REVIEW ARTICLE

From Challenges to Advancement for Bilayer Tablet Technology as Drug Delivery System

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ABSTRACT

Bilayer tablet technology is in focus because it advantageous for combination therapy, for combining two different release profile and it gives patent novelty to existing dosage. Hence its advantages, challenges and applications need to be discuss. The objective of preparing a review article on bilayer tablets is multifaceted, aiming to cover challenges at formulation development to scaleup and opportunity for new product development by integrating it bilayer tablet technology with other formulation technology. With reference to all the electronic data it was found that bilayer tablets face many challenges from formulation development till commercial manufacturing like interfacial bonding strength, layer separation, effect of environment on bonding strength bilayer tablet. But all these challenges can be over come by resolving appropriate remedies like using plastic diluent in both layers, manufacturing bilayer tablet using appropriate bilayer tablet manufacturing machine, etc. going forward with this challenges bilayer tablets puts advantage like it can be use for combination therapy, for chronotherapeutic therapy, enhancing therapeutic activity by altering micro environmental pH etc. Review comprises the information of key challenges to be consider while selection of excipients during formulation development, challenges related to process of bilayer tablet manufacturing and manufacturing bilayer tablet by integrating it with novel drug delivery systems and processes for enhancing therapeutic effectiveness and patient compliance

Keywords: Bilayer tablet, drug delivery systems, challenges, combination therapy, patient compliance, manufacturing processes.

Keywords: Ozenoxacin, Quinolone, Impetigo, Topical cream, Antibiotics

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INTRODUCTION

The most acceptable route for many drugs and administration of modified release formulations of new and existing formulations is solid oral dosage form.[1] Pharmaceutical drug product manufacturers have inclined product development approach in recent years towards fixed dose combination, osmotic pump, compression coated tablets, bilayer tablets, mucoadhesive tablets for treatment various treatment like HIV/AIDS, cancer treatment, type 2 diabetes, tuberculosis etc.[2] Considering all this approaches bilayer and multilayer tablet technology has appeal pharmaceutical manufacturers to support and initiate good life for product. Bilayer tablets has enabled development of product with administration of two incompatible API, predefined release of API in single unit dosage. Bilayer tablets technology is improving patient compliance and convenience. Combination of two different drugs in single dosage may reduce cost of product as compare to its individual therapy.[3] Despite all this advantages bilayer tablets are arduous to design due to its layer separation tendencies because of insufficient interfacial bond strength, improper hardness which leads to delamination, unable to controlled on individual weight during compression which could leads to patient may not receive important drug component in desired amount.[4] This review covers the challenges associated with bilayer tablet development and discusses factors to improve quality and resolve issues during large-scale manufacturing. Researchers are integrating technologies like pellets, localized delivery, and freeze-drying with bilayer tablets to enhance therapeutic effects in chronic treatments such as diabetes and hypertension. The techniques available for development of bilayer tablets were shown in Table 1.

Kinetic models for bilayer tablets

Tablets with predefined release profile can be achieved by transforming tablet design along with some components of each layer. Bilayer systems are become recognised for achieving different release profile like site specific delivery, quick/slow-release system, controlled delivery system in single unit dosage unit.[5]

Zero order release system

Drug release at constant rate is the desired goal of developing controlled release system, using bilayer tablets technology it can be achieve by compressing two different release components of same drug in single unit or coating bilayer tablet with polymer membrane which will release content at desired constant rate for longer period of time.[6,7]

Fast and slow-release system

Treatment of diseases like hypertension, diabetes includes combination therapy of drugs. Such combination treatment needs administration of some drug once daily and some twice or thrice a day. Combining this this segregated dosing frequency in a single dosage unit can be achieve using

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Table 1: current techniques available for the development of bilayer tablets.

Technique	Description	Advantages	Challenges
Direct Compression	Compressing the two drug layers directly without solvents or heat.	Simple, cost-effective, Suitable for heat-sensitive drugs	Difficult to achieve uniform layer separation, Limited for low-dose drugs
Wet Granulation	Using a liquid binder to form granules for both layers before compression.	Improved drug release control, Enhanced uniformity	Time-consuming, Risk of drug degradation due to moisture or heat
Dry Granulation	Compressing powders into granules without the use of binders or solvents, followed by compression.	No need for liquid binders, Suitable for heat-sensitive drugs	Requires specialized equipment, Challenges in uniform compression
Layer-by-Layer Compression	Compressing each layer separately before combining them into one tablet.	Precise control over composition of each layer	High precision needed for alignment of layers
Fluidized Bed Coating	Coating one layer over the other by spraying a liquid in a fluidized bed.	Provides uniform coating for controlled release	Complex and expensive, Time-consuming
Hot Melt Extrusion	Extruding the drug mixture using heat and pressure, followed by compression into tablets.	Improves drug stability, Complex drug release profiles	Requires specialized equipment, Limited to heat-stable drugs
Injection Molding	Molding the drug mixture into layers by injecting molten material into molds.	Precise, customizable tablet design	Expensive, requires specialized equipment
3D Printing	Using additive manufacturing to print tablets layer by layer.	High customization, Enables personalized medicine	Requires specialized equipment, Limited materials for use in printing

bilayer tablets which leads to patient compliance and also persist synergistic effect.[8,9]

