World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 8, Issue 3, 2019 ISSN: 2319-5622 USA CODEN: JPROK3

Review Article

A REVIEW ON BILAYER TECHNOLOGY

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Received on: 06-03-2019; Revised and Accepted on: 28-03-2019

ABSTRACT

Over the past 30 years, the expenses and complications involved in marketing new drug entities have increased with concomitant recognition of therapeutic advantages of controlled drug delivery. Now a days greater attention has been focused on development of controlled & immediate release drug delivery systems. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose. So use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, efficient pharmacological effect, better patient compliance etc. Bi-layer tablet is suitable for sequential release of two drugs in combination and/or to incorporate two incompatible substances in same tablet. This approach can be utilized for fabrication of sustained release dosage form (tablet) consisting of outer immediate and inner layer as a maintenance dose. To overcome the short comings of single layered tablet approach like bilayered tablet (immediate and sustained release) can be satisfactorily used. This review explains fundamentals of bilayer tablet system along with its fabrication techniques, different approaches, characterization, challenges in Bilayer tablet manufacturing, Quality & GMP requirements, for their production and recent developments in the field of bilayer technology. Present review mainly focuses on fundamentals of bilayer tablets and it's applications in Pharmaceutical industries

KEYWORDS: *Bilayer tablet Sustained release, Immediate release, GMP requirement.*

INTRODUCTION

There are many ways to deliver drugs into the body like oral (through swallowing), sub mucosal (through buccal and sublingual mucosa), parenteral (through injection), transdermal (through skin), pulmonary (through inhalation) etc [1, 2]. Tablets ("Pharmaceutical powder compacts") are the most common, convenient and preferred means of the existing administration methods for the systemic delivery of drugs [2]. It provides, ease of dose administration, patient compliance and flexibility in formulations. The effective oral drug delivery practice depends upon various factors like gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs [3]. Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues with undesirable toxicity and poor efficiency. Factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs [4, 5]. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form.

Need of Bilayer tablets: [3-5]

- For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- Controlling the delivery rate of either single or two different API'S.
- To adapt 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 controlled release.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
  1. For the administration of fixed dose combinations of different APIs, prolong the drug product life cycle,

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DOI: https://doi.org/10.5281/zenodo.2620324

buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery (bilayer tablet) has increased. The main objective of combination therapy is to encourage the utilization of lower doses of drugs to treat patients and also to minimize dose dependent side effect and adverse reactions [5]. To overcome the drawbacks of single layer combination tablet this concept was came into force [6]. 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) [7].

2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s).
3. 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.
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 Bi-Layer Tablets: [21, 23]

1. Greatest chemical and microbial stability compared to other oral dosage forms.
2. Objectionable odor and taste can be masked by coating technologies.
3. Bi-layer execution with optional single-layer conversion kit.
4. Cost is lower compared to all other oral dosage form.
5. Greatest chemical and microbial stability over all oral dosage form.
6. Objectionable odour and bitter taste can be masked by coating technique.
7. Flexible Concept.
8. Offer greatest precision and the least content uniformity.
9. Fit for large scale production.
10. It is prevent direct contact of two drugs and thus, maximize the efficacy of combination.
11. It can be designed in such a manner as to modified release as either of the layers can be kept as extended and the other as immediate release.
12. Patient compliance is improved and lead to improvement in dose regimen.

Disadvantages Of Bi-Layer Tablets: [21, 23]

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. 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.
5. Adds complexity and bi-layer rotary presses are expensive.
6. Insufficient hardness, layer separation, reduced yield.
7. Cross contamination between the layers.
8. Difficult to swallow in case of children and unconscious patients.
9. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.

Applications: [24-26]

1. Bi-layer tablets are suitable for sequential release of two drugs in combination.
2. It is improved technology to overcome the shortcoming of the single layered tablet.
3. Bilayer tablets are used to deliver the loading dose and
4. sustained dose of the same or different drugs.
5. Bilayer tablets are used to deliver the two different drugs having different release profiles.

Ideal Characteristics of Bilayer tablets:

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

Preparation of Bilayer tablets: [11-14]

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 form8. 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 bilayer tablet 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 compressibility and consolidation. Compression: it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

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 susceptibility 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 of the tablet. The extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity.

Consolidation:

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

Table-1: Various Advancements in the Field of Bilayer Tablet

Various Types of Bilayer Tablet Press:

1. Single Sided Tablet Press.
2. Double Sided Tablet Press.

Bilayer Tablet Presses With Displacement Monitoring.

1**. Single Side Tablet Presses:**

- There are many different types of bi-layer tablet presses have been designed over the years.
- The simplest design is a single sided press which have two chambers of the double feeder separated from each other.
- Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet.
- When the feeder fed the die with the powders (drugs), 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 (two = pre- and main compression).
- The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layerseparation occurs when the tablet is produced.

