a delayed-release layer that delays drug release until it reaches a certain pH in the small intestine. This method is utilized for medications that are prone to gastrointestinal breakdown [22, 34].

Examples: Omeprazole bilayer tablets are a proton pump inhibitor that protects the medicine in the stomach and releases it in the duodenum for optimal efficacy [35].

Advantages of Bilayer Tablets in Obesity Treatment:

1. Unit dosages are the most effective oral dosage type due to their superior capabilities. Highest dosage precision and lowest content variability.
2. Cost is lower than other oral dose forms.
3. Lighter and smaller.
4. The easiest and cheapest to package and strip.
5. Easy to swallow, with a low risk of hang-up.
6. Coating techniques can disguise unpleasant odors and bitter tastes.
7. Suitable for large-scale production.
8. Superior chemical and microbiological stability across all oral dose forms.
9. Using an embossed or monogrammed punch face allows for quick and easy product identification without the need for further processes [36].

Current Approaches in Obesity Treatment with Bilayer Tablets: The bilayer tablet method provides several significant benefits that meet the complex issues of obesity treatment. Novel drug delivery technology that overcomes the major drawback of non-linear release found in most diffusion-controlled matrix devices. This approach also has the benefit of being compatible with traditional manufacturing techniques [37].

These include dual medication administration for synergistic effects, controlled release to reduce side effects, and streamlined dose regimes that increase patient adherence [17, 27, 38, 39]. The use of bilayer tablet technology has opened up new options in obesity management by allowing medications to target numerous obesity-related pathways at once. These developments seek to improve therapy outcomes by tackling the complexities of obesity, which include systems such as appetite management, energy expenditure, and metabolic enhancement.

Dual Drug Delivery for Synergistic Effects: Bilayer tablets combine two medicines in a single formulation, allowing for complementary modes of action and enhanced treatment effects. For example, combining an appetite suppressant like phentermine in the immediate-release layer and a metabolic enhancer like bupropion in the sustained-release layer results in a synergistic effect that addresses both hunger regulation and metabolic rate augmentation. This dual strategy is especially beneficial in obesity, where treating the complex etiology is crucial [13, 40]. Furthermore, such combinations can address both short-term and long-term treatment objectives. While the immediate-release layer relieves food demands quickly, the sustained-release layer assures long-term efficacy by maintaining constant medication concentrations [6].

Controlled Release Leads to Reduced Side Effects: The controlled-release architecture in one of the layers reduces variations in plasma drug levels, lowering the possibility of dose-dependent side effects. This feature is especially useful for medications that have small therapeutic windows or are linked with gastrointestinal or cardiovascular side effects, such as GLP-1 receptor agonists [41]. For example, sustained-release formulations serve to reduce gastrointestinal discomfort, a typical problem with obesity medicines, by gradually releasing the drug and preventing high peak plasma concentrations [42, 43]. Furthermore, dividing medications into discrete layers minimizes the possibility of drug-drug interactions, which improves safety and tolerability [44].

Improved Patient Adherence Due to Simplified Dosing Regimens: Poor patient compliance frequently caused by complex dose schedules and heavy pill loads, is a key hurdle to obesity treatment. Treatment regimens are simplified when two medications are combined into a single bilayer tablet, which promotes adherence [45-47].

Approved Drugs and Formulations: Bilayer tablets provide an innovative drug delivery technology that combines multiple pharmacological substances into a single formulation, thereby improving efficacy and safety [48]. Several medications licensed for obesity therapy, such as orlistat, liraglutide, and the naltrexone-bupropion combo, have been investigated for use in bilayer tablet formulations.

Incorporation of key Anti-Obesity Drugs in Bilayer Tablets: Orlistat, a lipase inhibitor, reduces fat absorption in the gastrointestinal tract. Its integration into the sustained-release layer of bilayer tablets can offer consistent plasma levels while reducing gastrointestinal side effects such as steatorrhea that are frequent with immediate release [13]. Orlistat has a half-life of 1-2 hours due to its rapid release. Research primarily focuses on designing the technique to release the medicine in a controlled manner using different polymers such as sodium alginate, ethyl cellulose, and HPMC [49]. Naltrexone and Bupropion Combination This combination targets central hunger and reward areas, making it an excellent contender for bilayer tablet formulations. The immediate-release layer might include bupropion for quick action, while naltrexone, with its extended duration of action, is more suited to continuous release [24].