Pulsatile drug delivery systems (PDDS)

It's a specialised drug delivery system where drug is available into body in correlation with biological rhythm for better therapeutic effect. PDDS required release of predefined amount of drug at essential time during sleep, absorption at specific site in gastrointestinal tract for better therapeutic effect. Using bilayer tablets techniques dosage form can be designed for chronic ailments including asthma, migraine demanding prolong therapeutic effect.[10]

Bimodal release system

Primarily identified by quick first release phase, followed by a phase of constant release, and then a second rapid release phase. advantage of bimodal release system is it either gives zero order release or decreased release rate at substantial period of time. Bimodal release system has ability to deliver drug into system circulation at increase rate when body's ability of drug absorption decreased.[11]

Challenges in bilayer tablets development

In addition to the intended therapeutic effects, bilayer tablets must possess sufficient mechanical strength and hardness to withstand the typical stresses involved in processing, handling, packaging, and transportation. Given the complexity of designing and manufacturing these tablets, various issues that can impact the properties of the dosage form may arise during product development. Some of the principal challenges are shown in Figure 1[12-14]: Bilayer tablets add challenges in manufacturing as well as establishing regulatory controls to meet the product performance over lifetime as per relevant regulatory authorities to comply these requirements understanding risk of different factors like excipients and manufacturing process related to quality of product is much more important to avoid financial loss due to recall and failure of commercial batches. to conquer all these challenges, efforts to be focused on following parameters involved in bilayer tablets manufacturing[15]

Mechanical properties of material use in bilayer tablet

Surface free energy of material

Interfacial bonding strength between two layers

Optimization of compression force for the first layer.

Evaluation of factors contributing to delamination.

Analysis of the effects of layer sequence and weight ratio.

Development of small-scale material characterization techniques applicable during bilayer tablet design.

Characteristics of Composition Materials

Inadequate process of bilayer tablets manufacturing leads to separation of two layers at interface. The delamination may happen at various steps of manufacturing like compression, coating, storage or during transit. consequences of this contribute to loss of therapeutic value of product. Therefore, to reduce occurrence of this problem, understanding of material properties and its impact on manufacturing process of bilayer tablets is very important.[16] The appropriate selection of material by understanding its fundamental properties like brittleness, plasticity, elasticity, viscoelasticity is most important for development of high-quality bilayer tablets. compaction of bilayer is most important factor to get intact bilayer tablet. properties of excipients used for development of bilayer tablets will predominantly affect the compaction process of bilayer tablet formulation[17] material properties likely brittleness and plasticity will affect the compaction during

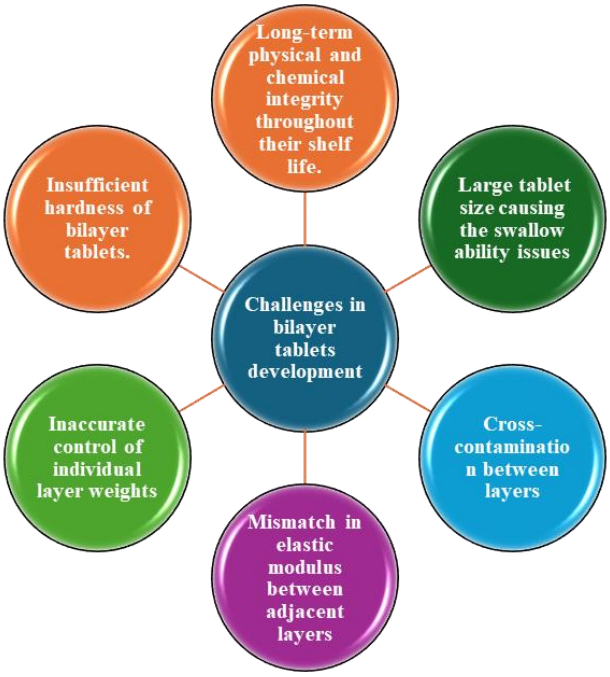

Figure1. Challenges in bilayer tablets development

compression process. material chosen for development should characterised by good compressibility and compatibility so that volume of each layer of the tablet should sufficiently reduce to develop mechanically strong intact bilayer tablet. Reports indicate that plastically deforming and brittle materials significantly influence the compression process. The compression of a plastic material occurs due to plastic flow, provided that the stress resulting from elastic recovery does not surpass the bond strength.[18] Delamination causes mainly due to differences in properties of material used in two layers of bilayer tablet i.e Young's modulus or elastic mismatch. Brittle and plastic materials decompress at different rates because of variations in Young's modulus. This difference creates radial stress at the interface of the two layers, weakening the bond strength and ultimately leading to delamination. Hence it is essential to concentrate on the material properties of the substance before utilizing it in the formation of bilayer tablets.[19]

