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# A Sequential Review on Bilayer Tablets

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**ABSTRACT:**

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 sustained 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:** Bilayer tablets, modified tablet press, Bilayer tablet press

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## INTRODUCTION[1,2,3]

Pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. These combined formulations function from a single dosage form, which simplifies the therapy and reduces or eliminates the chances of improper administration. Bilayer formulations carry more than one drug and deliver each of them without any pharmacokinetic or dynamic interactions, with their individual rate of delivery (immediate, timed or sustained). Bilayer tablet technology is improved beneficial technology to overcome the shortcoming of the single layered tablet. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor 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 as well as patient compliance. 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.

**Figure 1 Bilayer Tablet**

**Multi-layer tablet dosage forms are designed for variety of reasons**

1) To control the delivery rate of either single or two different active pharmaceutical ingredient(s).

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 swell able/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 BILAYERED TABLETS[4,5,6]**

These type of incompatibilities are commonly used to avoid chemical incompatibilities of formulation components by physical separation.

- Cost is lesser as compared to other dosage forms
- Greater chemical and microbiological stability
- Objectionable odor and bitter taste can be masked by coating technique
- Flexible concept
- Easy to swallow with least tendency for hang up
- Suitable for large scale production
- They are unit dosage form and often the greatest dose precision and least contact variability.

**DISADVANTAGES OF BILAYERED TABLETS[6,7,8]**

- Some drugs resist compression into dense compacts owing to amorphous nature
- Bitter testing drugs , drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating
- Difficult to swallow in case of children and
- unconscious patients
- Drugs with poor solubility , slow dissolution properties optimum absorption high in GIT may be difficult to formulate that will still provide adequate or full drug bioavailability.

**GENERAL PROPERTIES OF BILAYER TABLET DOSAGE FORM:[4,5,6]**

- It should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.
- It should have graceful product identity free of defects like chips, cracks, discoloration and contamination.
- Must have a chemical stability shelf life, so as notto fallow alteration of the medicinal agents.
- The bilayer tablet must release drug in a expectable and reproducible manner.
- It should have physical and chemical stability.

**VARIOUS TECHNIQUES FOR BILAYER TABLET[9,10,11,12,13,14]**

**a) 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. 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

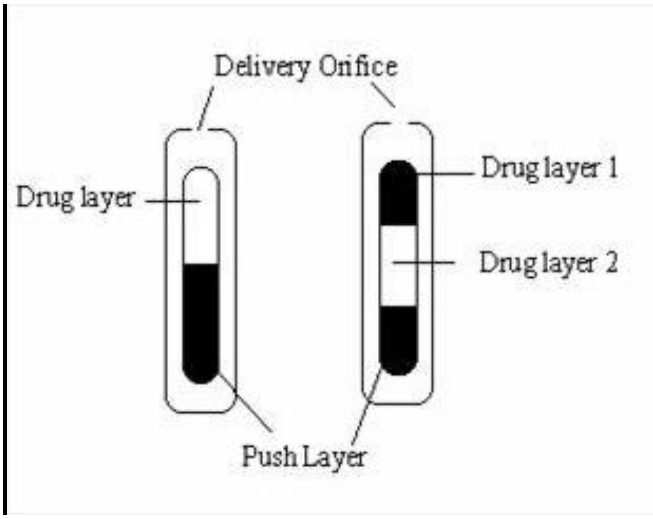


**Figure No.2** Push Pull Technology

**b) L-OROS 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 then a semi permeable membrane, drilled with an exit orifice.

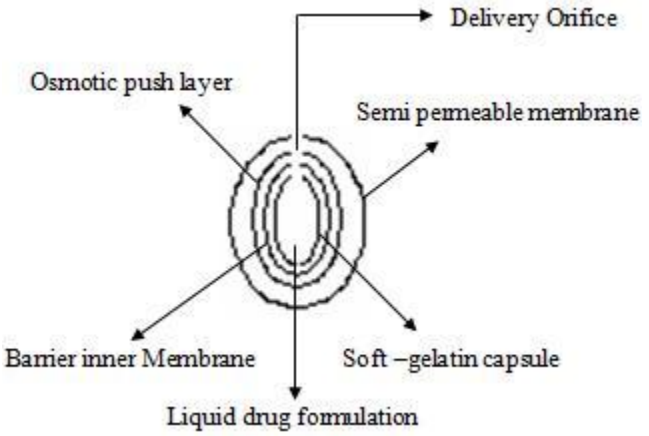


**Figure No. 3** L-oros technology

**c) EN SO TROL technology**

Solubility enhancement of an order of 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.

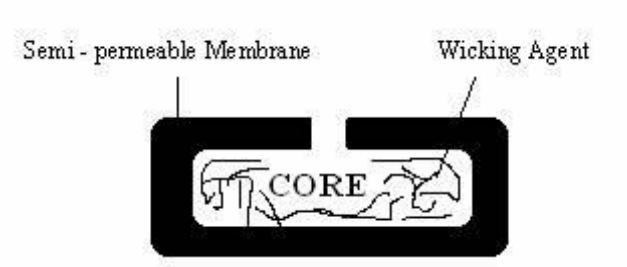


**Figure No. 4** EN SO TROL technololgy

**d) DUROS technology**

The system consists from an outer cylindrical titanium alloy reservoir. 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.