Synergistic Drug Combinations: Bilayer tablets are intended to provide medications that work on complimentary pathways, which improves efficacy [48].

For example: Appetite Suppression and Energy Expenditure: Studies that combined naltrexone (a central appetite suppressant) with bupropion (a dopamine/norepinephrine reuptake inhibitor)in bilayer formulations showed better weight loss results than monotherapy, with effects lasting 56 weeks [50, 51]. Thermogenesis Enhancement: Emerging bilayer tablets combine medications such ephedrine derivatives or newer beta-3 adrenergic agonists with metabolic enhancers such as GLP-1

receptor agonists to target thermogenesis and glucose balance [41, 52].

Drugs with Complementary Pharmacokinetics: Bilayer tablets combine medicines with different pharmacokinetic characteristics to enhance therapeutic benefits.

For Example: Immediate and Sustained Effects: Bilayer formulations of liraglutide (GLP-1 receptor agonist) for immediate release and orlistat for sustained release produce both acute appetite reduction and long-term fat absorption inhibition [28, 34].

Circadian Rhythm Alignment: Innovations match drug release to circadian cycles, increasing the efficacy of pharmaceuticals that target night-time hunger (e.g., melatonin receptor agonists) when paired with daytime stimulants [13].

Enhanced Drug Delivery Platforms: The use of sophisticated delivery technologies such as lipid nanoparticles and microsphere carriers into bilayer tablets increases medication solubility, stability, and absorption. These platforms are especially advantageous for lipophilic medicines such as orlistat, as they improve bioavailability and reduce gastrointestinal side effects [53].

Dual-Action Mechanisms: Novel bilayer tablets are being designed to incorporate medicines that address both peripheral and central causes of obesity.

Peripheral and Central Acting Agents: Bilayer systems combining phentermine (a sympathomimetic appetite suppressant) with topiramate (a GABA receptor modulator) demonstrated increased weight loss with less dosage-related adverse effects [54].

Appetite and Satiety Pathways: Recent preclinical studies show that delivering ghrelin inhibitors and PYY mimetics in bilayer tablets simultaneously reduces appetite and increases satiety. Good intake during a meal results in considerable PYY release, but fasting reduces circulating peptide levels. PYY3-36 administered peripherally reduces food intake in animal models as well as lean and obese humans [55].

Review of Clinical Trials and Preclinical Studies:

Clinical Trials on Combination Therapy: A phase III trial assessing naltrexone-bupropion found considerable weight loss in obese patients over a 56-week period, suggesting the feasibility of combining these drugs in a single dose form [53]. A study on liraglutide found that it improved weight loss and metabolic health, which supports its usage in sustained-release formulations [19]. (Clinical trial number not applicable).

Preclinical Research on Bilayer Tablets: Preclinical investigations have shown that mixing appetite suppressants and lipase inhibitors into bilayer tablets can result in both quick and regulated medication release [45].

New bilayer tablets (BLTs) were developed and preclinically tested for their efficacy and safety in the treatment of hyperlipidaemia and hypertension [56].

Studies utilizing bilayer tablets for medicines with varied solubility and stability, such as orlistat and metformin, have shown better bioavailability and patient adherence [57].

Polymer and Excipient Innovations: Advanced polymers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose have been employed to optimize the sustained release layer, whereas super disintegrants such as croscarmellose sodium improve the efficacy of the immediate-release layer [42, 44].

TABLE 1: COMPARISON OF CONVENTIONAL FORMULATIONS VS. BILAYER TABLETS

Aspect	Conventional Formulations	Bilayer Tablets
Efficacy	Moderate weight loss, variable outcomes	Synergistic effects, enhanced efficacy [6, 44]
Side Effects	Higher peak plasma levels, frequent GI issues (e.g., or list at)	Reduced due to controlled release
Patient Compliance	Lower due to complex dosing regimens	Higher adherence due to simplified dosing [43, 58]
Plasma Concentration.	Peaks and troughs, inconsistent release	Stable plasma levels with dual release profiles [41, 59]
Dosing Frequency	Multiple doses per day	Often reduced to once-daily formulations [42]
For low-half-life drugs, the tablet's two layers contain a loading and maintenance dose, increasing the drug's bioavailability [60]		

Advanced Manufacturing Techniques in Bilayer Tablets: Advanced manufacturing processes are transforming the design and performance of bilayer tablets, particularly for obesity therapy. Technologies like as 3D printing, nanotechnology, and complex coating processes improve the compositions' precision, efficacy, and patient compliance. The following is a summary of these procedures.