Surface free energy of material

The mechanical properties of bilayer tablets are influenced by material characteristics like surface morphology of excipients and its effect on deformation properties of bilayer tablets leads to lamination during tableting process. This effect is more marked when the plastic material compressed into first layer.[20] apart from the plastic/brittle behaviour of tableting material, morphological properties of material like size and shape of particles can affect rearrangement behaviour, interfacial adhesion and flow characteristics of the compressed powder. specific surface and surface free energy of materials has impact on adhesive and cohesive properties of material which may influence lamination.[21] Tendency of delamination is basically related to plastic and elastic behaviour of material but study indicate that it is significantly depend on surface characteristics of material like surface free energy. Utilization of high surface free energy or plastic deforming material in both layers can prevent lamination. If brittle elastic material is compressed into lower layer then lack of interlocking bond may be compensated by strong interfacial adhesion derived from van der wall forces. If the material is plastic in nature with high surface energy compressed into a lower layer off the tablet, then lamination tendency is very high due to creation of smooth contact surface at very low precompression forces. Lamination tendency is also very high when material use in upper layer having brittle elastic property associated with high surface energy. Hence it is concluded that properties of materials like surface free energy, adhesive and cohesive properties of material to balance interlocking bonds has to be considered for avoiding lamination issues in bilayer tablet compression.[22]

Interfacial bonding strength between two layers

Adhesive strength required for attachment of two layers of Bilayer tablets can be called as Interfacial bonding strength. The main manufacturing challenge is to obtain bilayer tablet with sufficient adhesive strength which will not delaminate during manufacturing and transit of product. Materials with less difference in elastic recovery to be use in two different layers of bilayer tablet to get sufficient interfacial bonding strength. In order to Produce bilayer tablet with sufficient interfacial bonding strength different manufacturing parameters like Interfacial curvature, water content of powder, particle size of the powder are examined. it is found that use of convex and concave punches increases interfacial bonding strength due to an increase in interaction between adjacent layers with larger surface area. These particle-particle interactions in the region close to the tablet edges have more significant influence on tablet interfacial strength, compared with the particulate interactions that occurred in the centre of tablet. hence tablets precompressed with convex punch has stronger strength as compared to concave punches.[23] Interracial bonding strength depend on percentage of water content. The existence of water content in tablet can lead to the increase of tablet interfacial strength for the following two reasons: the water monolayer eliminates the particle surface micro-irregularities, which leads to the formation of better bonds between particles the water monolayer results in the formation of pendular liquid bridges, enhancing the interparticular interactions hence the interfacial strength. Study carried out to evaluate effect on Trent of tablet using MCC and different concentration of water content. In study it is observed that Tablet with 6% water content has higher international strength. Significantly decrease in compatibility of tablet please all the add water content of 8 to 10%. Particle size in the first layer in pre-compressions affected the interfacial strength. It was shown that the first layer using a coarse powder (i.e. large particle size) had a rougher interfacial surface. The increase in the interfacial roughness facilitates particle interactions across layers, enhancing the particulate interactions and resulting in a higher interfacial bonding strength.[24]

Aassessment of the impact of layer sequence and layer weight ratio

Bilayer tablets are generally compressed by using 1:1 and 1:2 ratio between the two layers. It becomes challenging to compress bilayer tablets having layer ratio of 1:3 to 1:6, in

such cases where difference between the ratio of two layers is high it becomes more challenging to maintain weight of smaller layer. The downside smaller part in upper layer tobe process first in order avoid the weight variation but commercially available tablet presses do not offer such possibilities at scale up batches. hence formulator have to place larger layer portion in first layer and above which second layer has to compressed by considering related hurdles. The layer by layer arrangement with perceptible compactability properties decides tensile strength due to interfacial roughness. Effect of layer sequence on tensile strength of tablet evaluated by First layer was compressed with methyl cellulose and starch in second layer resulted to low tensile strength of tablet due to low surface roughness on first layer leads to decline in interfacial bonding with second layer. Interchanging of layer sequence (i.e starch in first layer and methyl cellulose in second layer) shows increase in tensile strength of tablet as compare to previous sequence. It happens due to increment in interfacial roughness leads to more interfacial attraction between two layers.[25]

Adsorption/desorption properties of material

The impact of different grades of excipients on the quality of bilayer tablets was studied by assessing how humidity affects layer separation and delamination. This involved two grades of colloidal silicon dioxide: Aeroperl® 300 and Aerosil® 200. Although both are amorphous, Aeroperl® 300 has a larger relative surface area compared to Aerosil® 200. When exposed to high humidity levels, Aeroperl® 300 exhibited a greater capacity for moisture adsorption than Aerosil® 200. However, at lower humidity levels, Aerosil® 200 demonstrated superior moisture retention compared to Aeroperl® 300. The moisture that Aeroperl® 300 failed to retain in Layer II A became available for interaction with other excipients in Layer I, such as microcrystalline cellulose and crospovidone (a disintegrant), which can lead to delamination of the two layers.[26]

