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Bilayer Tablets of Antihypertensive Drugs: An Overview

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ABSTRACT

Bilayer tablets are a type of modified-release dosage form designed to deliver two active pharmaceutical ingredients (APIs) simultaneously or sequentially from different layers of the tablet. This formulation technique is particularly useful when combining multiple antihypertensive agents in a single dosage form. By using bilayer tablets, two different mechanisms of action or two complementary drugs can be delivered in a controlled and systematic manner, improving both patient compliance and therapeutic efficacy. One layer can be designed for immediate release (IR), providing a rapid onset of action, while the second layer can be designed for controlled or sustained release (SR), maintaining therapeutic levels over an extended period. This allows for the reduction of dose frequency, leading to better patient adherence to the treatment regimen. Antihypertensive drugs often work more effectively when used in combination, targeting different mechanisms involved in hypertension. Bilayer tablets offer the advantage of combining two complementary antihypertensive drugs in one formulation, ensuring their simultaneous release. By using a combination of drugs with different release profiles, bilayer tablets can reduce the incidence of side effects. For instance, the immediate release layer can handle acute symptoms, while the sustained release layer can control long-term blood pressure regulation. Certain drugs in combination can have enhanced bioavailability when administered in a bilayer tablet format, potentially leading to a more consistent therapeutic effect. Instead of taking multiple tablets or capsules for combination therapy, patients can take one bilayer tablet, improving convenience and compliance. Bilayer tablets represent an innovative approach to combination therapy in hypertension management. By providing controlled, sustained, and immediate release of two antihypertensive drugs, these tablets offer a convenient, effective, and patient-friendly solution for managing high blood pressure. The use of bilayer tablets not only improves therapeutic outcomes but also enhances patient compliance by reducing the pill burden and simplifying the dosing schedule.

Keyword: Bilayer Tablets, Antihypertensive Drugs, Overview, Immediate release, Bioavailability

1. INTRODUCTION

Oral Drug Delivery System

The oral drug delivery market is the largest segment of the drug delivery market and there's no sign that it is slowing down. Oral route of drug administration has wide acceptance up to 50-60% of total dosage form and is the most convenient and preferred route for systemic effect due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation. The major aim of controlled drug delivery is to reduce dosing frequency. The design of modified release drug products is to optimise a therapeutic regimen by providing slow and continuous delivery of the drug over the entire dosing interval and provide better patient compliance and patient convenience. Over 90% of the formulations manufactured today are ingested orally.[1]

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (Immediate, Extended or Controlled release) and the design of dosage forms(either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. This shows that oral formulation is the most popular worldwide and the major attention of the researcher is towards this direction.[2, 3]

Introduction of Tablet[4, 5]

Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. When a tablet is given orally, it undergoes *In- vitro* administration and dissolution, followed by absorption through the gastrointestinal tract (GIT) and then the *In-vivo* bio-distribution of the drug, which enters in to the systemic circulation then occurs.

Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated.

The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behaviour of the preparation in the digestive tract, colouring matter authorised by the component authority and flavouring substances

Layer Tablets[6]

In Layer tablet, there are two fractions, i.e. loading fraction which provides the loading dose and maintain fraction which provides maintenance dose by extended release. Layer tablets are composed of two or three layers of granulation compressed together. As the edges of each layer are exposed, they have the appearance of a sandwich. Fig: 1a, 1b shows various types of layered tablets. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow-release portion in the second. A third layer with an intermediate release might be added.

