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Review Article

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Bimodal Release Bilayer Tablet: A Review

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Abstract Approximately 90% of the medications produced globally are intended for oral consumption. Researchers worldwide primarily focus on this class of formulation. Bilayer tablets offer a versatile approach for controlled drug release, combining immediate and sustained effects within a single dosage form with cost-effective way. Bilayer layer tablets have been consist of two layers which is slow release and immediate release layer. Bilayer tablets have various advantages over the traditionally used formulations because, these are appropriate for sequential release of active substances from combination it also has the capacity to separate incompatible substances. The preparations of bilayer tablet were needs due to separate incompatible active pharmaceutical ingredient (APIs) for each other. Bilayer tablets material involves both the compressibility and consolidation. Various types of bilayer tablet press currently available in the market, various approaches used in bilayer tablet system, characterization as well as evaluation of the bilayer tablet system.

Keywords Bilayer Tablet, Bimodal Drug Release, Immediate Release, Sustained Release, Controlled Release

Introduction

Approximately 90% of the medications produced globally are intended for oral consumption. Researchers worldwide primarily focus on this class of formulation. Their attention is directed toward improving drug delivery methods. Bilayer or tri-layer drug delivery systems aim to reduce the frequency of dose intake[1]. By using multiple layers, these systems can release drugs at different rates (e.g. controlled, sustained, or immediate release), optimizing therapeutic effects. The techniques of a modified release over the entire dosing interval improved greater patient convenience and compliance. By tailoring drug release, they enhance therapeutic outcomes while minimizing side effects. Researchers continue to innovate in this field to optimize drug delivery and minimize side effects[2].

Bilayer tablets offer a versatile approach for controlled drug release, combining immediate and sustained effects within a single dosage form with cost-effective way. Bilayer tablets have various advantages over the traditionally used formulations because, these are appropriate for sequential release of active substances from combination it also has the capacity to separate incompatible substances[3]. In the context of bilayer tablets, best one is that tablet has 'bimodal release' means one layer provide immediate release for instant relief and second layer contribute controlled release of drug for maintenance of drug in blood or tissues. Sometimes one bilayer tablets contains two different drug in same drug release pattern[4].

Bimodal drug release refers to a sophisticated pattern where the release of a drug alternates between fast and slow profiles. Initially, a certain amount of drug is rapidly released within short time periods. This phase provides an immediate therapeutic effect. Following the fast release, there are predetermined off-release periods. During these intervals, drug release slows down significantly. The slow-release phase ensures a sustained therapeutic effect over time[5].

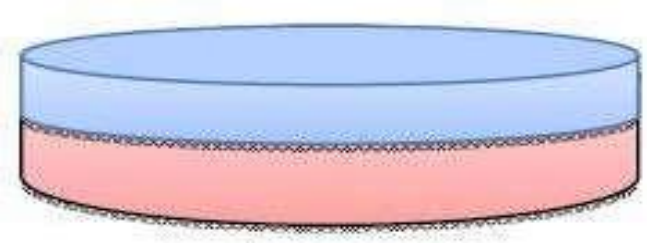

Figure 1: Bilayer tablet

Goals for designing bilayered tablets[6,7]:

- To control the delivery rate of either single or two different active pharmaceutical ingredients(s).
- To separate incompatible APIs from each other, to control the release of one API from one layer by utilizing the functional property of other layers (such as osmotic properties).
- To modify the total surface area available for API layer by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.

Advantages of bilayer tablets[8]: Multi-layer tablet dosage forms are designed for variety of reasons:

- To separate incompatible APIs from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).
- To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.

Ideal Characteristics of Bilayer Tablets[9,10]:

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
- It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.
- It should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Challenges related to bilayer technology[11, 12]: The formulators and process scientists need to overcome the challenges to deliver a robust bilayer tablet and manufacturing process. Some of the key challenges are:

- In accurate individual layer weight control
- Cross contamination between the layers
- Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low interfacial strength.

Quality and GMP requirements for bilayer matrix technology[13]:

- To produce a quality bilayer tablet, in accordance with GMP, it is important that the selected press should be capable of:
- Preventing capping and separation of the two individual layers that constitute the bilayer tablets.

- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.