Magnesium stearate is very commonly used lubricant in tablet dosage form to avoid sticking during compression process. It's concentration in bilayer tablets demonstrate critical role to achieve optimum interfacial interaction between two layers of bilayer tablets. Lower concentration of lubricants in first layer leads to achieve greater interfacial interaction between the adjacent layer and can produce bilayer tablets with sufficient tensile strength. Tye et al. reported that plastic material is more sensitive to lubricant (magnesium stearate) level on tablet strength than brittle materials. (levels tested: lower 0.25%, centre 0.5%, higher: 0.75%)[27]

Bilayer tablet manufacturing Process challenges

Bilayer tablet along with many advantages comes with the challenges of successfully manufacturing it on tablet compression machine, tablet coating and environmental effect on tablet quality. Principally compression process is same as of single layer tablet but operation requires more attention in details to monitor and overcome the challenges occurs during processing like compression force, cross contamination, preventing excess loss of yield due to waste of material by incorrect press setup. To produce bilayer tablets as per GMP requirements, it is essential to use compression press with required mechanical modification, which will be capable to produce bilayer tablet by resolving following issues.[28,29]

Preventing capping and separation of two layers

Plasticity of material is crucial with respect to compaction of each layer of bilayer tablet, capping or delamination occurs at large scale manufacturing press due change in dwell time or different loading rate. new bilayer tablets having compression rollers of equal diameters which can help to make good tablets having strain rate sensitive material

Controlling product quality by appropriate machine setup

Cam tracks are used in tablet compression machines to control the movement of the upper and lower punches during the tablet compression process. The cam track determines the force and speed at which the punches move, which can have an effect on the quality and properties of the resulting tablets. In the case of bilayer tablets, where two layers of different formulations are compressed together to form a single tablet, the cam track can have a significant impact on the final product. Specifically, the cam track can affect the bonding between the two layers, the thickness and hardness of each layer, and the overall appearance of the tablet. The bonding between the two layers is affected by the force applied during compression, which is controlled by the cam track. If the force is too high, the layers may merge and lose their individuality, resulting in poor layer separation and possibly affecting drug release properties. On the other hand, if the force is too low, the two layers may not bond together properly, leading to layer separation and instability. The thickness and hardness of each layer are also influenced by the cam track. A steeper cam track can result in a thinner and harder layer, while a flatter cam track can result in a thicker and softer layer. It is important to choose the appropriate cam track to achieve the desired layer properties. Finally, the overall appearance of the tablet can be affected by the cam track. The shape and size of the tablet, as well as its surface texture and embossing, can be influenced by the cam track design. In summary, the choice of cam track can have a significant impact on the quality and properties of bilayer tablets, particularly in terms of layer bonding, thickness and hardness, and overall appearance. It is important to select an appropriate cam track design to optimize these properties and ensure consistent quality of the final product.

Produce high yield

Many variables like turret speed, fill cam, Crosscontamination, shorter Dwell time playing critical role to achieve high yield. Fill camp is component located under the lead section of feeder, controls the tablet weight by allowing desired amount of powder or granules that are fed into the die cavity during the compression process. Different fill cam like flat fill cam, concave fill cam cause change in amount of die fill and final weight and thickness of tablet hence selecting appropriate fill cam during manufacturing will help to improve the yield of product. For avoiding crosscontamination factors like vacuum pressure, distance between feeder table and turret are controlled it will also lead to increase in yield of product due to

controlling excess of loss of material because of appropriate vacuum pull of material from feeder & avoiding excess powder feeding on turret by adjusting minimum distance between feeder table and turret.

Effect of external application of lubricant

Research on external lubrication, in which an external lubricant is applied to the punches and dies, has demonstrated that this technique can enhance the crushing strength of monolayer tablets by 40% without prolonging their disintegration and dissolution times.This finding suggests that external lubrication offers significant benefits for monolayer tablets and indicates potential applicability for multilayered tablets. Nevertheless, additional research on external lubrication is necessary to establish proof of concept for its use in multilayered tablet formulations.

Effect of microenvironment condition on tablet coating

Temperature and humidity conditions during storage is important for physical stability of tablets. While compaction characteristics of the individual layers contribute to the overall stability, they are not the sole reason for delamination. Some factors like temperature and humidity may significantly alter the integrity and performance of tablets over time. Study done to evaluate the effect of microenvironment condition during pan coating of bilayer tablet which effectively shows that microenvironmental conditions can leads to delamination during storage of tablets hence that need to be monitored critically.

