International Journal of Research and Reviews in Pharmacy and Applied science

www.ijrrpas.com

AN OVERVIEW ON BILAYER TABLETS

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ABSTRACT

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is better than the traditionally used mouthwash,sprays,gels. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. 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. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are currently developing bilayer tablet for a variety of reason: patent extension, therapeutic, marketing to name a few. To reduce capital investment quite often existing but modified tablet presses are used to develop such tablets. The present article provides an introduction to bilayer tablet technology, advantages and disadvantages, various techniques, quality and GMP requirements, characterization and evaluation of bilayer tablets.

KEY WORDS: Bilayer tablet, various techniques, bilayer tablet presses, GMP requirements for bilayer tablets.

INTRODUCTION[1,2]

In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance.

Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation, and to enable the development of different drug release profiles (immediate release with extended release)

NEED OF BILAYER TABLETS[3,4,5]

1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/ mucoadhesive delivery systems, fabricate novel drug delivery systems such as chewing divice and floating tablets for gastro-retentive drug delivery.
2. 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.
3. Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
4. 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).

ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM[6,7,8]

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Objectionable odour and bitter taste can be masked by coating technique. Suitable for large scale production.
3. Cost is lower compared to all other oral dosage form. Lighter and compact. Easiest and cheapest to package and strip.
4. Greatest chemical and microbial stability over all oral dosage form.

DISADVANTAGES OF BI-LAYER TABLET DOSAGE FORM[6,7,9]

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. 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
4. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

TYPES OF BILAYER TABLETS

The term bilayered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous)[10]

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, wither as second dose or in an extended release manner.

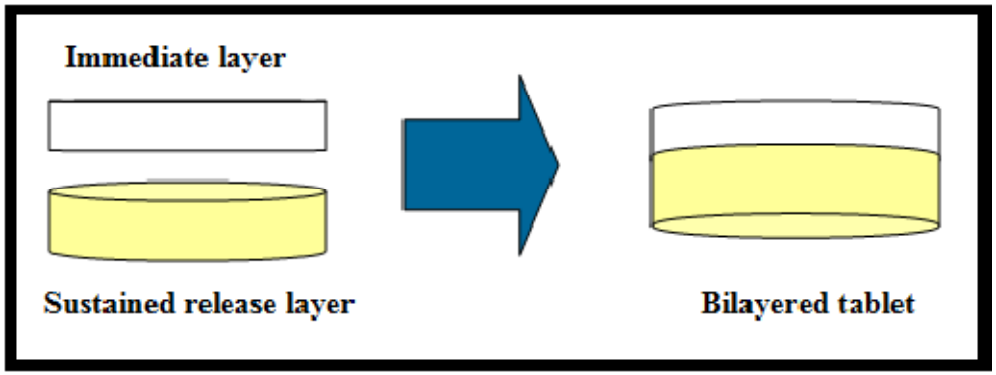

Fig.1 Bilayered tablets (same drug with different release pattern-homogenous)

Heterogenous type

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

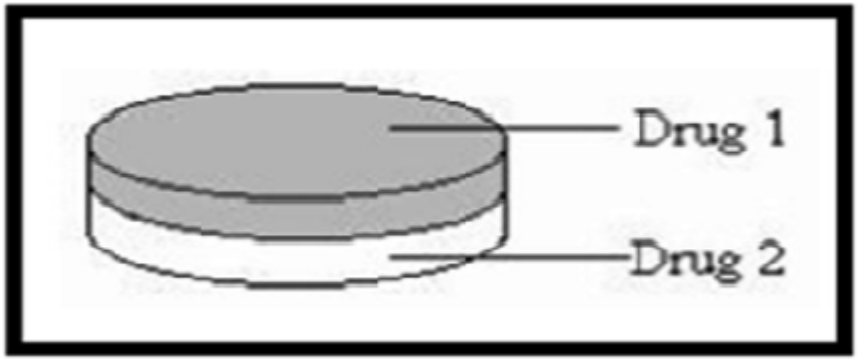

Fig.2 Bilayered tablets (with two different drugs-heterogenous)

VARIOUS TECHNIQUES FOR BILAYER TABLET

DUREDAS[11,12]

Duredas or dual release drug absorption system (Elan Corporation) utilizes bilayer – tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct – compression steps that combine and immediate release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.