Nanotechnology Integration: Nanotechnology improves the efficacy of bilayer tablets by solving difficulties such as drug solubility, bioavailability, and targeted delivery: Nanoparticle Incorporation: Embedding nanoparticles in one of the layers increases the bioavailability of poorly soluble medicines such as orlistat [6].

Controlled Medication Release: Nanostructures enable precise control over medication release rates, reducing side effects while increasing therapeutic efficacy [42, 44].

Targeted Delivery: Nanotechnology offers targeted targeting of adipose tissues, increasing medication efficacy while lowering systemic exposure. Preclinical research has demonstrated that combining nanotechnology with bilayer tablets greatly enhances the pharmacokinetics of GLP-1 agonists [53].

Advanced Coating Techniques: Sophisticated coating processes enhance the structural integrity and functional performance of bilayer tablets.

Functional Coatings: Enteric coatings protect acid-sensitive medicines during gastric transit, ensuring effective delivery to the intestines [24, 61]. The delayed drug release and bedtime dose regimen employing an enteric-coated bilayer tablet combining TEL and PRA, which corresponds to the circadian rhythms of hypertension and hyperlipidaemia, can provide therapeutic benefits for older patients by maximizing therapeutic effects [62].

Dual-Release Coatings: Advanced polymer coatings allow for dual-release profiles, in which one layer releases quickly and the other gradually over time.

Taste Masking and Stability: Coatings cover disagreeable flavors and improve stability, especially in pediatric and geriatric formulations. Examples include multi-polymer coatings that optimise the release of appetite suppressants and metabolic stimulants in bilayer formats [43, 53].

Emerging Techniques and Future Directions: Other unique strategies that contribute to the improvement of bilayer tablets are [63]. Hot-melt Extrusion Is used to produce homogenous layers with controlled release qualities, which improves reproducibility and scalability [44, 50]. Laser drilling is used to develop precise release mechanisms in bilayer tablets, especially for high-potency medicines [64]. Geminex is a dual drug delivery system that can give one or more medications at separate times. The geminex technology adjusts the release rate of the two medications to enhance their individual therapeutic benefit while minimizing unwanted effects [10, 63].

Green Manufacturing Approaches: Sustainability oriented technologies, such as the use of biodegradable polymers, are gaining popularity in bilayer tablet manufacture [41].

Techniques in 3D printing for Bilayer Tablets: Three-dimensional (3D) printed drug delivery medical devices are becoming increasingly popular, offering significant advantages over traditional drug administration systems. Several 3D printing techniques are used to fabricate bilayer tablets, each giving unique benefits: [65] Fused Deposition Modeling (FDM) creates tablets by extruding layers of drug-loaded filaments. This approach is especially useful for heat-stable medicines [24, 66]. Stereolithography (SLA) creates exact tablet structures using photopolymerization, making it perfect for elaborate designs [53]. Binder Jetting: Deposits liquid binders onto powder beds, allowing the production of porous bilayer tablets with rapid disintegration qualities [67].

Biopharmaceutical Enhancements in Bilayer Tablets: Advancements in Solubility, Stability, and Targeted Delivery: Bilayer tablets are a significant improvement in pharmaceutical dosage forms, allowing them to solve a variety of therapeutic difficulties such as low drug solubility, instability, and the need for precise drug administration. These unique technologies enable the combining of two different medications or

release patterns in a single dosage form, making them a viable choice for improving biopharmaceutical performance [68].

Solubility Enhancement: One of the most difficult difficulties in medication formulation is increasing the solubility of poorly water-soluble medicines, which account for almost 40% of marketed drugs and up to 90% of those in development. Bilayer pills address this issue in a unique way by using solubility enhancers and customized formulations. Techniques such as using solid dispersions, amorphous solid solutions, and nanocrystalline formulations inside one layer of the tablet show great promise. For example, including hydrophilic polymers such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) into the immediate-release (IR) layer allows for faster dissolution of poorly soluble medicines, resulting in increased bioavailability [69, 70]. Furthermore, sophisticated spray-drying procedures were used to prepare micro- or nanoparticles encapsulated in a single layer, increasing the dissolving profile [71].