Integration of new technologies and bilayer tablets

Bilayer tablet manufacturing using 3D printing technique

The practical use of 3-Dimentional print in bilayer tablet manufacturing offers several advantages over traditional manufacturing techniques. Some of the benefits include precise control over drug release profiles, personalized dosing, elimination of problems like lamination, cracks, layer splitting due to inadequate interfacial bonding strength, increase in yield by reducing waste and the ability to incorporate multiple drugs or complex drug combinations in a single tablet. Various printing techniques that can be employed towards bilayer tablet manufacturing, including fused deposition modelling (FDM), stereolithography (SLA), selective laser sintering (SLS) and inkjet printing. Guaifenesin bilayer-controlled release tablet manufactured using desktop 3D based extrusion printer and these tablets were evaluation parameters like dissolution profile, hardness, weight variation was compared with marketed guaifenesin bilayer tablet (Mucinex®) manufactured using conventional compression technique. all evaluating parameters are equivalent as to the commercial guaifenesin bilayer tablet. Bilayer tablet of hydrochlorothiazide and Lovastatin were mass customised using integration of 3D printing method of fused filament fabrication (FFF) and Injection moulding (IM) technique. during study of development of this technique drug release is essential to control the control the surface area to volume ratio to control drug release rate through 3D printed layer.[30] Flexible dose combinations of two antihypertensive drugs were created in a single bilayer tablet using a dual fused deposition modeling (FDM) 3D printer. Filaments containing Enalapril maleate (EM) and hydrochlorothiazide (HCT) were produced through hot-melt extrusion (HME). Innovative methods for creating personalized fixed-dose combinations (FDCs), such as 3D printing (3DP), are being developed and could significantly influence the production of FDC medications in hospital and community pharmacies. This advancement facilitates personalized therapies and enhances patient compliance. Additionally, 3DP can quickly and flexibly tackle critical challenges, such as the need for personalized therapies against emerging pathogens like COVID-19, in ways that are often not feasible for pharmaceutical companies due to stringent regulatory requirements.[31] Polypills were engineered by utilising Pressure Assisted Microsyringe (PAM) 3D printing technology. For treatment of Diabetes Mellitus type II and hypertension three different drugs were combined in single pill having different release profile. Captopril release controlled by osmotic agent due to which it releases content over sustained period at zero order kinetic and nifedipine and glipizide were combined with hydrophilic polymer which release content at first order over sustained period. using PAM 3D printing technique five different drugs were combined together in two different layers with different release profile. Immediate release layer contains acetylsalicylic acid and hydrochlorothiazide and in second layer is sustained release part contains pravastatin, atenolol and ramipril. These two layers were separated by cellulose acetate layer.[32]

Bilayer tablet manufacturing for localised drug delivery

Targeted delivery at intestinal site time-controlled explosion system developed in which drug release from dosage form achieved by explosion of membrane after definite time period. formulation developed in the form of capsules and bilayer tablets. Release time from dosage unit is controlled by rate at which disintegration extended by balancing thickness and tolerability of a water insoluble membrane and concentration of swellable low substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate. Ethyl cellulose (EC) used for making shell of capsule formulation. thickness of shell is approx. 120μm, which contains micropores at the bottom of body, through which fluid enters into shell and cause disintegration of capsule cap which leads to release of active content through bilayer tablet inserted inside capsule body.[34]

Mesalamine bilayer tablet were formulated to overcome drawback of high frequency of loading dose in immediate release dosage form and insufficient loading dose in sustained release dosage form to achieve effective therapeutic concentration. Enteric coated bilayer mesalamine tablet formulated by using HPMC K4M and HPMC K15M as sustained release polymer and bilayer tablet were coated with Eudragit® S100 for releasing content into intestinal site. Invitro dissolution profile and In Vivo roentgenographic and pharmacokinetic studies indicate that mesalamine is targeted at colon site.[33] Propranolol Hydrochloride (PROP) is beta blocker antihypertensive drug. Its BCS class I drug, daily administration of 3-4 times a day required for desired therapeutic effect. Its available in different dosage forms in market i.e tablet, capsule, solution. Pharmacokinetic data

indicate that its after oral administration it undergoes extensive first pass metabolism and bioavailability of administered dose is15 to 25%. In order to avoid first pass metabolism different dosage form for localised delivery of drug, mucoadhesive buccal patches, tablet and patches reported. PROP mucoadhesive sustained release buccal bilayer tablet were develop to release PROP systemic circulation through buccal route and other layer of tablet helps to keep tablet intact with buccal tissue. bilayer tablet was prepared by using Polyethylene oxide (PEO), Carbopol (CB) and Polyvinyl alcohol was matrix forming polymer with different mucoadhesive properties and PEO and CB posses the ability to sustain release of PROP. Dosage form evaluated using *in vivo and in silico* based strategy indicate about improved biopharmaceutical properties.[34] Chemotherapeutic agent administered through localised route offers advantages like i) delivery of drug at site of action ii) lower dose requirement iii) reduction in side effects and systemic toxicity. Cervical cancer originates from the cells of the cervix. Vaginal tablets represent a dosage form that offers several advantages, including straightforward manufacturing processes and ease of administration. These tablets ensure precise dosing and enhanced drug stability, while also eliminating the need for antimicrobial agents for preservation. Furthermore, they are easier to handle and store, and their cost-effectiveness is bolstered by large-scale production capabilities. Consequently, vaginal tablets are particularly suitable for use in low-resource settings. The bilayer vaginal tablets developed passed all physical test parameters and mucoadhesion properties required for delivery of drug at vaginal site. for evaluation of combination of disulfiram and 5 fluorourasil Ca-Ski cell has been used which shows additive and potentially synergistic effect at low concentration.[35] Gastro retentive tablets were manufactured by most common method i.e creating gaseous bubble into the tablet after coming in contact with stomach fluid. But it fails in case of floating and premature gastric emptying. to overcome this problem Bilayer tablet developed with one layer is Gastro Retentive (GR) porous layer and other layer is drug layer.[35] GR layer is formed by swellable polymers with porous structure form due to evaporation of volatile material during sublimation process and other layer contains drug with hydrophilic polymer which will release drug for sustain period of time, using this technique bilayer tablet prepared by utilising ranitidine as model drug. bilayer tablet prepared by compressing drug layer over GR layer. GR layer contains camphor as volatile material, after bilayer tablet compression it dried under vacuum at 60^0c for 12 hrs for evaporation of camphor which create pores into tablet. Using this system, the drug layer immerses in water due to the difference in density and releases the drug into the gastric chyme. On the other hand, the porous GR layer provides immediate buoyancy due to its low density and high wet strength by incorporating a large amount of swellable polymer.[36]