Different Techniques for Bilayer Tablet[13]

- OROS® push pulls Technology
- L-OROSTM Technology
- EN SO TROL Technology
- DUREDAS™ Technology
- DUROS Technology

Types of bilayer tablet press[14]

- Single sided tablet press.
- Double sided tablet press.
- Bilayer tablet press with displacement monitoring.

Single sided press: The simplest intend is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Double sided tablet press: In most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

Bilayer tablet press with displacement monitoring: The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

Various Approaches Used in the Bilayer Tablet[15, 16]

(a) Floating Drug Delivery System: Foundation the formulation and technological point of view, the floating drug delivery systems are significantly easy and logical approach in the development of Gastro retentive dosage forms (GRDFs). The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

Intra gastric bilayered floating tablets: These are also compressed tablet as shown in figure and contain two layers i.e. Immediate and sustained release.

Multiple unit type floating pills: These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

(b) Polymeric Bio adhesive System: These are designed to swallow fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should support gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bio adhesive property.

Disadvantages: The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans. The system adheres to mucous not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form

with it. Therefore, bio adhesive dosage form would not appear to offer a solution for extended delivery of drug over a period of more than a few hours.

(c) Swelling System: These are planned to be adequately small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule –shaped tablet whereas 10- 12mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

Recent Developments in the Field of Bilayer Tablets

The introduction of bilayer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit dosage form. Large number of work has been done in this field. Some of the recent findings are explained in the table-1

Shankrayya M, et al (2023) developed bilayer tablet to improve dosing convenience and decrease daily fluctuations in serum CBZ concentration, thereby lowering the incidence of adverse events. In bilayer tablet one layer provides the loading dose by immediate drug release and another layer provides the maintenance dose up to 12 hours by sustained release. The prepared granules were evaluated for its pre-compression, post- compression parameters. In-vitro dissolution study was carried out for 12 hours using USP dissolution apparatus I using 1.2 pH and 7.4 phosphate buffer as dissolution medium. The bilayer tablet showed initial burst release to provide the loading dose of drug followed by sustained release up to 12 hours. Concentration of polymer and super disintegrant ratio influenced drug release profile. As the polymer concentration was increased in sustained release layer the % drug release decreased[17].

Kumar, et al (2023) Formulated and evaluated of bilayer tablet formulation of Telmisartan and Amlodipine. The results concluded that formulation of immediate release layer of Amlodipine using 4-2% concentration of Crospovidone & PVA K30 and 30-20-1.5%. Order of release of drug was found to be zero order, in which R2 value was close to 1. The n value of Korsmeyer Peppas equation was found to be 0.746. Good correlation coefficients are obtained for Higuchi equation. Thus, this optimized bilayer tablet formulation can be successfully used in the treatment of hypertension. It was found that formulation F4 was the best formulation amongst the 5 formulations. Thus, formulation F4 was selected for stability studies. Formulation F4 was analyzed for % Friability and % Drug Release (min), Drug Content Uniformity and Hardness at the end of each month up to three months[18].

Ramakant Sharma, et al (2022) designed sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. For the purpose of enhancement, the bioavailability of furosemide (FR), with controlled release of FR was designed in this study. Because of the low half-life of active material, it was first enhanced by preparing a Bilayer drug delivery system. The major aim of sustained drug delivery is to reduce the frequency of dosing[19].

Israr M, et al (2022) developed controlled-release floating bilayer tablets of clarithromycin and esomeprazole (F1–F4) with different rates of polymeric materials by a direct compression method. The floating lag time and total floating time of all formulations were found to be < 25 s and 24 h, respectively. It can be concluded that such controlled-release effervescent floating bilayer tablets can be efficiently used in clinical practice to reduce dosage frequency and increase patient compliance with continuous drug release for 24 h, which ultimately might enhance therapeutic efficacy[20].

Dong Han Won et al., (2021) developed a fixed dose combination (FDC) bilayer tablet, consisting of high-dose metformin HCl in a sustained release layer and low-dose evogliptin tartrate in an immediate release layer, was developed based on a quality by design (QbD) approach. In addition, the in vitro drug release and in vivo pharmacokinetic studies showed that metformin HCl and evogliptin tartrate in the bilayer tablet is bioequivalent to

those of the respective reference drugs. Furthermore, the physicochemical stability of the optimized bilayer tablet during storage under long-term and accelerated conditions was also confirmed. Therefore, it can be concluded that the QbD approach is an effective way to develop a new FDC bilayer tablet that is easy to scale up for successful commercialization[21].