Drug Stability: The bilayer structure of these tablets allows for the physical and chemical segregation of incompatible medications or excipients, hence improving drug stability. This is especially useful for medications that deteriorate in the presence of water, oxygen, or light. Manufacturers can reduce degradation by separating unstable components in a controlled-release (CR) layer. For example, medications like aspirin, which are susceptible to hydrolysis, can be efficiently stabilized by adding desiccants or stabilizing excipients into the CR layer. Furthermore, layering technologies enable the application of enteric coatings to a single layer, giving additional protection against stomach breakdown[72, 73].

Targeted Delivery Mechanisms: Bilayer tablets improve medication delivery precision by combining immediate-release and sustained-release features. Advancements in technology have addressed the disadvantages of single-layered tablets, resulting in practical bilayer tablets [31]. This dual-release profile is very useful in sustaining therapeutic plasma concentrations over long periods of time, lowering dose frequency, and avoiding side effects. For example, in diabetes treatment, bilayer tablets containing metformin in the IR layer and a sulfonylurea in the CR layer provide immediate glycemic control followed by long-term blood glucose level maintenance [74]. Similarly, the incorporation of pH-sensitive polymers in the CR layer enables site-specific drug release, resulting in tailored administration to the gastrointestinal system [75]. Advanced compression techniques can also integrate osmotic systems or floating matrices in tablet layers, offering gastro-retentive drug delivery for medicines with restricted absorption windows [76, 77].

Additional Innovations: Recent breakthroughs in manufacturing technology include the ability to make bilayer tablets using hot-melt extrusion (HME)-based dual-nozzle fused deposition modeling (FDM) three-dimensional (3D) printing processes [78]. These approaches provide precise control of layer thickness, drug distribution, and excipient selection, resulting in improved drug performance. The use of biodegradable polymers in the CR layer, such as polylactic acid (PLA), has received attention for its capacity to offer prolonged drug release while limiting environmental damage [79]. 3D printed tablets have superior extended drug release rates than directly compressed tablets because they have smoother surfaces and tighter structures. Furthermore, novel analytical techniques, such as near-infrared spectroscopy (NIRS), have been used to maintain consistency and quality control during manufacturing [80].

Personalized Medicine: The introduction of artificial intelligence (AI) and precision medicine has transformed pharmaceutical formulation, paving the door for bilayer pills that are tailored to individual patient needs. By taking into account a patient's genetic, physiological, and metabolic profile, these advancements allow for tailored therapy regimens that optimize drug efficacy while minimizing side effects [24].

AI in Bilayer Tablet Formulation: AI and precision medicine provide prospects for developing patient-specific bilayer tablets in the treatment of obesity. AI algorithms can discover the best combinations of lipase inhibitors, appetite suppressants, and glucose regulators, ensuring that each layer treats a unique element of obesity.

Furthermore, precision medicine can predict how specific patients will react to these treatments, lowering the likelihood of adverse effects and increasing long-term outcomes [81].

AI-powered technologies, including as machine learning (ML) and predictive analytics, have accelerated the development of bilayer tablets. These technologies can anticipate ideal drug release patterns, identify potential drug-drug interactions, and model different formulation situations prior to physical trials [69, 82]. For example, machine learning algorithms can assess extensive datasets on patient demographics, illness development, and medication pharmacokinetics to prescribe precise drug combinations and release mechanisms for bilayer systems. AI also allows for the modification of excipient selection, assuring layer compatibility and improving the overall stability and performance of bilayer tablets. Predictive modeling has proved effective in solving difficulties such as layer separation and weight variation, which are crucial in personalized treatment [83].

Precision Medicine and Genomics: Precision medicine is based on the integration of genomic data to adapt therapies to an individual's genetic profile. In the context of bilayer pills, this technique enables genotype-based drug selection, ensuring that each layer provides the correct dose and type of medication. Patients with drug-metabolizing enzyme polymorphisms, such as CYP2D6 or CYP3A4, can, for example, be given bilayer tablets that are tailored to their metabolic capability [67, 84].

Recent advances, such as 3D printing technology, enable patient-specific customisation of bilayer tablets, which improves therapeutic outcomes by adjusting medication combinations and release profiles. Furthermore, biomarkers can be used to drive the design of bilayer systems, in which one layer delivers immediate-acting medication for acute symptoms and the second layer provides sustained release dependent on the patient's illness condition and genetic predispositions [24].