Benefits offered by the DUREDAS technology include

- Bilayer tableting technology
- Capability of two different controlled release formulations combined
- Capability for immediate release and modified release
- Components in one tablet.
- Unit dose, tablet presentation

Geomatrix technologies[12]

Geomatrix system is a multilayer tablet with a matrix core containing the active ingredient and one or more modulating layers (barriers) applied to the core during the tableting process. The function of these barriers is to delay the interaction of the core with the dissolution medium. Eight geomatrix technologies are designed to meet a wide range of therapeutic objectives: zero – order release provides a constant rate of drug release over a defined period of time; binary release is used to provide the controlled release of two different dugs in a single tablet; quick-slow release provides a quick burst of drug release followed by a constant rate of release over a defined period of time; slow-quick release provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time; positioned release delivers the drug to a predetermined position in the digestive system before it begins to release the active drug components.; accelerated release provides a constantly accelerating rate of drug release; delayed release provides a predetermined time lag before it begins releasing drug molecules; multiple pulse provides an initial quick burst of drug release followed by a predetermined period of no release. Some of the drugs that are marketed based on this technology are diltiazem hydrochloride, nifedipine and diclofenac sodium.

OROS push pull technology[13]

This system Consist of mainly two or three layer among which the one or more layer are essential of the drug and other are consists of push layer (Fig.1). The drug layer mainly consist of drug along with two or more different agents. So this drug layer comprises of addition of suspending agent and osmatic agent.

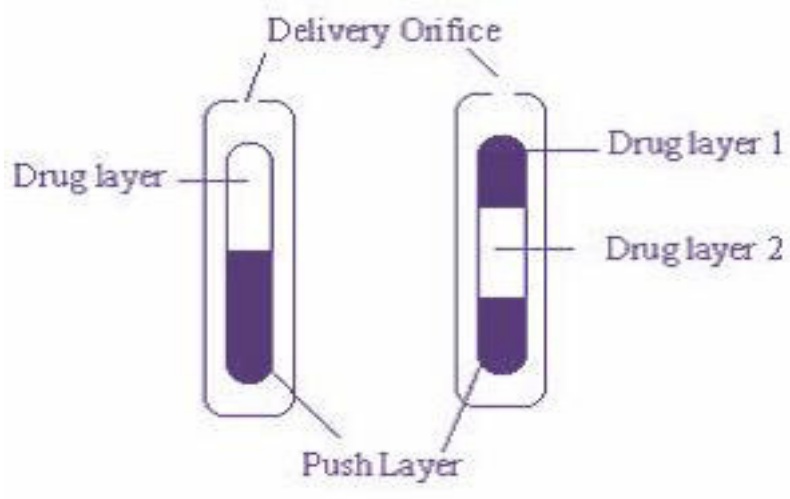

Fig.3 Oros Push Pull Technology

L-OROS tm technology[13]

This system used for the solubility issue Alzadevolped the L-OROS system whwre a liquid soft containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmatic push layer and then a semi permeable membrane drilled with an exit orfice