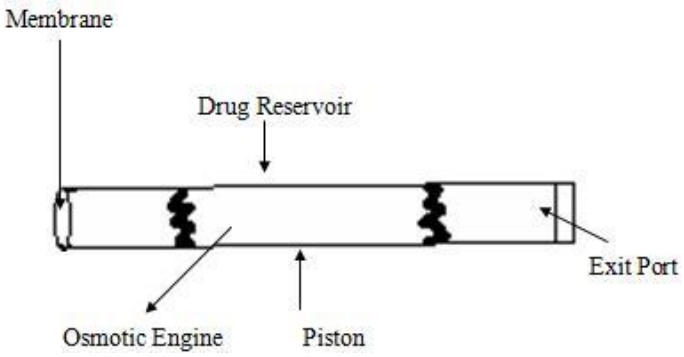


**Figure No. 5 DUROS technology**

**e) Elan .drug. technologies' .Dual release drug delivery system**

(DUREDAS™ Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting 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.

**Benefits offered by the DUREDAS™ technology include**

1) Bilayer Tableting 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

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bilayer. 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 bilayer 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.

**Evaluation of Bilayer Tablets [13,14,15]**

**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**

Standard procedures are followed as described in the official books.

**5. Friability**

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 Roche friabilator. 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 lesser 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) X 100

**6. 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.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 diametrally to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced 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). 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.

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.

| Study | Storage condition | Minimum time period covered by data at submissi |
|---|---|---|
| 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 ± 5% RH. **If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

**Table No. 1 Troubleshooting of processing problems in bi-layer tablet compression [16,17,18]**

| Trouble | Possible cause | Remedies |
|---|---|---|
| Tablet weight variation | 1. Poor flow characteristics of material | a. Wrong setting of hopper.<br>b. Material bridging in hopper<br>c. Too much recirculation |
| | 2. Dies not filling | a. Press running too fast<br>b. wrong feeder paddle speed or shape |
| | 3. Material loss or gain after proper die fill | a. Recirculation band leaking<br>b. Excessive vacuum or nozzle improperly located |
| Product yield | 1. Incorrect feeder fit to die table | a. Feeder bases incorrectly set (too high or not level)<br>a. Gap between bottom edge and die table |
| | 2. Incorrect action on recirculation band | b. Binding in mounting screw<br>c. Too little hold down spring pressure |
| | 3. Die table scraper action insufficient | a. Scraper blade worn or binding<br>b. Outboard edge permitting material to escape |
| | 4. Loss at compression point | a. Compressing too high in the die<br>b. Excessive or misdirected suction on exhaust nozzle |
| Low hardness | 1. Factors related to machine | a. Tablet press having pre-compression and main compression facilities |
| | 2. Lubricant level | b. Press speed is reduced to increase total compression time<br>a. Over mixing can reduce tablet hardness |
| Capping and laminatio n | 1. Non-optimized formulation | a. Incorporate plastically deforming matrix |
| | 2. High compression force | a. Reduced compression force<br>b. Reduced press speed |
| | 3. Ratio of pre-compression to main compression is insufficient | a. Pre-compression force high can be harmful<br>b. Use large compression roller diameter |
| | 4. Curled or damaged punches | a. Tools should be rewashed or replaced |
| Picking and sticking | 1. Excessive heat generation during compression<br>2. Fouling the punch faces | a. Use of cooling system for the compression section<br>b. Lower mechanism section may be helpful<br>a. Startup should always be close to optimum conditions |
| Separation of two individual layers | 1.Insufficient bonding between the two layers during the final compression of bilayer tablet | a. First layer should be compressed at a low compression force so that this layer can still interact with second layer during final compression of the tablet |
| Mottling | 1. Improper setting of both feed frame<br>2. Due to weak suction | a. Both feed frame should set properly.<br>a. Suction capacity should be such that, all waste material is sucked. |

**Table No. 2 Bilayer tablets with polymers[19,20,21,22,23,24]**

| Drugs | | Super disintegrant used in | Polymer used in Sustained |
|---|---|---|---|
| First layer | Second layer | Immediate release layer | release layer |
| Glimepride | Metformin HCL | Sodium starch glycolate | HPMC K4M, sodium carboxymethyl cellulose |
| Paracetamol | Acetamino-phen | Microparticles by ethyl cellulose | Microparticles by ethyl cellulose |
| Valsartan | Metformin HCL | Crospovidone | HPMC K100M, sodium CMC, PVP K90 |
| Glipizide | Glipizide | Starch | HPMC, xanthan gum, guar gum, karaya gum, |
| Zolpidem tartrate | Zolpidem tartrate | Sodium crosscarmellose | HPMC K100M |
| Ranitidine | Ranitidine | Starch | Carbopol, HPMC |

**CONCLUSION**

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. 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 are used . Whenever high quality bi-layer tablets are needed to be produced, high speed and use of an 'air compensator' in combination with displacement control appears to be the best solution.

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