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Review Article

BI-LAYER TECHNOLOGY- AN EMERGING TREND: A REVIEW

Pradeep Reddy*.T[1], Divya Rao.V[2], Ravi Kumar.K[2]

1. Priyadarshini College Of Pharmaceutical Sciences, Chowdaryguda, R.R District-501301, AP, India.
2. Mallareddy Institute Of Pharmaceutical Sciences, Dulapalli, R.R District-500014, AP, India.

***Corresponding Author: Email** ravi445@gmail.com

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ABSTRACT

Combination therapy has various advantages over monotherapy. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (monolithic or bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield etc. Using a modified tablet press may therefore not be best approach in producing a quality bi-layer tablet under GMP conditions, especially when high production output is required. There are various applications of the bi-layer tablet consists of monolithic partially coated or multilayered matrices.

Keywords: Combination therapy, Monolithic tablets, Bilayer tablets, Bilayer tablet presses, Common bilayer problems.

INTRODUCTION

Nowadays various developed & developing countries move towards combination therapy for treatment of various diseases & disorders requiring long term therapy such as hypertension, diabetes and Cardio vascular diseases. Combination preparation plays an important role in clinical treatment because of its better and wider curative synergism and weaker side effects[1]. Combination therapy may be achieved by giving separate drugs or where available by giving combination drugs (monolithic or bilayer dosage forms) which are dosage forms that contain more than one active ingredient[2].

Monolithic Tablets (Matrix or Single layer): The term monolithic tablet refers to tablet containing no sub units that have different drugs[3].

Advantages

Less cost production over bilayered tablets.

Disadvantages

There should be compatibility between the two active ingredients.

Bilayered Tablets

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layered tablets for a variety of reasons: patent extension, therapeutic, marketing to a name, a few

Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit[4].

Types of Bilayer Tablets

The term bilayered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous)[5].

Homogenous type

Bilayer tablets are preferred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution and release characteristics . 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.

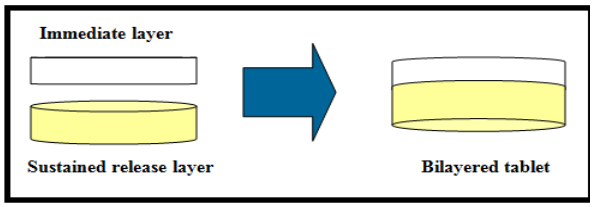

Fig.1 Bilayered tablets (same drug with different release pattern-homogenous)

Heterogenous type

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances.

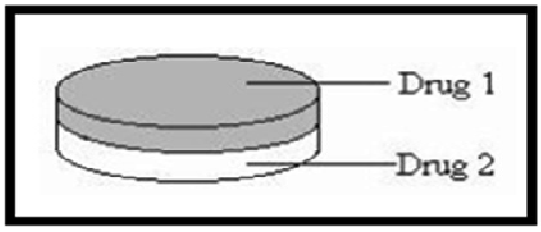

Fig.2 Bilayered tablets (with two different drugs-heterogenous)

Advantages

They are used as an extension of a conventional technology

- Ability to combine different release rate. IR and SR in the same tablet for chronic condition requiring repeated dosing.
- Promoting patient convenience and compliance because fewer daily doses are required compared to traditional delivery system.
- Two different drugs in the same dosage form.
- Separation of incompatible components thus minimizes physical and chemical incompatibilities.
- Solve degradation problem.
- Reduce pill burden to patient.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy[6].

Advantages of Bilayer tablets over conventional tablets

- Blood level of a drug can be held at consistent therapeutic level for improved drug deliver, accuracy, safety and reduce side effects. Reduction of adverse side effect can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced.
- Patient convenience is improved because fewer daily doses are required compared to traditional systems. Patient compliance is enhanced leading to improved drug regimen efficacy.
- Bilayer tablets readily lend themselves to repeat action products; where in one layer on layered tablet provides the initial dose, rapidly disintegration in the stomach, the other layer are insoluble in gastric media but are released in the intestinal environment.
- Separate physically or chemically incompatible ingredients[7].

Disadvantages

- In accurate individual layer weight control.
- Cross-contamination between the layers.
- Insufficient hardness.
- Reduced yield.
- Adds complexity and bilayer rotary presses are expensive[8].

GENERAL PROPERTIES OF BI-LAYER TABLET DOSAGE FORMS

- It should have graceful product identity free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.

- Should have physical and chemical stability
- The bi-layer tablet must release drug in an expectable and reproducible manner.
- Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents[9].

APPROACHES FOR LAYERED TABLETS

1. Multi Layered tablets – two to three component systems.
2. Compression coated tablets – tablet within a tablet.
3. Inlay tablet – coat partially surrounding the core.