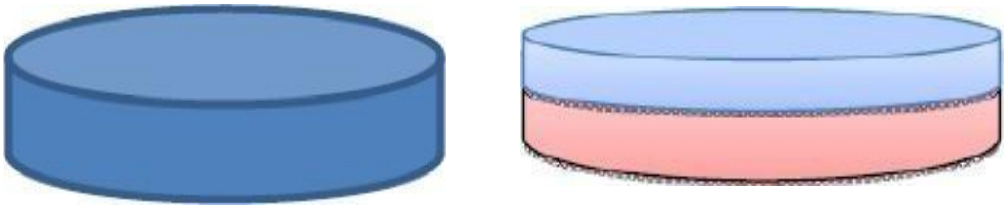


Figure 1.1(a): Single layer tablet Figure1.1 (b): Bilayer tablet

Introduction to Bilayer (Multi component or Dual component) Tablet 1

Bilayer tablet is the new era for the successful development of controlled release formulation. It is also called Dual or Multi component tablet. Bilayer tablet is better than the traditionally used dosage form. It is suitable for sequential release of two drugs in combination. It also capable of separating two types of incompatible substances and also for sustained release tablets in which one layer is immediate release as the initial dose and the second one is maintenance dose. Bilayer tablet contains immediate and sustained release layers. In which immediate release layer delivers the initial dose, which contains super disintegrates (promotes drug release rate and attains the onset of action rapidly). It is also called as a loading dose. Seco nd layer is sustained sustained-release (maintenance dose) layer that releases the drug in a sustained or prolonged time period.

Coronary vasodilators, antihypertensives, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery. Some bilayer tablets have both layers as the sustained release layers for example, certain anti diabetic agents. Use of bi-layer tablets is a very different aspect for anti-hypertensive, anti-diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used.

Bi-layer tablets are made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes. Figure 1.2 shows picture of bi-layer tablet.

Figure1.2: Bilayer tablet

Advantages of Bilayer Tablet[8, 9]

Incompatible substance can be separated by formulating them in separate layer as a two layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two.

Two layer tablet may be designed for sustain release; one layer for immediate release of the drug and second layer for extended release, thus maintaining a prolonged blood serum level.

The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating.

Monograms and other distinctive markings may be impressed on the surfaces of the multi-layer tablets.

Analytical work may be simplified by separating the layers before assay.

They are used as an extension of a conventional technology.

Bi-layer execution with an optional single-layer conversion kit.

Disadvantages of Bilayer Tablet[8, 9]

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.

Difficult to swallow in case of children and unconscious patients.

Adds complexity and bilayer rotary presses are expensive.

Some drugs resist compression into dense compacts, owing to their amorphous nature, low density character.

Necessity of Bilayer Tablets[9]

For the supervision of fixed dose combinations of drugs, prolong the drug product lifecycle, buccal/mucoadhesive delivery systems, manufacture novel drug delivery systems such as a chewing devices and floating tablets for gastro-retentive drug delivery systems.[7]

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 a chewing device and floating tablets for gastro- retentive drug delivery.

Controlling the delivery rate of either a single or two different active pharmaceutical ingredients.

To modify the total surface area available for API layer, either by sandwiching with one or two active layers to achieve swellable/erodible barriers for modified release.

To separate incompatible Active pharmaceutical ingredients (APIs) from each other, to control the release of API from one layer by utilising the functional property of the other layer (such as, osmotic property).

Rationale in Designing Bilayer Tablet[8, 9]

To get a synergistic effect

Reduce the frequency of dosing

To prepare a novel drug delivery system, e.g. Buccal system, HDBS (hydro dynamically balanced System)

The safety margin of high high-potency drug can be increased

To inhibit drug interaction

Therapeutic justification

To control the delivery rate, e.g. Single or two different APIs

Reduce pill burden

Ideal Characteristics of Bilayer Tablet[8]

It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.

It should have a graceful product identity, free of defects like chips, cracks, discolouration and contamination.

Must have a chemical stability shelf life, so as not to undergo alteration of the medicinal agents.

The bilayer tablet must released medicinal agent's expectable and reproducible manner

Challenges in Bilayer Tablet Manufacturing[8, 10]

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross-contamination.

Production yields: To prevent cross-contamination, dust collection is required, which leads to losses. Thus, bilayer tablets have lower yields than single-layer Tablets.

Cost: Bilayer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is a must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimised, in one way or another will impact the bilayer compression and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

Bilayer Tablet: Quality and GMP-requirements[12]

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 bi-layer 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.