Manish Kumar Gupta, et al (2021) successfully developed of controlled release formulation along with various features to provide successful drug delivery. Bilayer layer tablets consist of two layers which are slow release and immediate release layers. Controlled release dosage forms have been extensively used to improve therapy with several important drugs[22].

Singh, Neha et al (2021) worked on the formulation development, optimization and In-vitro evaluation of bilayer tablet containing Lansoprazole in the immediate release layer and Amoxycillin in the sustained release layer, using sodium starch glycolate as a super disintegrant for the immediate release layer and the hydrophilic matrix HPMC K100M, hydrophobic matrix Ethyl cellulose are used in the sustained release layer. Bilayer tablet showed as initial burst effect to provide dose of immediate release layer Lansoprazole to control the acid secretion level and the sustained release of Amoxycillin for 24 hours. Immediate and sustained release tablets were formulated by wet granulation method because of the poor flow property of the blends. The prepared bilayer tablet was evaluated. Lansoprazole potentiates the effect of Amoxycillin. Hence the bilayer tablets of Lansoprazole and Amoxycillin were used to improve patient compliance towards the effective management of ulcer[23].

Niranjan, Abadhesh et al (2021) made Bosentan SR Floating Bilayer Tablets with HPMC K4M, HPMC E-15, and HPMC E-15 alone (80%) and in combination with varying percentages of polymer (20&60 percent, 40&40 percent, and 60&20 percent). The hydrophilic polymer HPMC is used to make three different formulations (M4, M8, and M12) of floating Bosentan SR tablets, each with a viscosity grade of 80 percent. M12 formulation was shown to be suitable for SR tablet formulation. According to the findings of this investigation, as floating duration increases, the release rate drops. As a result, it's appropriate for long-term formulation[24].

Ramakant Gundu et al., (2020) developed Push-pull Osmotic Pump (PPOP) bi-layered tablets for Ondansetron HCl ER tablets. The granulation was carried out using non-aqeous solvents followed by compression, seal coating, semi permeable coating, laser drilling (0.6mm) and drug film coating with loading dose. The drug release was controlled by swelleable osmotic polymers of pull layer and push layer and orifice on the surface of tablet. The formulations were optimized for its core composition, extended-release coating (Semipermeable membrane) polymer as to plasticizer ratio and orifice diameter. Optimized formulations were evaluated for micromeritic properties and in-vitro drug release. Stability studies were done as per the ICH guidelines. The results of In-vivo study concludes that the once OSH ER dose consistently maintains plasmaconcentration of drug within the therapeutic window over a period of 24 hours[25].

Maddiboyina B, et al (2020) aimed to progress an ideal gastro retentive drug delivery system intended for directing Losartan and Hydrochlorothiazide as a fixed-dose combination for anti- hypertensive therapy. The bilayer tablets were primed through direct compression method. Losartan was formulated by means of a floating layer expending hydrophilic swellable polymer Hydroxy Propyl Methyl Cellulose K4M, ethyl cellulose (4cps) as a buoyancy enhancer, sodium bicarbonate as a gas spawning agent. The amount of polymer blends remains optimized using 2^3 full factorial designs. The stability revision exhibited no substantial alteration in the appearance of tablets, floating characteristics, drug content and *in-vitro* drug dissolution. Consequently, a biphasic drug release design was effectively accomplished over the formulation of floating bilayer tablets[26].

Sikdar, K.M. et al (2019) focused on formulation and in-vitro evaluation of a fixed dose bilayer tablet of two prominent antihypertensive agents, atenolol and amlodipine. The tablets were designed to immediately release atenolol (ATF1-ATF5) by using different percentage of sodium starch glycolate as super-disintegrant for prompt blood pressure lowering activity and sustain release amlodipine (AMF1-AMF5) by varying the percentage of hydroxy propyl methylcellulose (HPMC) for prolonged activity[27].