Gluing Pill Technology (GPT)

Bilayer tablets are manufactured by conventional method of compressing second layer over precompressed first layer using single or double rotary compression machine. Layer density control, delamination leads to high rejection rate and low production yield. To overcome all these challenges GPT is developed, in this technique two layers of tablet compressed separately and two layers bind together by binding agent using automated machine. selection of gluing agent is very crucial step in GPT, humidity and elevated temperature causes stress into glue layer which will affect tack ability of gluing agent. GPT offers more flexibility with regard to combination of incompatible API, less wastage and higher process efficiency compared to conventional bilayer tablet manufacturing. GPT is potential technology for manufacturing of Fixed Dose Combination (FDC) used in treatment of diabetes, hypertension, HIV etc., GPT can be easily scalable for continuous manufacturing process.[37]

Nanotechnology in Bilayer Tablets

Delivery of two different drug with different release pattern for achieving desired therapeutic effect and improvement of patient compliance achieved by bilayer tablet technology. Atorvastatin and clopidogrel bilayer tablet manufactured for treatment of atherosclerosis. Atorvastatin has poor water solubility hence to enhance its solubility its nano particles prepared using top-down high-pressure homogenization technique. Using this technique nano suspension prepared then is freeze dried to convert into powder form. Clopidogrel ha slow bioavailability and high chances of bleeding due to generation of high concentration of metabolite by interaction at stomach environment in its conventional dosage form and clopidogrel also has drug-drug interaction with atorvastatin when mix in single tablet. To overcome all this challenges bilayer tablet prepared which having immediate layer as nano form of atorvastatin and sustained release layer of clopidogrel. Invitro and Invivo study perform on bilayer shows satisfactory result with increment in bioavailability of atorvastatin and sustained release pattern of clopidogrel.[38] Development of bilayer tablets for Velpatasvir (VLP) and Sofosbuvir (SOF) loaded mesoporous silica nanoparticles (MSNs) hepatitis C. bilayer tablet developed by using direct compression technique. Immediate release layer contains Velpatasvir loaded MSNs (VLPMSN) and sustained release layer contains sofosbuvir loaded MSNs (SOFMSNs). Sustained release of SOFMSNs achieve by functionalizing it with 3-aminopropyl-triethoxysilane (APTES) and Hydroxy Propyl Methyl Cellulose (HPMC). Bilayer tablet prepared using mesoporous nanoparticles of both drugs complies all physical and chemical parameters. Scanning Electron Microscopy used for confirming intactness of nanoparticles into bilayer tablet. Fourier Transformed Infrared Spectroscopy (FTIR) analysis shown that no interaction between drug-silica-polymer. X-ray diffraction (XRD) analysis and transmission electron microscopy (TEM) confirmed the ordered 2D hexagonal mesoporous architecture; moreover, XRD also indicated that both drugs present in amorphous and entrapped between pores of MS. Stable nano-based bilayer tablet has shown new approach for treating hepatitis C by releasing VLP in 1 hr and release of SOF for sustained period upto 20 hrs. This approach not only address intrinsic issue of the drug but it also shown desired therapeutic effect with minimum side effects.[39]

