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A review on bilayer tablets of multi drug combination of anti-retro viral drugs

Patil Sagar N*, Dr. Shailesh Sharma

Department of Pharmaceutics, NIMS University of Pharmacy, NIMS University, Jaipur, Rajasthan, India-303121

***Corresponding Author: Patil Sagar N**

ABSTRACT

Multilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug(s) action. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Trilayer tablets are prepared with one layer of drug for immediate release while second and third layers designed to release drug, later, either as second dose or in an extended release manner. These Multilayer tablets are suitable for sequential release of two or more drugs in combination, separate incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Acquired immune deficiency syndrome epidemic is one of the greatest challenging facing the medical community today. Combination of three drugs commonly used in the management of the Human Immunodeficiency Virus (HIV) infection. Zidovudine (AZT), the first anti-HIV compound approved for the clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents and Zidovudine is water soluble and soluble at all pH ranges and absorbs throughout the gastrointestinal tract and so sustained release tablet is better approach than the conventional dosage form. Lamivudine is a potent antiviral agent used in the treatment of AIDS. Lamivudine is a potent nucleoside analog reverse transcriptase inhibitor. Lamivudine is rapidly absorbed with a bioavailability of over 80% following oral ingestion. Lamivudine are administered multiple times a day because of its moderate half-life of 5 to 7 hours. Tenofovir disoproxil is an antiretroviral medication used to prevent and treat HIV/AIDS and to treat chronic hepatitis B. The active substance is tenofovir, while tenofovir disoproxil is a prodrug that is used because of its better absorption in the gut.

Keywords: Multilayer tablets, HIV, Zidovudine, Lamivudine, Tenofovir disoproxil

INTRODUCTION

Bilayer tablets material involves both the compressibility and consolidation. The bilayer tablets preparing by using different techniques such as OROS® push pulls Technology, L-OROSTM Technology, EN SO TROL Technology, DUREDAS™ Technology and DUROS Technology. 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. Now a day's bilayer tablets are prepared such as Atorvastatin, Atenolol, Nifedipine, Aspirin, Isosorbide 5-mono-nitrate, Pioglitazone HCl, Gliclazide, Losartan potassium, and Trimetazidine hydrochloride, clopidogrel bisulphate. On the basis of these considerations, we have proposed a bilayer tablet, in which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer [1].

Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredients (API), 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, to administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery[2].

Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers [3]. However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. Therefore, the major problem, that has to be overcome, is to understand in detail the sources of these problems in micro-and macroscales and to develop remedies to solve them during solid dosage delivery design [4, 5].

Applications [6]

- Bi-layer tablet is suitable for sequential release of two drugs in combination.
- Separate Two Incompatible Substances.
- Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.
- Promoting Patient Convenience and Compliance.
- Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet
- Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
- Bilayer tablets are used to deliver the two different drugs having different release profiles.

Advantages [7, 8]

- They are used as an extension of a conventional technology.
- Potential use of single entity feed granules.
- Separation of incompatible components.
- Patient compliance is enhanced leading to improved drug regimen efficacy.
- Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy.

Disadvantages [9]

- Adds complexity and bilayer rotary presses are expensive.

- Insufficient hardness, layer separation, reduced yield.
- Inaccurate individual layer weight control.
- Cross contamination between the layers.

Need of Bilayer Tablets [10-12]

- For the administration of fixed dose combinations of different APIs, prolong the drug product lifecycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
- Controlling the delivery rate of either single or two different active pharmaceutical ingredients
- To modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release.
- To separate incompatible Active pharmaceutical ingredient (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).

Challenges in Bilayer Manufacturing [13]

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

Delamination

Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination

When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

Production yields

To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets.

Cost

Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

TYPES OF BILAYER TABLET PRESS [14-15]

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

Single sided press

The simplest design 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 powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of single sided press

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping, and hardness problems.

Dwell time

Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

Compression force

Many bilayer formulations requires a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer. Above 100daN, this ability may be lost and bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.

Double sided tablet press

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 the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

Bilayer tablet press with displacement

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 pre- compression force.

Preparation of Bilayer Tablets [16-19]

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included. To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation

It is the property of the material in which there is increased mechanical strength due to interparticulate interaction (bonding). The compression force on layer 1 was found to be major factor influencing tablet delamination.

General properties of Bi-Layer Tablet Dosage Forms [20]

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- 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.
- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

CHARACTERIZATION OF BILAYER TABLET [23-24]

Particle size distribution

The particle size distribution was measured using sieving method

Photo-microscope study

Photo-microscope image of TGG and GG was taken (X450 magnifications) by Photomicroscope.

Angle of repose

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

Tan ø=h/r

Where, h = Height, r = Radius of the powder cone.

Moisture sorption capacity

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture Sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate Uniformly

distributed in petri-dish and kept in stability chamber at 37±1°c and 100% relative Humidity for 2 days and investigated for the amount of moisture uptake by difference Between weights.

Density

The loose bulk density (lbd) and tapped bulk density (tbd) were determined and Calculated using the following formulas.

LBD ¼ weight of the powder=volume of the packing ð2þ

TBD ¼ weight of the powder=tapped volume of the packing ð3þ

Compressibility

The compressibility index of the disintegrate was determined by Carr's compressibility index.

C = 100 x (1-þb/þt)

ANTI-RETRO VIRAL DRUGS [26-31]

In development of the dosage forms for the treatment of the infectious diseases such as HIV there is need to shift from single active drug dosage form to the multiple drug dosage forms. Human immune deficiency virus (HIV) has been identified etiological agent responsible for Human Immune Deficiency Syndrome (AIDS), a serious diseases characterized by destruction of immune system and inability to fight life threatening opportunistic infections.