Various Techniques for Bilayer Tablet

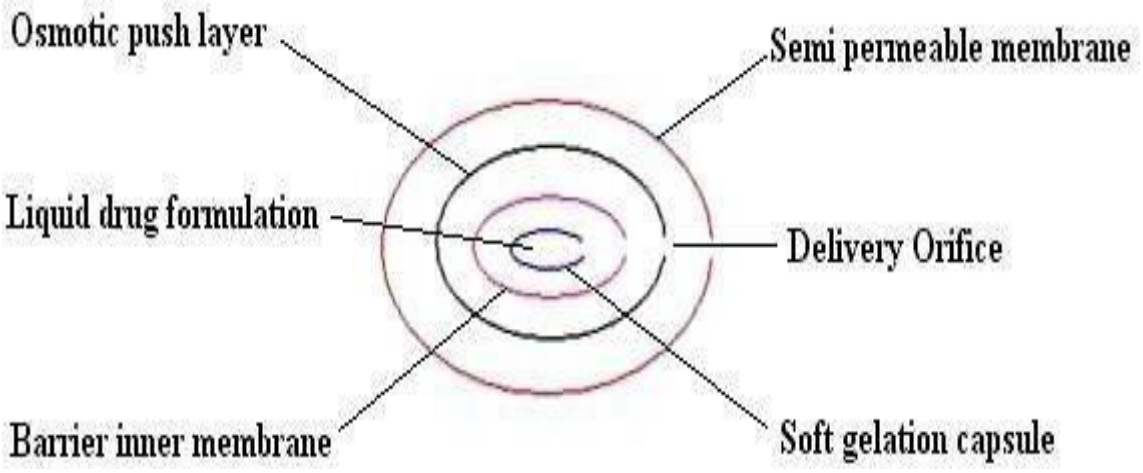
OROS® Push Pull Technology[12]

This system consists 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.

Figure1.3: OROS®Push Pull Technology

L-OROS Technology[13]

This system used for the solubility concern. A1za developed the L-OROS system Lipid soft gel product containing drug in



a dissolved state is initially manufactured, then coated with a barrier membrane, next osmotic push layer, after that a semi permeable membrane which drilled with an exit orifice.

Figure1.4: L-OROS Technology

DUROS Technology[14]

The system consists from an outer cylindrical titanium alloy reservoir (Fig.1.5).This reservoirhashighimpactstrengthandprotectsthedrugmoleculesfromenzymes.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.

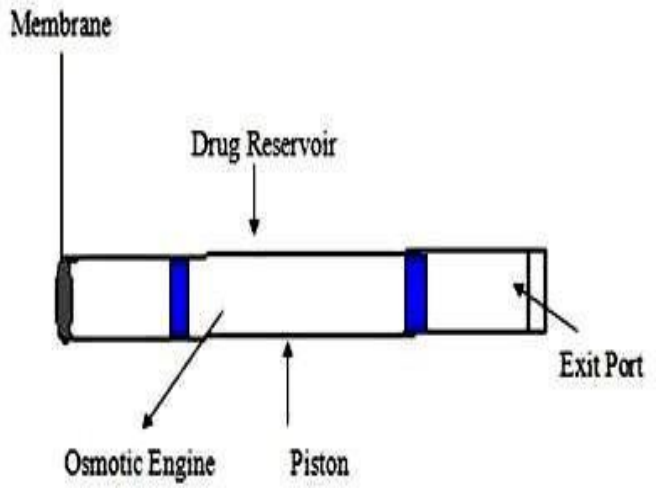


Figure1.5: DUROS Technology

ENSOTROL Technology[12]

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

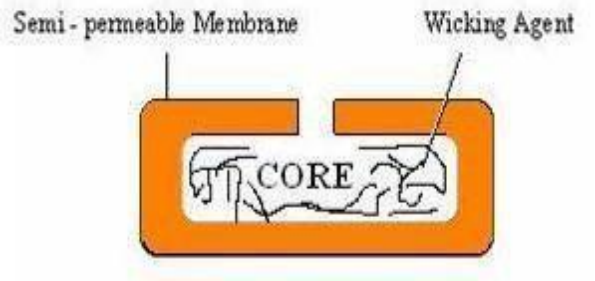


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Figure1.6: ENSOTROL Technology

DUREDAS™ Technology[8]

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.

PRODAS (Programmable Oral Drug Absorption System) [15, 16]

PRODAS is a multi-particulate drug delivery technology that is based on the encapsulation of controlled release mini tablets

in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multi particulate and hydrophilic matrix tablet technologies and thus provides the desired release rates.

These considerations may include immediate release, delayed release and / or controlled release mini tablets. In addition to controlled release 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 possible by using mini tablets formulated with different ingredients.