Freeze-Dried Orodispersible bilayer Tablets

Orodispersible tablets (ODTs) are solid oral dosage forms that quickly disintegrate upon contact with the tongue, eliminating the need for water. According to the British Pharmacopeia, ODTs disperse rapidly before being swallowed and must disintegrate within 3 minutes. The US Pharmacopoeia (USP) specifies that ODTs should disintegrate in less than 30 seconds, with a tablet weight not exceeding 500 mg. additionally, for freeze-dried ODTs, the drug dose should be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs.[40] Such product manufactured by direct compression (DC) technique, because it is considered that by DC process tablets form will be highly porous due to which it disintegrates rapidly once comes in contact with saliva. Because of high porosity saliva can easily penetrate into tablet through pores and rapid disintegration occurs. apart from DC process some novel process like Freeze drying (lyophilization), Spray drying and moulding are utilised for making ODTs, disintegration time observed from this technique is from 3 seconds to 3 minutes, but freeze-drying technique has fastest disintegration time. Freeze drying is solvent removal process from frozen mixture of solid and solvent due to which it forms highly porous structure.[40] Study has been done for developing methodologies for fabricating bilayer ODT tablet by layers freeze dried (lyophilized) technology. This technique will create opportunity to formulate combination product for different therapies and also helpful for patient having swallowing difficulty. It will also help for improving solubility of some drugs which result into increase of bioavailability. Two separate solutions (A and B) were prepared and each solution freeze dried into separate layer which forms Bilayer ODT, having different release profile. Solution A injected into empty blister to the half and freeze at -80^{0}C for one hour in freezer then solution B injected into remaining part of blister and freeze at -80°C for another one hour. After completion of freezing process both layers were freeze dried to remove solvent from tablet core and then resulting bilayer tablet were evaluated for physical and chemical parameters. Investigation of frozen ODT tablet prepared by layer-by-layer freeze drying technique shown that different disintegration time followed by different dissolution rate of bilayer ODT cab be fabricated using freeze drying technique. Optimization of adhesion layer is required for getting intact bilayer tablet as well as concentration of gelatine and mannitol can affect tablet characteristics.[41]

Bilayer tablet for adjusting microenvironmental pH

The oral bioavailability is mostly depending on its stability, dissolution in gastrointestinal fluid and permeation trough cell membrane into systemic circulation. Weakly acidic/basic drug solubility is depended on pH of medium. Many studies reported that by addition of organic and inorganic acid/bases used as pH modifier to alter microenvironmental pH around the solid particle, which leads to increase in solubility and pH independent release dissolution release achieved. Studies has shown than addition of pH modifier has played critical role in enhancing solubility of poorly soluble weakly acidic/basic drug at diffusion layer and followed by dissolution rate. It was also found that nucleation inhibitors are also important to enhance dissolution by preventing crystallization of dissolved drug. Though pH modifier and nucleation inhibitors helps to enhance solubility and dissolution rate of weakly acidic /basic drugs, in some cases it might be incompatible with the drug in tablet dosage form which alter desired application of microenvironmental pH modification for enhancement of dissolution rate.[42] To overcome this problem bilayer table technology used for drug AMG009 indicated for anti-inflammatory activity. Bilayer tablet manufactured by adding pH modifier in one layer and drug in one layer, so that any incompatibility issues between drug and pH modifier can be minimised. Addition of gel former i.e HPMC K100LV in both layers avoid uncontrolled release of pH modifier in dissolution medium which helps to maintain microenvironmental pH till the desired release time of drug into dissolution medium. Release profile of bilayer tablet was compared with the bilayer tablet without gel former in pH modifier layer shows minimal dissolution enhancement.[42] The study has been done to evaluate effect of alkalizing agent on controlling adverse effect like gastroduodenal lesion and enhancement of drug solubility by developing controlled release bilayer tablet of aceclofenac tablets. Bilayer tablet develop in which alkalizing agent Na_2CO_3 added into extended-release layer, dissolution of tablet done in simulated gastrointestinal fluid at pH6.8 and it compared with monolithic matrix tablet (Airtal®) not containing Na_2CO_3. Pharmacokinetic study carried out in begal dogs shows that increased drug plasma concentration and sustained release pattern of bilayer-controlled release tablet as compare to Airtal®. Addition of Na_2CO_3 create maintenance of microenvironmental pH cause significant reduction in gastrointestinal bleeding and reduction of drug particle size due to microenvironmental pH by addition of alkalizer. hence it proved that modified bilayer tablet dosage form provides better patient compliance and pain control.[43]

Chronological release using bilayer tablets

Chronotherapeutic dosage forms are designed to release medication in a time-controlled manner, aligning with the body's circadian rhythms or specific patterns of disease activity. These formulations aim to optimize drug delivery by synchronizing drug release with the timing of the patient's symptoms or the physiological processes that influence drug absorption, metabolism, or efficacy. Chronotherapeutic dosage forms have been explored for various medical conditions, including cardiovascular diseases, asthma, rheumatoid arthritis, and sleep disorders. The goal is to optimize treatment outcomes by aligning drug availability with the body's natural rhythms or specific disease patterns. Several dosage forms and delivery systems are designed for chronotherapeutic purpose like Transdermal patches, osmotic pulsatile system, Implants, Modified release tablets and capsules etc. in case of modified release tablet dosage forms bilayer tablet technology is evaluated for achieving desired chronotherapeutic effect.[44] Nocturnal asthma is a type of asthma that worsens by creating symptoms like narrowing of the airways which leads to coughing, wheezing, shortness of breath, chest tightness during the night.