Kumari Roshani, et al. (2017) prepared bilayer tablet is innovative period for the successful improvement of controlled release formulation along with a variety of features to provide a technique of successful drug delivery system. Controlled release dosage forms have been comprehensively used to improve therapy with several important

drugs. Numerous approaches are presently utilized in the prolongation of Gastric Retention Time, including floating drug delivery system, swelling and expanding systems, polymeric bio adhesive systems, high-density systems, modified shape systems and other deferred gastric emptying strategy[28].

Ram Pentewar, et al (2016) developed a stable formulation of antihypertensive drugs of angiotensin II receptor antagonist (ARB) as an immediate release and β1-Selective Adrenergic Receptor Blocker (β1-SARB) as sustain release bilayer tablet and evaluate their precompression and post-compression parameters. This further confirms the integrity of pure drugs and no incompatibility of them with excipients. The stability studies were carried out for the optimized batch for one months and it showed acceptable results. The present studies concluded that bilayer tablet of Telmisartan and Metoprolol Succinate is novel approach to prevent hypertension[29].

Ryakala H, et al (2015) investigated combine Nebivolol and Nateglinide for better patient compliance. IR layer was formulated using various superdisintegrants like Crospovidone, Croscarmellose sodium, and sodium starch glycolate and SR layer was formulated using polymers and gums like HPMC E15, ethyl cellulose, Gaur gum, and Xanthan gum. The disintegration and dissolution study of both layers showed that inclusion of surfactant (sodium lauryl sulphate) to the tablet formulation (IR) and dissolution medium (SR) enhanced the release of drugs from both layers. The results reveal that the optimized IR layer of Nebivolol (NBL8) and SR layer of Nateglinide (N9) might be suitable for the treatment of diabetes and hypertension by sequential release of the two drugs in a bilayer tablet. IR-immediate release, SR- sustain release, NBL8-Nebivolol 8, N9-Nateglinide 9[30].

Momin MM, et al (2015) developed a bilayer tablet of venlafaxine hydrochloride for bimodal drug release. In the present investigation authors have tried to explore fenugreek mucilage (FNM) for bioadhesive sustained release layer. The attempt has been made to combine FNM with well-studied bioadhesive polymers like hydroxy propyl methyl cellulose (HPMC), Carbopol, and Xanthan Gum. The formulations were evaluated for swelling Index, ex vivo bioadhesion, water uptake studies, in vitro drug release and dissolution kinetics was studied. The natural mucilage like FNM could be successfully incorporated into tablet with only 20% replacement with HPMC and it showed good bioadhesiveness and sustained drug release[31].

Varu, Mittal et al (2015) formulated, optimized and evaluated of bilayer tablet of Lornoxicam and Thiocolchicoside. In this study Lornoxicam is in immediate release layer and Thiocolchicoside is in sustain release layer. For immediate release layer sodium starch glycolate was used as supredisintigration. And Sustain release layer Xanthan gum was used. From the result formulation L4 was optimize which given the % drug release at 30 min 99.02 %. For sustain release layer check point batch was optimize which gives % drug release at 8 hr 93.19 %[32].

Patel D, et al (2012) prepare and characterize Bilayer tablet formulation containing Metformin HCl in extended-release matrix form and Pioglitazone HCl in immediate release form for the treatment of diabetes mellitus. Different formulations containing Metformin HCl were manufactured using 3^2 factorial designs. Influence of hydrophilic carrier, hydrophobic polymer on drug release was studied. Immediate release layer of Pioglitazone was optimized using different super disintegrants. All formulations were evaluated for percentage drug release. Results confirmed that Bilayer tablet formulation containing extended release of Metformin HCl and immediate release of Pioglitazone HCl could be developed by using melt granulation technique[33].

Conclusion

The bilayer tablet is an improved advanced technology to overwhelm the inadequacy of the single-layered tablet. It offers an excellent opportunity for manufacturers to separate themselves from their competitors, improve the efficacy of their products, and protect against impersonator products. There are numerous applications of the bilayer tablet it consists of massive partially coated or multi-layered matrices.

Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products efficacy and protect against impersonator products. Bilayer layer tablets have been consist of two layers which is slow release and immediate release layer proposed a bilayer tablet, in which the one layer is

formulating to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time.

Bilayer tablets offer several advantages over conventional single layer tablets in that respect and also offer an excellent opportunity for manufactures to separate themselves from their competitors, improve their product efficacy, and protect against impersonator products. To overcome this hurdle a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management.

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