GEMINEX Technology[17]

In this drug delivery system at different time more than one drug can be delivered. This technology basically increases the therapeutic efficacy of the drug by decreasing its side effects. It is useful both to industry as well as patient as in single tablet it provides delivery of drug at different rates.

Erodible Molded Multilayer Tablet[17, 18]

Egalet erodible molded tablets in an erosion based platform. It has the advantage of delivering zero order or delayed release with minimal impact from the gastrointestinal conditions. Egalet erodible molded multi-layered tablets are prepared by injection mouding egalet 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 by altering the matrix, the coat, the geometry to achieve either a zero order release ora delayed. For a zero order, 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 promote 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. Egalet delivery technology is developed based on standard plastic injection molulding to ensure accuracy, reproducibility and low production cost.

Geomatirx Tablet[19, 20, 21]

One of the examples of bilayered tablets is geomatrix tablet. Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with

a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers system. The biphasic system some time may contain two drugs in separate release layers. There are clearly number of issues of concern to the production of bilayer tablets. While the mechanical strength of layered tablets has been observed not to be a controlling factor in drug release the determination of this property could be beneficial in understanding the adhesion between various layers and provide an improved characterization of the systems. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer However, many floating systems reported are single-unit systems such as HBS, which are unreliable in prolonging the GRT owing to their ‘all-or-nothing’ emptying process. These systems thus, may result in high variability in bioavailability and local irritation due to a large amount of drug delivered at a particular site of GIT. The conventional dosage forms are retained in the stomach for 0.5-2 hrs. This then passes to small intestine, where it gets designed to release drug, later, either as second dose or in an extended release manner. 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. Control release systems that have been proposed for providing controlled release formulations showing how the different designs can be used to control the drug release profile such as constant, delayed pulsatile and multi modal release profiles. Several different geometries are described and to prepare these by compression will require various strategies.