1. The 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. This may be corrected by reducing the turett-rotation speed (to extend the dwell time) but with the result 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.
- **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. To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press.
- **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.

2. Double Sided Tablet Press or "Compression Force" Controlled Tablet Presses:

- It is one of the best system of tablet press to eliminate the limitations of single-sided press, due to that A double-sided tablet press is preferred over a single-sided press.
- It 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 .
- 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 maximum turret speed.
- Maximum prevention of cross contamination between two layers. A clear visual separation between the two layers.
- 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.
- Most of the double sided tablet presses is provided with automated controller for monitoring compression force and control tablet weight, but compression force control system is always based on measurement of compression force at main compression but not at pre compression.
- At higher production speed, the risk of separation and capping increases,but It can be reduced by sufficient dwell time at compression stages.

3. Bilayer Tablet Press with Displacement

- "The displacement tablet weight control principle is basically 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 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.
- The upper pre-compression roller is attached to an air-piston which can move up and down in air cylinder and at that time 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 is 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 pre-compression height,

At every precompression 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 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.

Evaluation of Bilayer Tablets:

1. Pre-compression evaluation:

Particle size distribution: The particle size distribution was measured using sieving method [35, 36].

2. Photo-microscope study:

Photo-microscope image of TGG and GG was taken (X450 magnifications) by Photomicroscope [35, 36].

3. Angle of repose:

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plan [37, 38].

Tan -1 (h/r) Where, h= height, r = radius

4. Determination of bulk density and tapped density:

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas [39-41].

Bulk density = W / VO

Tapped density = W / Vf

Where, W = weight of the powder, VO = initial volume, Vf = final volume

5. Compressibility index (carr's indices):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material [39-41].

CI = 100 (VO – Vf)/V

Where, CI = Compressibility index, VO = initial volume, Vf final volume.

6. Hausner's ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density [39-41].

7. 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 [36, 37].

Post-Compression Evaluation :

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 [42, 43].

2. Size And Shape:

The size and shape of the compressed tablets were examined under the magnifying lens [42, 43].

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 [44].

4. Friability Test:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (w0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w) [45]. The % friability was then calculated by:

Percentage of Friability = 100 (1-w/w0)

Percentage friability of tablets less than 1% is considered acceptable.

5. Weight Variation Test:

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and none deviates by more than twice the percentage. USP official limits of percentage deviation of tablet are presented in the table [35].

6. Swelling Studies:

Swelling property of tablet was determined by placing it in the dissolution test apparatus, in 900 ml of 0.1 N HCl at 37 ± 2 0C. The weight and volume reached by the matrix tablets over time was determined by withdrawing the tablets periodically from dissolution medium. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess test liquid. The volume of the tablets was obtained by measuring the thickness and diameter, considering a right circular cylinder form. The determined weight and volume were used to calculate the tablet density over the dissolution study. Swelling characteristics were expressed in

terms of percentage water uptake (WU %) according to the equation: [46]

WU % = Wt. of swollen tablet – Initial wt. of tablet / Initial wt. of tablet × 100

7. Hardness (Crushing Strength):

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. Monsanto hardness tester 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 measures 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 (3 kg) and some sustained release tablets are much harder (10 -20 kg). Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression [47].

8. Disintegration Test:

Disintegration test apparatus is generally used to measure disintegration time of tablet. For Disintegration time, one tablet is placed in each tube and the basket arch is positioned in 1 L beaker containing water at 37°C ± 2°C. A standard motor driven device is used to move the basket assembly up and down. To comply with USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified [48].

9. Dissolution Studies:

Drug release studies are carry out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. The samples withdrawn during dissolution test are analyzed by UV spectrophotometer using multi component mode of analysis [45].

10. Stability Study:

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. 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°C.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcomings of the single layered tablet. There is various application of the bi-layer 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 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. Bilayer tablet quality and GMPrequirements can vary widely. Present review mainly emphasizes, why bilayer tablet is considered as better option than conventional tablet Bi-layer tablets offer an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products' efficacy, and protect against impersonator products. Bilayer 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. When a quality bilayer tablet needs to be produced in conjunction with accurate weight control of both layers, compression forcecontrolled presses are clearly limited because of their insufficient sensitivity and hence lack of accuracy at low compression forces required to secure interlayer bonding. Such problems become even more apparent when the tableting speed is high or increased. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk can be achieved with the displacement weight control system based presses.

ACKNOWLEDGEMENT

The authers are thankful to Prof. Ms. Deshmukh M.T. and Principal Dr. Shete R.V. Rajgad Dnyanpeeth's College Of Pharmacy, Bhor, Pune. For their kind support in preparation of this article.

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How to cite this article:

Ganesh Deokate, et al. A REVIEW ON BILAYER TECHNOLOGY. J Pharm Res 2019;8(3):81-87.
DOI: https://doi.org/10.5281/zenodo.2620324

Conflict of interest: The authors have declared that no conflict of interest exists.
Source of support: Nil