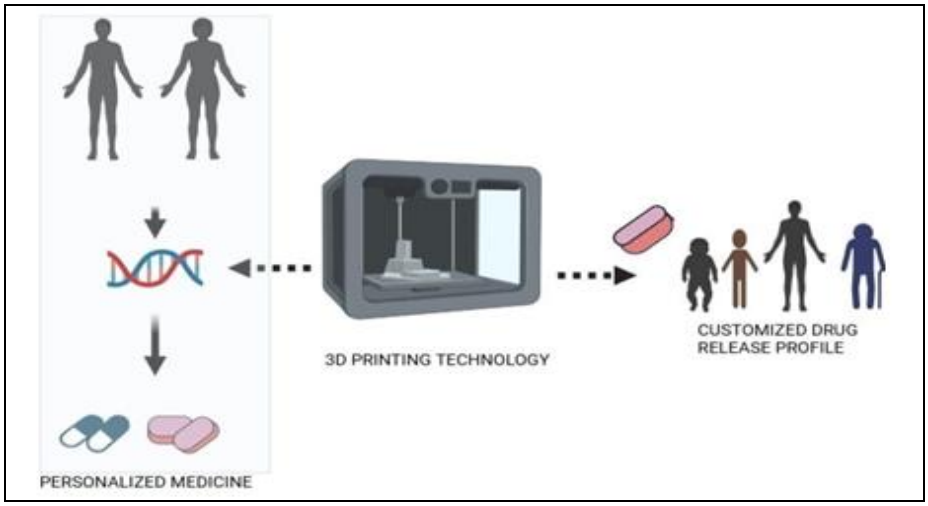

FIG. 2: APPLICATION OF 3D PRINTING TECHNOLOGY IN PERSONALIZED MEDICINE FOR CUSTOMIZED DRUG RELEASE PROFILES

Challenges and Limitations in Bilayer Tablets for Obesity Treatment: Bilayer tablets are a promising pharmaceutical invention for addressing the challenges of obesity treatment, since they allow the mixing of various therapeutic agents or release patterns in a single dose form. Despite their potential, developing and commercializing bilayer tablets presents major obstacles. These include manufacturing challenges, the possibility of drug-drug interactions, and legal and economic impediments to large-scale manufacture [85, 86].

Technical Challenges in Manufacturing: Bilayer tablet manufacture is technically hard, with challenges such as layer separation, delamination, and insufficient layer adhesion offering substantial obstacles [25]. These difficulties are mostly caused by changes in the layers' compressibility, elasticity, and moisture content [87]. For example, incorrect excipient or compression parameter selection might cause insufficient interlayer bonding, resulting in mechanical breakdowns during handling or transportation [88, 89].

Furthermore, attaining homogeneity in drug distribution between layers remains difficult, particularly for low-dose active pharmaceutical ingredients (APIs). Advanced production approaches, such as multilayer compression with accurate force monitoring and the use of binding agents, have been investigated to address these concerns, but scaling remains a challenge [90, 91].

Another key challenge is stability, as bilayer systems are frequently subjected to physical and chemical deterioration as a result of interfacial interactions. For example, medicines in one layer may move to the other over time, resulting in changed release patterns and decreased efficacy [69]. Stability studies must follow ICH criteria for drug-drug and drug-excipient interactions, manufacturing process, heat and humidity impact on bi-layer integrity, and drug release during expiration [92].

Potential Drug-Drug Interactions: Multiple medicines are widely used in obesity treatment, including appetite suppressants, metabolic modulators, and lipase inhibitors. In bilayer systems, the medications are compacted into separate layers, increasing the possibility of inter-drug interactions at the layer interface. For example, various APIs may be incompatible due to pH variances, solubility profiles, or chemical reactivity, resulting in diminished efficacy or undesirable effects [93]. The physical features of the neighbouring layer can also influence each drug's release kinetics. For example, compression-induced changes in surface area or porosity might cause a sustained-release layer to mistakenly influence the dissolution rate of an immediate-release layer. Computational modelling and compatibility studies during formulation development can address some of these difficulties; nevertheless, such efforts demand substantial time and money [94].

