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A REVIEW: ON VARIOUS TECHNIQUES FOR BILAYERED TABLETS

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ABSTRACT

Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer 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). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly. Bi-layer tablets offer definite advantages over conventional release formulation of the same drug. 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.

KEYWORDS: Bi-layered tablet, API (Active Pharmaceutical Ingredients), adjacent layer, conventional release, insufficient hardness.

INTRODUCTION

A tablet is mixture of active substance and excipients usually in powder form pressed or compacted into a solid. The excipients includes binders, glidents (flow-aids), and lubricants to ensure efficient tableting, disintigrants to ensure that the tablet breaks up in the digestive tract; sweeteners or flavours to mask the taste of the bad tasting active ingredients and pigments to make uncoated tablets visually attractive. A coating may be applied to hide the taste of tablets components, to make the tablet smoother and easier to swallow and to make it more resistant to environment extending its self life.

The compressed tablet most popular dosage form is used for today. About two third prescriptions are dispensed as solid dosage forms and half of these are compressed tablets.

Bi-layer tablet is new era for successful development of controlled release formulation along with various features to provide successful drug delivery system. Bi-layer 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.

The manufacture of bi-layer tablets, produced by sequential compaction of loose powder layers has become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. 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 loading dose and second layer is maintenance dose. In case of bi-layered tablets drug release can be rendered almost unidirectional if drug can be incorporated in the upper non adhesive layer its delivery occurs into the whole oral cavity.

The immediate release layer of bi-layer tablet has worked as the loading dose and the sustained release layer has maintained therapeutic plasma drug concentration for prolonged time. 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 the best approach in producing a quality bi-layer tablet under GMP-conditions, especially when high production output is required.

Adavantages Of Tablet Dosase Form[1]

1. Tablet is unit dosage form and offers the best capabilities of all oral dosage forms for accuracy in size and content of the lowest variability
2. Tablet dosage form which is the lowest cost of manufacture (if it is calculated per dose)
3. Tablet is an oral dosage form of the lightest, most compact, easiest and most inexpensive way to packed and shipped
4. The product identification on the tablets the most easy and inexpensive, requiring no additional work steps when using the printer surface that monogram or arising accesories
5. Tablet can be used as a product of specific release profiles, such as the release in the intestine or slow release products
6. Tablet is an oral dosage form of the most easy to be produced in bulk (large scale)

Disadavantages of Tablet Dosase Form[2]

1. Some drugs cannot be compressed into solid and compact, depending on its amorphous state, flocculation, or low density.
2. Drugs moistened difficult, slow dissolves, moderate or high dose, high optimum absorption via the gastrointestinal tract or any combination of the properties above, it would be difficult or impossible to be formulated and fabricated in the form of tablets that produce sufficient drug bioavaibility
3. Medicine that tastes bitter, a drug with the smell was terrible and cannot be eliminated, or drugs that are sensitive to oxygen or air humidity needs to encapsulation or compression cloaking before (if possible) or require coating first. In this case, the capsule is a cheaper way out Ideal Characteristics of Bilayer Tablet[4-5]
4. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
5. It should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
6. 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.
7. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Objectives Behind Designing Bilayer Tablet[6-10]

1. To control the delivery rate of either single or two different active pharmaceutical ingredient
2. 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).
3. 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
4. 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

Advantages of The Bilayer Tablet

1. It is the dosage form and offers the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lower compared to all other oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to pack and strip.
5. Easy to swallow with least tendency for hangup.
6. Objectionable odour and bitter taste can be masked by coating technique.
7. Suitable for large scale production.
8. Greatest chemical and microbial stability over all oral dosage form.

Disadvantages of bilayer tablet

Difficult to swallow in case of children and unconscious patients.

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
3. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

Type of Bi-Layer Tablet

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement.

(1) Single sided tablet press

The simplest design is the single sided press with both chambers of the double feeder separation from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first-layer powder followed by the second layer powder. Then the intact tablet is compressed in one or two steps.

Limitations of the single sided press

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

(2) Double sided tablet press or "compression force" controlled 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 mandatory.

Advantages

- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at

- A clear visual separation between the two layers.

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.

(3) Bi-layer 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 operation point, but depends on the applied precompression 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.

The upper pre-compression roller is attached to an air piston which can move up and down in air cylinder. The air pressure in the cylinder is set as a product parameter at initial product set-up -and is kept at a constant value by the machine's control system. This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller are pushed downwards against affixed stop. The lower pre-compression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower pre-compression determines the precompression height. At every pre-compression the upper punch hits the upper roller and is initially pushed downwards into the die. As the lower punch is pushed upwards by the lower roller the power is being compressed, while the exerted compression force increases. At a certain point the reaction force exerted by the power on the Upper punch equals the force

exerted by the air pressure on the piston. The punch has to continue its way under the roller because the torrent is spinning.