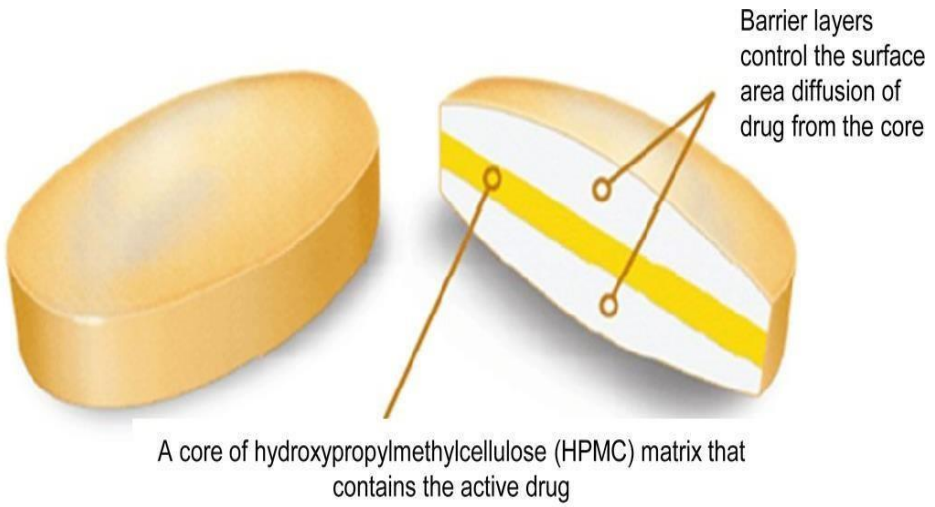


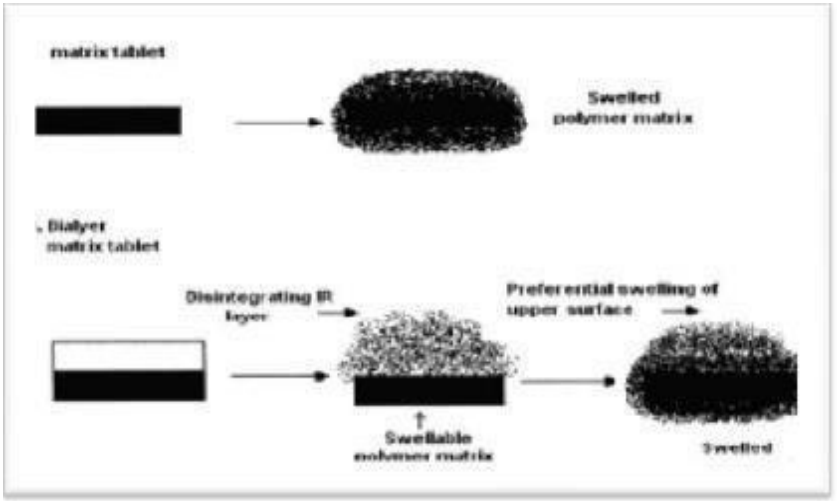
Figure1.7:Geomatrix Tablet

Various Approaches of Bilayer Tablets[22, 23]

Floating Drug Delivery System

They are designed to have a low density and thus float on the gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying. The bi-layer tablet is designed in such way that, one layer gives immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which forms a gastro retentive system. Release pattern of floating bi-layer tablet is shown in figure 1.8.

Figure1.8: Floating Drug Delivery System



Intra Gastric Bilayer Floating Tablets

These are also compressed tablet as shown in figure and contain two layers i.e.

Immediate release layer

Sustained release layer.

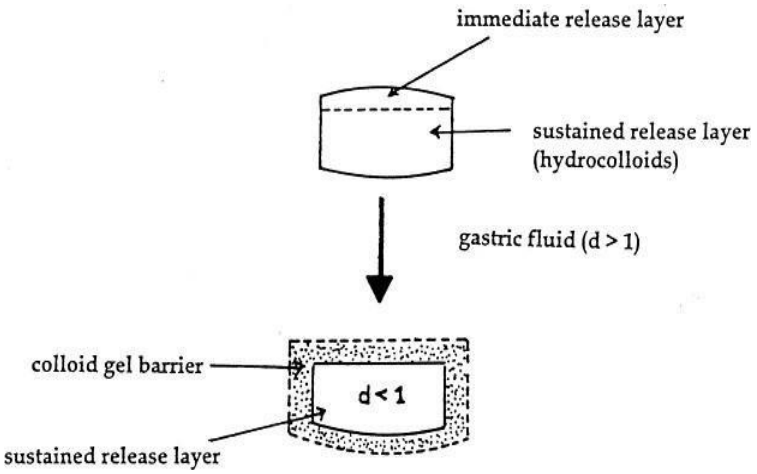


Figure1.9: Intra Gastric Bilayer Floating Tablet

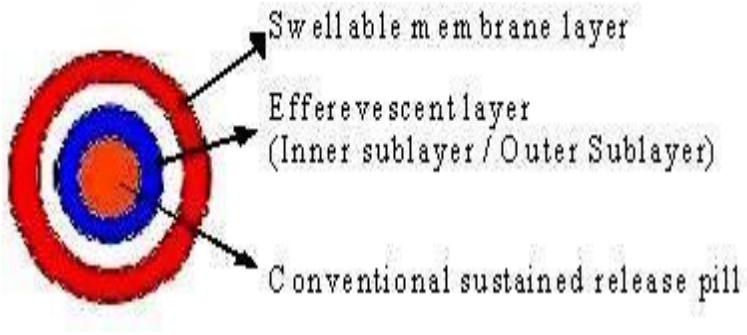
Multiple Unit Type Floating Pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

Figure1.10: Multiple Unit Type Floating Pills

Polymeric Bio Adhesive System

These are designed to imbibe fluid flowing administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened.



These are prepared as a one layer with immediate dosing and other layer with bio adhesive property.

Disadvantages: The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans. The system adheres to mucous not mucosa. Therefore, bio adhesive dosage form would not appear to offer a solution for extended delivery of drug over a period of more than a few hours.

Swelling System

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g. less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet whereas 10-12 mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave stomach. The simple bi-layer tablet may contain an immediate release layer with the other layer as extended release or conventional release or both as controlled release layer.