Regulatory Hurdles and Cost Considerations: Bilayer tablets have a complex regulatory system since they integrate numerous medicines or release mechanisms into a single dose form. This necessitates demonstrating the combined system's safety, efficacy, and stability through extensive preclinical and clinical testing. Furthermore, regulatory agencies frequently require independent evaluations for each layer's release profile, stability, and performance, which increases the cost and schedule of medication development [89, 95]. From a production standpoint, bilayer tablet manufacture requires more sophisticated equipment and experience than regular tablet manufacturing, resulting in a greater capital expenditure. Specialized presses, for example, require accurate force distribution and real-time monitoring capabilities to minimize layer flaws, but these devices dramatically raise manufacturing costs [36, 89, 95, 96].

Future Perspectives: The development of biodegradable bilayer tablets and sensor-embedded drug delivery devices represents a game-changing prospect for improving obesity treatment outcomes. These developing technologies are intended to increase patient compliance, reduce adverse effects, and maximize treatment efficacy.

Biodegradable Bilayer Tablets: Biodegradable bilayer tablets are a big step forward, especially for long-term and targeted medication administration. These methods use biocompatible polymers like polylactic acid (PLA) and polycaprolactone (PCL), which ensure long-term release and breakdown within the body with no hazardous residue. Such pills can be customized for dual-action mechanisms, where one layer releases appetite suppressants and the other provides lipase inhibitors, improving total treatment efficacy [69].

Recent studies highlight their potential to overcome concerns such as layer separation, a typical challenge in classic bilayer systems, by combining improved polymer mixes and 3D printing technologies for precise layering and stronger interfacial adhesion [97].

Sensor-Embedded Drug Delivery Systems: Smart sensors integrated into bilayer tablets have the potential to transform real-time monitoring and adherence to obesity treatment programs. For example, ingestible electronic sensors can monitor drug release profiles, pH levels, and stomach retention duration, providing significant information to both patients and healthcare practitioners. These approaches have demonstrated promise in clinical studies for individualized dosing, optimizing therapeutic window, and reducing side effects [93].

Interdisciplinary Research and Collaboration: The successful implementation of these advances requires significant multidisciplinary collaboration among academia, industry, and regulatory organizations. Academic research generates fundamental information and new prototypes, whereas industry resources are critical for large-scale manufacturing and dissemination. Furthermore, regulatory frameworks must adapt to accommodate these novel technologies while maintaining safety, efficacy, and ethical considerations [98]. Joint endeavours, such as public-private partnerships and multinational consortia, have proven critical in advancing drug delivery systems. For example, cooperation projects in biodegradable polymers and sensor technologies have shown encouraging results in preclinical trials [98].

Investigation of Novel Drug Combinations: Drugs such as semaglutide and tirzepatide are being investigated for integration into bilayer tablets, with the potential to address broader metabolic dysfunctions associated with obesity [6, 42].

Addressing Regulatory and Ethical Challenges: Regardless of its promise, regulatory hurdles are a substantial challenge. The incorporation of electronics into ingestible tablets, for example, necessitates rigorous regulatory processes to assure biocompatibility and long-term safety [94]. Ethical problems around data privacy and patient autonomy in sensor-embedded systems require careful attention.

CONCLUSION: Bilayer tablets represent a game-changing innovation in obesity treatment, providing a versatile platform for addressing the condition's complex and multifaceted nature. These technologies enable exact drug release patterns by integrating immediate and sustained-release layers in a single dose form, resulting in quick symptom relief and consistent plasma drug levels for long-term therapeutic effects. This dual-action mechanism improves patient adherence, lowers dose frequency, and reduces side effects, making bilayer tablets a possible alternative to standard obesity treatments. Furthermore, advances in materials science, such as hydrophilic polymers and nanotechnology, as well as cutting-edge manufacturing processes like 3D printing and hot-melt extrusion, have greatly enhanced the solubility, stability, and bioavailability of essential anti-obesity drugs.

Looking ahead, the combination of artificial intelligence (AI) and precision medicine provides unprecedented prospects for individualized obesity treatments via bilayer tablets. AI-powered predictive models can optimize drug combinations, release mechanisms, and excipient selection, whereas precision medicine customizes medicines based on an individual's genetic and metabolic profile. Despite manufacturing constraints, regulatory hurdles, and high prices, emerging advances such as biodegradable polymers and sensor-embedded systems show promise for improving patient compliance, environmental sustainability, and real-time therapy monitoring. Bilayer tablets have the potential to change obesity management by increasing therapeutic outcomes and more effectively tackling this global health concern through interdisciplinary collaboration and ongoing research.

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