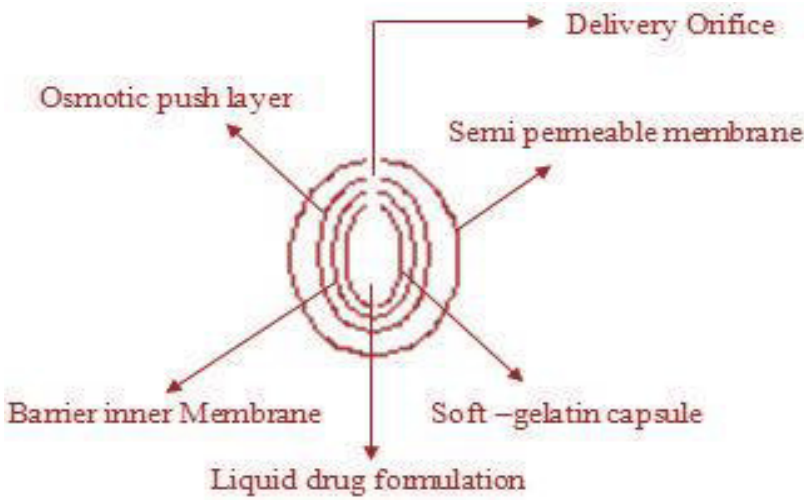

Fig.4 L-OROS tm technology

EN SO TROL technology[13,14]

Solubility enhancement of an order magnitude or to 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.

Fig.5:EN SO TROL technology

DUROS[12,13]

Duros (alza corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including peptides, proteins, and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year.

Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is manufactured from titanium because such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, Viadur(leuprolide acetate implant), which is based upon this technology, has been approved for once-yearly palliative treatment of advanced prostate cancer.

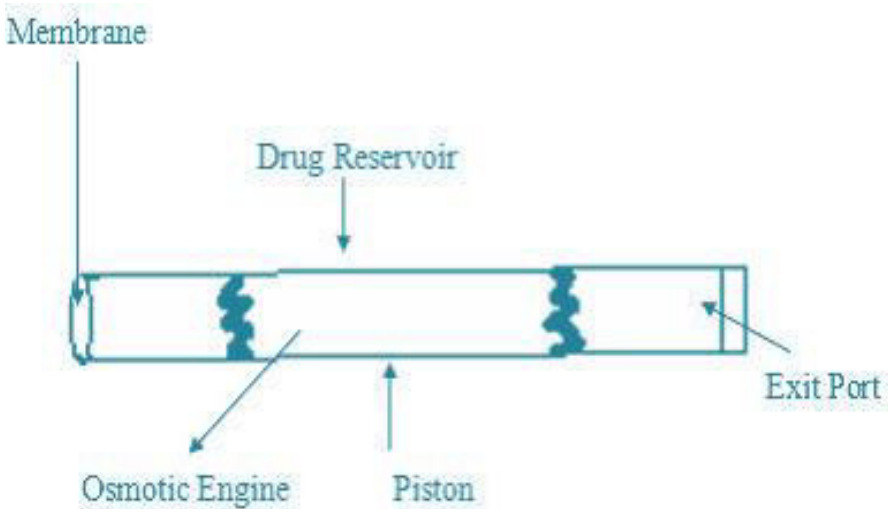

Fig.6 Duros

GEMINEX [15]

Geminex is a dual drug delivery technology that can deliver one or more drugs at different times. The geminex technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize side effects. The benefit of geminex to the pharmaceutical industry, and ultimately to patients, is that two different actives or the same active can be delivered at different rates in a single tablet. Penwest is actively applying its geminex technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer, and disorders of the central nervous system.

PRODASor programmable oral drug absorption system.

Prodas or programmable oral drug absorption system (elan corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled release minitablets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Minitablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate release, delayed release, and controlled release minitablets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitablets formulated with different active ingredients.