Advantages

- Weight monitoring /control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

Various Techniques For Bilayer Tablet

1) OROS Push Pull Technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.1). The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

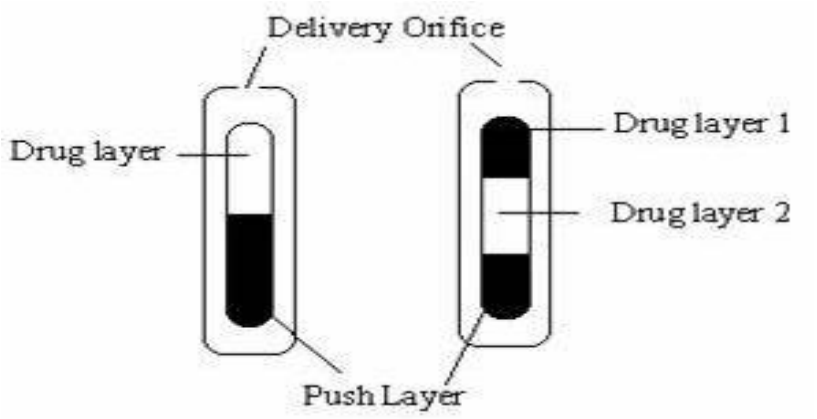

Fig. 1: Bi-layer and tri-layer OROS Push pull technology.

2) L-OROS tm Technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi-permeable membrane, drilled with an exit orifice (Fig.2).

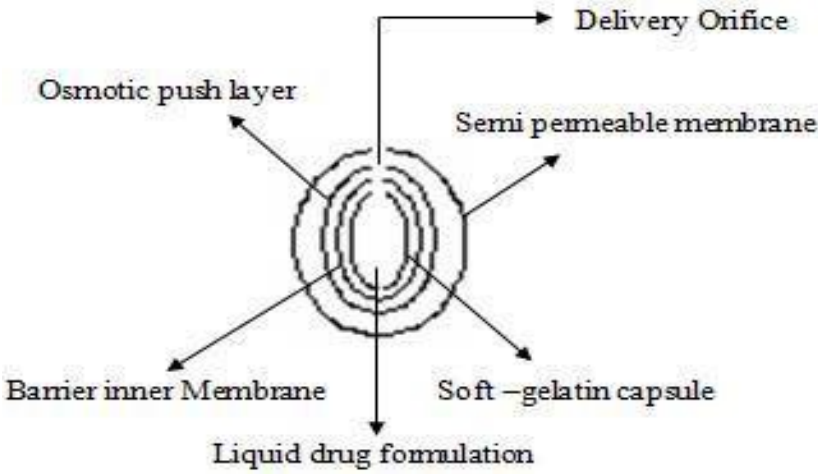

Fig. 2: L – OROS tm technology.

3) EN SO TROL Technology

Solubility enhancement of an order of magnitude or create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.

4) DUROS Technology

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 3).This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or Year. Fig. 3 DUROS Technology.

Elan drug technologies' Dual release drug delivery system (DUREDAS™ Technology) is a bi-layer tablet which can provide immediate or sustained release of two drugs or different-release rates of the same drug in one dosage form. The tab letting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

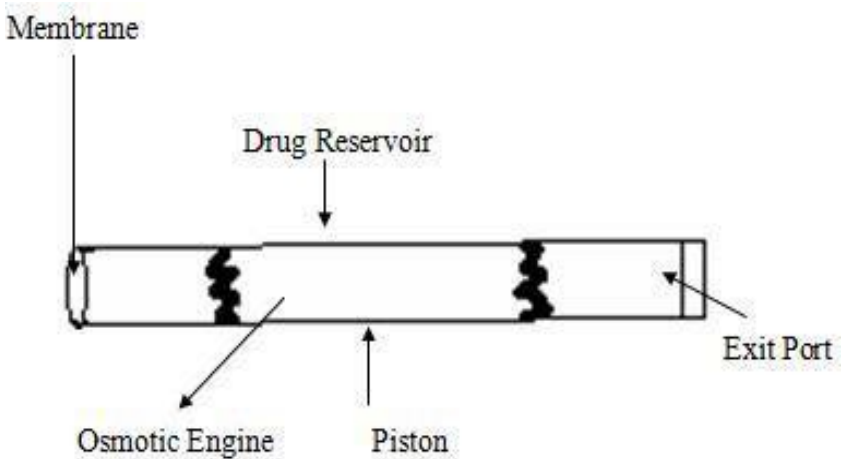

Fig. 3: DUROS Technology.

Benefits offered by the DUREDAS™ technology includes

1) Bi-layer tablet technology.
2) Tailored release rate of two drug components.
3) Capability of two different CR formulations combined.
4) Capability for immediate release and modified release components in one tablet.
5) Unit dose, tablet presentation.

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix (http://www.port/ technology.com).

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