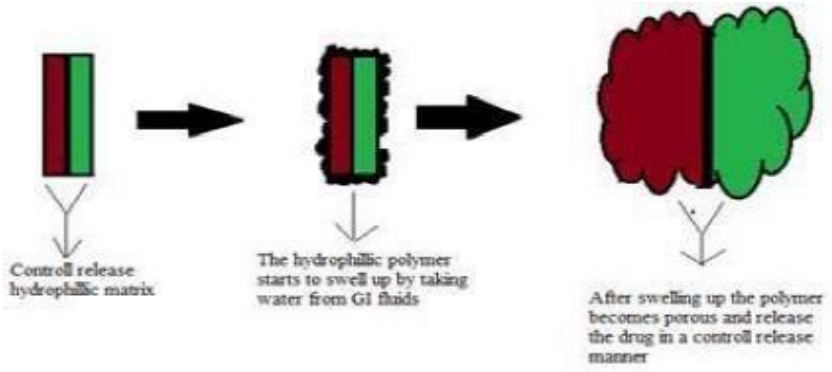


Figure1.11: Swelling System

Bilayer Tablet Press

2. TABLET LAYER PRESS

A tablet multiple layer press is simply a tablet press that has been modified so that it has two die-filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two-layer tablet and a second time for the second layer. Three-layer presses are equipped with three such compression cycles.

There are two types of layer presses presently in use one in which each layer can be ejected from the press separately for the purpose of weight checking, and the second in which the first layer is compressed so hard that the second layer will not bond to it, or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper weight adjustments have been made by adjusting the die fill, the pressure is adjust to the proper tablet hardness and bonding of the layers.

Once hazard of layer tablet production is the lack of proper bonding of layers. This can result in a lot of 100,000 tablets ending up as 200,000 layers after several days if the layers are not sufficiently bonded.

In a two layer tablet press, two hoppers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continues, gentle circulation of the material through the hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carry over to the second layer and affect layer weight, tablet hardness, and, in the case of differently colored granulations, the press with three hoppers for the tree granulations instead of two.

Types of Bilayer Tablet Press[24, 25]

Single sided tablet press.

Double sided tablet press

Bilayer tablet press with displacement monitoring.

Multilayer compression basics.

Piccola bilayer

RoTab Bilayer

Single Sided Press[33]

Various types of bilayer presses have been designed over the years. The simplest design is a single sided press with both chambers of the double feeder separated from each other. Each chamber in gravity fed, or force fed with a different powder, thus producing the 2 individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first layer of powder followed bythe second-layer powder then the entire tablet is compressed in one or 2 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 layer separation occurs when the tablet is produced this is the simplest way of producing a bilayer tablet.

Limitations of Single Sided Press

No weight monitoring or control of the individual layers

Nodistinctvisualseparationbetweenthe2 layers

Dwell time due to the small compression roller possible resulting in poor deareation capping and hardness problems.

Figure1.12: Single Sided Tablet Presses

\Double Sided Tablet Presses[33]

Most of the double sided tablet presses which are automated production control use the compression force to monitor and control the weight of the tablet weights. The effective compression force exerted on each individual tablet with the help of the compression system at the main compression of the layer. This system helps in to reject out the tolerance tablets and correct the dies fill depth when required.

Advantages

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

Displacement weight monitoring for accurate and independent weight control of the individual layer.

Maximized yield.

3. 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.

Figure1.13: Double Sided Tablet Presses

Bilayer Tablet Presses with Displacement[26]

The principle of bilayer tablet press is fundamentally different from the principle of compression force. In this case the accuracy increases with reduced compression force. At higher production speed the risk of capping and separation increases but can be reduced by sufficient dwell time at all four compression stages.

Advantages

Displacement weight monitoring/control for accurate independent weight control of the individual layers. Low compression force exerted on the first layer to avoid capping and separation of the 2 individual layers.

Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed

A clear visual separation of the layers

Maximized yield.

Figure1.14 (a) **Figure1.14 (b)**

Courtoy R292f Bi-Layer Press Bilayer Tablet Presses with Displacement

Multilayer Compression Basics[27]

Presses can be designed specifically for multilayer compression or a standard double press can be converted for multilayers. The multilayer tablets concept has been long utilized to develop sustained release formulations such tablets have fast releasing layer and may contain bilayers or triple layers to sustain drug release from the tablet. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to sudden rise in blood concentration however the blood level is maintained at a steady state as the drug is released from the sustained granules.