Erodible molded multilayer tablet[16]

Eaglet erodible molded tablets arean erosion-based platform. It has the advantage of delivering zero order or delayed release with minimal impact from the gastrointestinal conditions. Eaglet erodible molded multilayered tablets are prepared by injection molding eaglet technology contains a coat and a matrix. Drug release is controlled through the gradual erosion of the matrix part. The mode and rate of release are designed and engineered by altering the matrix, the coat, and the geometry to achieve either a zero-order release or a delayed release. For a zero-order release, a drug is dispersed through the matrix. The coat is biodegradable but has poor water permeability to prevent its penetration. The matrix tends to erode when in contact with available water. The erosion of the matrix is caused by GI fluids and promoted by gut movements in the GI tract. The drug release is mediated almost wholly by erosion because the dosage form is designed to slow down the water diffusion into the matrix. It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water. Eaglet delivery technology is developed based on standard plastic injection molding to ensure accuracy, reproducibility, and low production cost.

BILAYER TABLETS: QUALITY AND GMP REQUIREMENTS[17]

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.
- Providing sufficient tablet hardness
- Preventing cross contamination between the two layers
- Producing a clear visual separation between the two layers
- High yield
- 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 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.
- Maximum prevention of cross contamination between the two layers.[18,19]

BILAYER COMPRESSION BASICS

a) Initial layer die filling and compaction
b) Initial layer compaction showing the predominant stress transmission profile.
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.

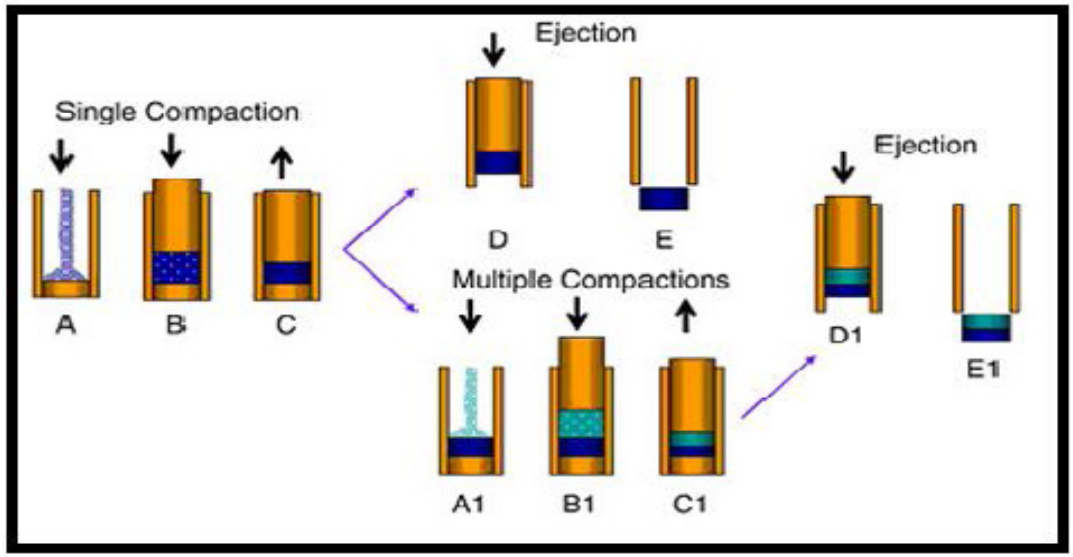

Fig.7.Schematic diagram showing the manufacture of single and bilayered tablets utilizing uniaxial compaction

Dashed arrows show the postulated radiant expansion due to energy dissipation. Black areas correspond to regions of localized high density. Arrows show the direction of the applied stress[20,21]

a) Die filling
b) Compression
c) Decompression
d) Lower punch removal and reapplication of load to the upper punch
e) Tablet fully ejected.

PREPARATION OF BILAYER TABLETS[17,22,23,24,]

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. The compression force on layer 1 was found to be major factor influencing tablet delamination.