Multilayered tablets (Bi, Tri)

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different colour to produce a distinctive looking tablet. Dust extraction is essential during compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down. This avoids granules intermixing if the machine vibrates.

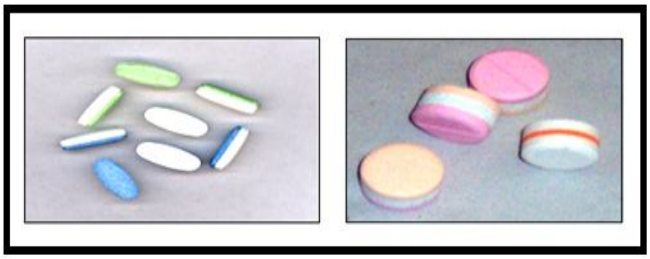

Fig.3 Bilayer tablets, Tri layer tablets

Compression coated tablets

This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet and --------- -prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.

Inlay tablets

A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet.

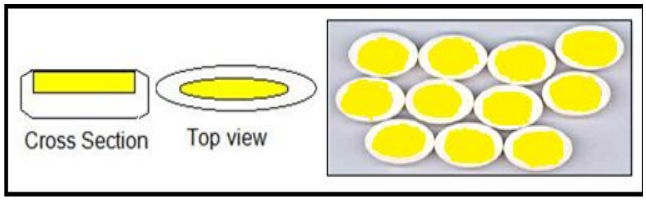

Fig.5 Inlay tablets

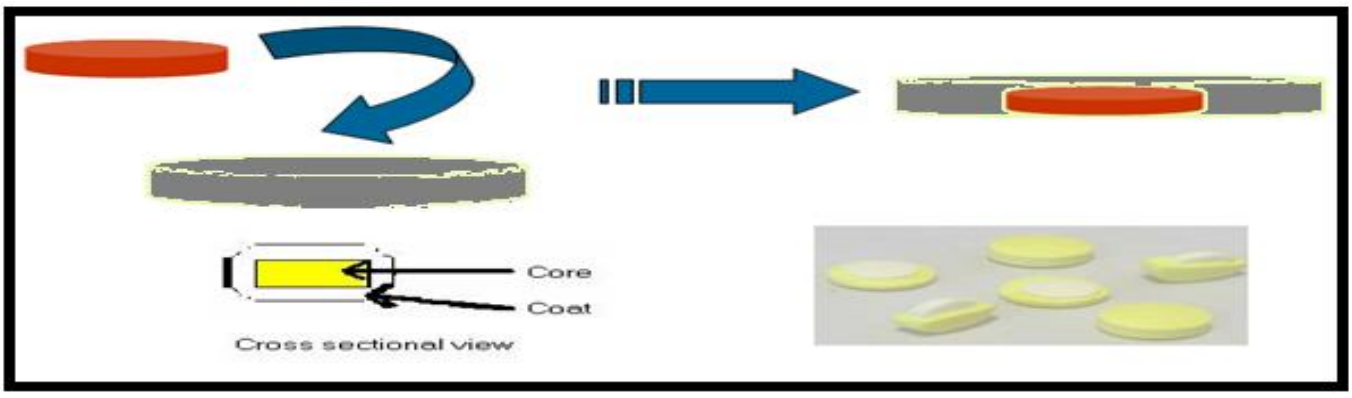

Fig.4 Core coated tablets

To reduce capital investment quite often existing but modified tablet presses are used to develop and produce such tablets. The development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required[10].

BILAYERED TABLETS: QUALITY AND GMP-REQUIREMENTS

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of preventing capping and separation of the two individual layers that constitute the bilayer tablet[11].

Ideal properties for bilayer tablet press

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- Providing sufficient tablet hardness and High yield.
- Preventing cross-contamination between the two layers
- Producing a clear visual separation between the two layers
- Accurate and individual weight control of the two layers

TYPES OF BILAYER TABLET PRESS

1. Single sided tablet press.
2. Double sided tablet press or "compression force" controlled tablet press.
3. Bilayer tablet press with displacement monitoring.

Single sided tablet 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 force 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 tablet 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. This may be corrected by reducing the turret- rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

Double sided tablet presses

A double sided press offers an individual fill station, pre – compression and main compression for each layer. In fact the bi-layer tablet will go through four compression stages before being ejected from the 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 main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when required.

Advantages

1. Displacement weight monitoring for accurate and independent weight control of the individual layer.
2. Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
3. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross contamination between two layers.
5. Maximized yield.