The medication used to treat HIV/AIDS is known as anti retrovirals (ARVs). These drugs are not a cure for HIV infection and AIDS but help to suppress the virus for a period of time thereby allowing the immune system to recover to some extent. HIV (human immunodeficiency virus) infects a certain type of immune cell known as the CD4+ T-cell, replicates within it and then destroys it. By doing so the viral population increases within the body while the numbers of CD4+ T-cells gradually declines. This means that the virus grows in numbers infecting an ever increasing number of CD4+ T-cells. At the same time the host defenses through the action of the CD4+ T-cells is gradually diminished. This gives other types of infectious microbes the chance to infect the host and cause severe infections that can be fatal. Anti-retroviral is therefore the most effective way to manage HIV/AIDS by slowing down disease progression. It spares the immune system for long periods of time and ultimately prolongs one's lifespan.

The antiretroviral therapy (ART) has transformed infection with HIV into manageable chronic condition; complete viral eradication is still not possible. Even prolonged suppression of plasma viremia, latently infected, CD4(+)T cells still persist[1].Therefore treatment goal still focuses on the reducing HIV related morbidity, prolonging action, improve quality of life and reducing the viral replication.

Treatment with a single drug targeting a specific receptor is no longer considered optimal in the treatment and management of complex diseases such as HIV/AIDS, diabetes, and cardiovascular disease. To achieve this goal we researchers should move from current medication practice (i.e. administration of single drug dosage form which is unable to keep viral replication at low for longer period and produces the resistance early, capable of less long lasting therapy for AIDS and also have to take more number of dosage forms for treating AIDS. Example of single dosage forms: Nevirapine – 50 mg/5ml - Oral suspension - Cipla Ltd – INDIA, Lamivudine – 150 mg Tablets - Aspen Pharmacare - SOUTH AFRICA, Stavudine – 1 mg/ml Oral solution - Bristol-Myers Squibb - USA) to a potent antiretroviral regimen from multiple drugs which preferably include 2 or more drugs.

These anti retrovirals work in different ways to counteract HIV replication. Highly active antiretroviral therapy (HAART) is a combination of three or more mutually compatible and synergistic antiretroviral agents belonging to different groups. Usually the drugs selected are such as the different molecular mechanism of action meaning that it works in different ways to suppress HIV replication. The purpose of HAART is to:

1. maximize the antiviral activity
2. minimize the toxicity of ARVs
3. restrict the development of drug resistance

Henceforth, there is a need to develop combination of drug therapy to treat AIDS called as fixed dose combinations (FDC's). FDC's are recommended by the world health organization [WHO] treatment guidelines and several generic FDC's, which have been pre-qualified by the WHO with a majority of them being marketed quite actively for some time now in a number of countries in Africa and Latin America. The various

advantages of FDC's when compared to the separate ARV regimens are ease of use, better adherences to the dosage schedules, reduced risk of drug resistance and increased affordability and hence there is need to develop stable compositions for FDC's. Also from patient perspective poly pharmacy and the complexity of the medication regimen are important factors for noncompliance[3]. Bangalore et al. conducted a review of randomized, controlled trials and a retrospective analysis of medication compliance for nine studies with one for HIV that compared FDC's with three-drug regimens of the same medication and concluded that FDC's resulted in a 24–26% greater patient compliance across all groups.

In general, regulatory guidelines have demerited FDC's products that promote convenience claims without providing additional health benefits. However, improving compliance and adherence to therapy brought about by reducing the pill burden or simplifying the dosing regimen, such as once daily, may be sufficient proof to provide regulatory flexibility[5]. Hence the FDC's is also advantageous for the regulatory.

Formulation and manufacturing of the multi active components dosage form present unique challenge:

1. Physico-chemical incompatibility.
2. Change in the rate and extent of *in-vitro* and *in-vivo* bioavailability.
3. Undesirable mechanical powder flow and compression characteristics.
4. Increase in the dosage bulk volume due to additional drug loading particularly high dose combination and FDC's.

For these reasons, a conventional tablet or capsule dosage form may rarely be sufficient to meet the various stability, bioequivalence, and commercial manufacturing requirements.

Multilayer tablet / Bilayer tablet technology is particularly useful for formulating FDC's. It allows for compression of separate drug layers, thus minimizing physicochemical incompatibility and stability problems that may arise from the intimate contact of individual drug compositions. Bilayer tablet technology also provides flexibility in combining formulations with sustained-release and immediate-release layers in the same dosage unit. This was utilized in developing combinations of extended release niacin (controlled-release layer) and immediate release layer of laropiprant with simvastatin or atorvastatin (Tredaptive in European Union [EU]).

The present invention relates to stable bilayer tablets for multi active combination of antiretroviral agents. More particularly, the present invention relates to stable dosage form comprising zidovidune, lamivudine, tenofovir/ tenofovir disoproxil fumarate by suitable tablet technology. Thus FDC's of multi active components continues to be in the forefront of innovations and enhanced drug therapies for the treatment and management of complex diseases.

CONCLUSION

Multilayer tablets are novel drug delivery systems where combination of two or more drugs in a single unit having different release profiles which improves patient compliance, prolongs the drug(s) action. These Multilayer tablets are suitable for sequential release of two or more drugs in combination, separate incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Acquired immune deficiency syndrome epidemic is one of the greatest challenging facing the medical community today. Combination of three drugs commonly used in the management of the Human Immunodeficiency Virus (HIV) infection.

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