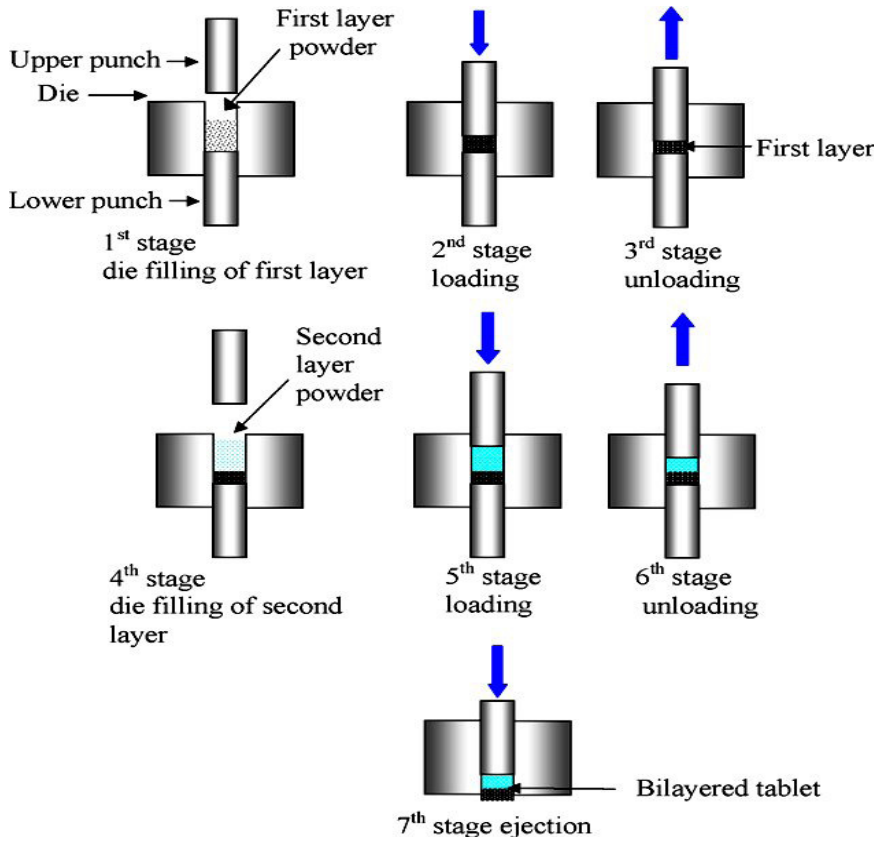

Fig.8. Preparation of bilayer tablet compaction

CHARACTERIZATION OF BILAYER TABLET[25, 26]

1. **Particle size distribution:**
   The particle size distribution was measured using sieving method.
2. **Photo microscope study:**
   Photo-microscope image of TGG and GG was taken (×450 magnifications) by photomicroscope
3. **Angle of repose:**

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

$$\tan \theta = h/r$$

Where h and r are the height and radius of the powder cone.

4. **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.

5. **Density**

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas

LBD$^{1/4}$ weight of the powder = volume of the packing

TBD$^{1/4}$ weight of the powder = tapped volume of the packing

6. **Compressibility**

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

EVALUATION OF BILAYER TABLETS

1. **General Appearance**

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

2. **Size and shape**

The size and shape of the tablet can be dimensionally described, monitored and controlled.

3. **Tablet thickness**

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4. **Weight variation[27]**

Standard procedures are followed as described in the official books.

5. **Friability[27]**

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the rochefriabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall

6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap where as thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

% friability = 1 – (loss in weight / initial weight) × 100

6. Hardness (crushing strength)[28]

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. The strong-cobb Pfizer and schleuniger apparatus which were later introduced measured the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications. If it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg: however, hypodermic and chewable tablets are usually much softer(3kg) and some sustained release tablets are much harder (10-20kg). Tablet hardness have been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

7. Stability study (temperature dependent)

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH. **If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (visual defects, hardness, friability and dissolution etc) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25^{o}C.

CONCLUSION:

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substance and also for sustain 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 multilayers is used to provide systems for the administration of drugs, which are incompatible and to provide control release tablet preparations by providing surrounding or multiple swelling layers. Bilayer 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 form simple single sided presses to highly sophisticated machines. Whenever high quality bilayer 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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