Nocturnal asthma specifically refers to a worsening of these symptoms during the night. for treating this disease conventional dosage form is less effective hence modified release dosage system required in which release of drug from dosage form will happen as per the circadian rhythms. The Dual Release Drug Absorption System (DUREDAS) was utilized to develop a modified-release bilayer tablet containing Fexofenadine HCl and Montelukast Sodium. The formulation was created using Quality by Design (QbD) principles. The bilayer tablet was evaluated for its release profile, demonstrating an immediate release of Fexofenadine HCl, followed by a sustained release of Montelukast Sodium over a period of 8 hours after passing through the gastric region.[45] Rheumatoid arthritis (RA) is a chronic autoimmune disease causes inflammation in the affected joints leads to pain, stiffness and over time causes joint damage and deformities. In the case of rheumatoid arthritis, there is evidence to suggest that symptoms and disease activity may exhibit a circadian pattern. For example, joint stiffness and pain may be more pronounced in the morning upon waking and improve throughout the day. Additionally, the levels of certain inflammatory markers, such as cytokines, may vary throughout the day.[46] Etodolac (ETD) is a widely used non-steroidal anti-inflammatory drug for treatment; however, conventional delivery systems often lead to complications such as nausea, epigastric pain, heartburn, and indigestion. To address these issues, various formulation strategies can be employed using bilayer tablet systems coated with controlled-release materials. By multi-coating tablets with time-dependent polymers that create a lag time before drug release begins, it is possible to achieve the desired pulsatile release profile. Bilayer tablet contains one layer is immediate release layer which loaded with superdisintegrant and PEG6000 for fast release and immediate solubility of drug and sustained release layer contains HPMC based high viscosity polymer which will release ETD for sustained period of time. bilayer tablet coated with isolation layer of Opadry II, then Swellable layer of E5/K4M, followed by rupturable layer of Surelease of ethylcellulose. The present formulation optimised formula demonstrated the pulsatile and sustained release of bilayer tablet which delayed the drug release for 4 hours due to triple coating and avoid contact with stomach, then release ETD as per predetermined release time profile. In-vivo response of rats clearly illustrated the chronological anti-inflammatory effect of etodolac from coated bilayer tablet formulation.[47,48] In the context of hypertension, which is a condition characterized by elevated blood pressure, chronotherapy involves adjusting the timing of antihypertensive medications to better align with the body's circadian rhythm. azelnidipine (AZL) and Olmesartan medoxomil (OLM) bilayered core-in-cup buccoadhesive tablet was formulated by using liquisol technology to enhance the poor solubility of both drug. Bilayer tablet designed for chronologically delivering both drugs through two opposing mechanisms: immediately releasing OLM synchronized with controlling the release of AZL in a zero-order manner and maintaining plasma concentration within the therapeutic window in attempt to control circadian BP rhythms.[49] In vitro and in vivo evaluation of bucoadhesive bilayer tablet shows promising result like significant increase in AZL bioavailability and controlled release by following zero order kinetic and fast release of OLM by following first order kinetic.[50,51]

CONCLUSION

Bilayer tablet technology offers significant advantages over single-layered tablets, addressing several limitations of the latter. This innovative approach allows for the incorporation of incompatible drugs with different indications or the same drug with varied release rates within a single dosage unit. Bilayer tablets are ideal for the sequential release of two drugs in combination therapy, as well as for sustained-release formulations where one layer provides an immediate dose and the second layer serves as a maintenance dose. This design ensures that each drug is delivered without pharmacokinetic or dynamic interactions, maintaining their individual delivery rates. Bilayer tablets present a unique opportunity for pharmaceutical manufacturers to differentiate their products from competitors, enhance therapeutic efficacy, and protect against counterfeit medications. However, the quality and adherence to Good Manufacturing Practices (GMP) for bilayer tablets can vary widely. This variability necessitates the use of different types of presses for bilayer tablet production, from basic single-sided presses to sophisticated machinery. Precise weight control of both layers is crucial for high-quality bilayer tablets, but compression force-controlled presses often lack the sensitivity needed for accurate interlayer bonding at lower compression forces. This challenge is exacerbated at higher production speeds. To address these issues and achieve precise control over individual layer weights while minimizing the risk of layer separation, displacement weight control systems offer accurate monitoring and control of each layer's weight, even at high production speeds, ensuring consistent tablet quality. Many pharmaceutical companies are currently developing bilayer tablets for various therapeutic applications using different manufacturing technologies. Research efforts focus on enhancing the efficacy and effectiveness of therapies by integrating bilayer tablet technology with novel approaches. For instance, localized drug delivery in cervical cancer therapy can benefit from bilayer tablets and 3D printing techniques can overcome commercial manufacturing challenges such as interfacial bond strength, consistent release profiles, and manufacturing yield improvements. Nanotechnology is being utilized to improve the bioavailability of drugs used in combination therapies and sustained release pH-independent tablets are being developed by adjusting the microenvironmental pH for drugs with pH-dependent solubility profiles. By considering flexibility of bilayer tablet technology of integrating with other technique which will help patient for better treatment and it can be put forward at large scale by complying all GMP parameters and make unique identity of product in market for pharmaceutical manufacturers.

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