Limitations

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression. Bonding is too restricted if first layer is compressed at a high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet

weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

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 pre compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

Advantages

- Weight monitoring/ control for accurate and independent weight control of the individual layers.
- Low compression force extends on the first layer to avoid capping and separation of the two individual layers.
- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers[12, 13].

BI-LAYER COMPRESSION BASICS

A) Initial layer die filling and compaction.

B) Initial layer compaction showing the predominant stress transmission profile.

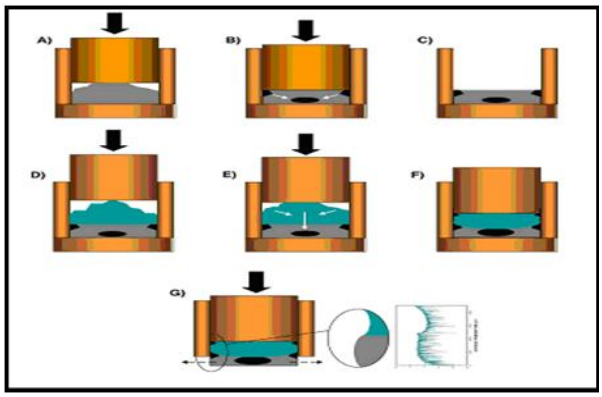

Fig.6 A schematic diagram showing the different stages occurring during bilayer tablet uniaxial compaction.

C) Density profile of initial layer before die filling of the final layer.

D) Final layer die filling and compaction.

E) Final layer compaction showing the predominant stress transmission profile.

F) Density profile of bilayer tablet before ejection.

G) Ejection of a bilayer tablet.

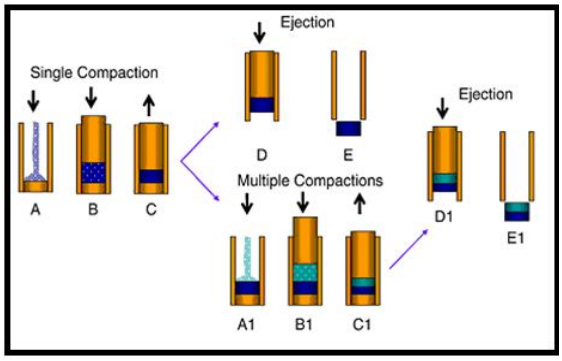

Fig.7 Schematic diagram showing the manufacture of single and bilayered tablets utilising uniaxial compaction.

Dashed arrows show the postulated radial expansion due to energy dissipation. Black areas correspond to regions of localized high density. Arrows show the direction of the applied stress[14, 15].

A .Die filling

B .Compression

C. Decompression

D. Lower punch removal and reapplication of load to the upper punch

E. Tablet fully ejected.

MANUFACTURING PROCESS OF BILAYER TABLET

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's propensity for delamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their

vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet[16]. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity[17].

Compaction

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 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 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 one was found to be major factor influencing tablet delamination.

Compression force for bilayer tablets

Since the material in the die cavity is compressed twice to pro- duce a bi-layer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually making the tablet interface weaker. This may result in capping or de-lamination of the tablet along the interface either during manufacturing or immediately after the level of compression force used in the first layer compaction determines the degree of surface rough- ness of the first layer. The higher the first layer compression force, the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first layer compression force. It implies that the extent of plastic/elastic deformation of the first layer has profound effect on the strength of the interface. Thus, understanding the interaction and adhesion behavior between different layers composed of various ingredients with differing physico-chemical properties during compaction is critical to understand the failure mechanisms of bi-layer tablets. Understanding of material attributes of the excipients and API that undergo compression and compaction is decisive in predicting the interaction[18].

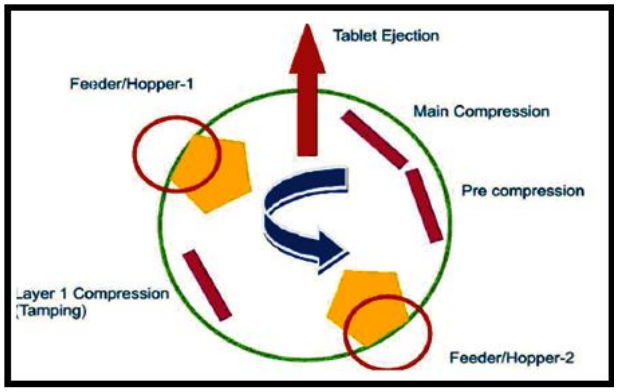

Fig.8 Bilayer compression process

CHALLENGES IN THE FORMULATION OF BILAYERED TABLETS

- Lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping).
- If the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent

layers, first layer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per sure (inefficient or uncontrolled process) 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[10].

CONCLUSION

Bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. To develop a dynamic bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management. Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines. Whenever high quality bi-layer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution.

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