Piccola Bilayer[1]

This rotary press was designed to represent two-layer tablet production conditions at small scale, according to the needs of new product development. Piccola Bi-layer press meets CGMP standards and can use type D or B tooling complying with TSM or EU standards, which allows the employment of the same punches used in production. For an appropriate adjustment in tablet production, there are totally independent systems for weight, height and hardness adjustment, both for the first and second layers. A PLC system having a touch screen and software designed for Galenic Development and Production Control allows the integrated control of all parameters, including production rate and, separately, the rate of each of the star forced feeder. There are varied accessories and options for the software used; such as the possibility of weight control during production and the use of data obtained for calculation and statistics.

Figure1.15 Piccola Bilayer

Rotab Bilayer[26]

Software

It is modular designed software to which additional functions can be added. PC system with 15” touch screens is an advanced system which provides fast graphical evaluations with accurate results.

Working

RoTab bilayer when using is switched to production mode. Dose and compression force is automatically regulated by adjusting filling speed and die table. Hardness is also regulated when required.

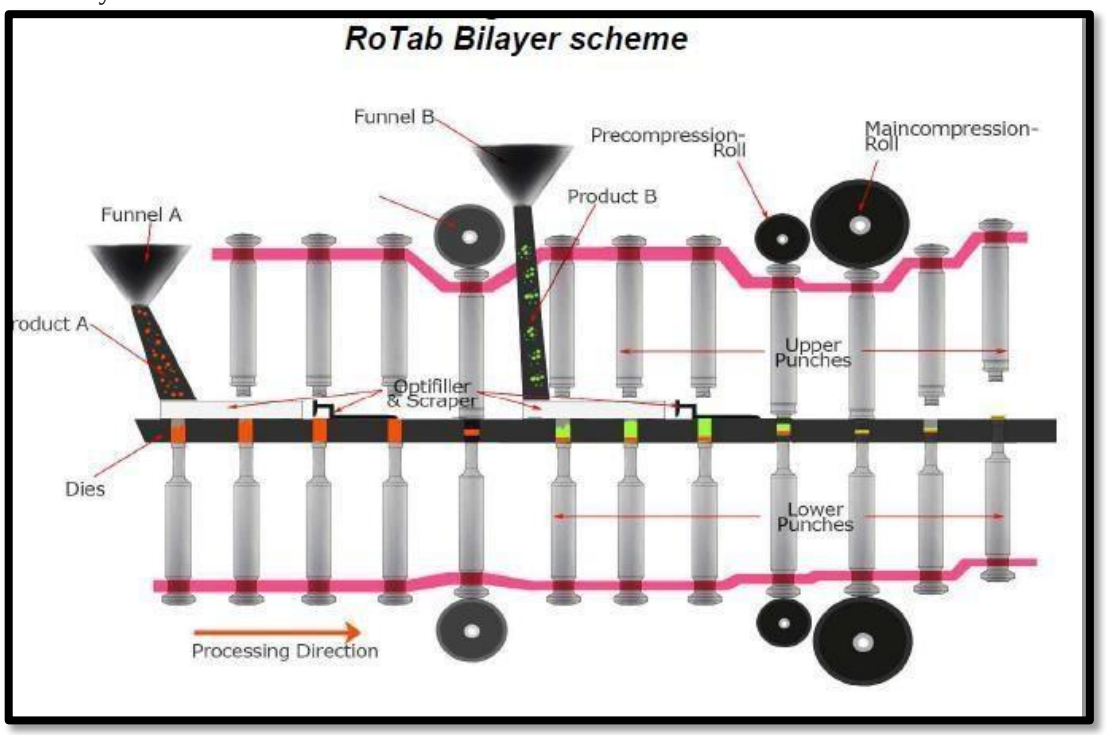
Rand D modified technique

RandDmodifiedRoTabBilayerisfeaturedwithmeasuringpointsonwhichthereare graphical visualization and evaluation are possible. There is an additional alarm function on which punch tightness is controlled. Anytime upgration is possible which is R and D Plus.

RandD Plus

R and D Plus provides improved standards in tableting technology with all important functions such as punch tightness control, display of force displacement and tablet scraper force.

Figure1.16 Rotab Bilayer



Bilayer Tablet Press[28, 29]

The Xm bilayer tablet press features a rectangle second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, which the main compression station will automatically compress, the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the dis table and completely eliminates any potential of cross contamination.wip con® solution available for potent for layer tablet press is a small scale press which is ideal for product development, scale up, clinical trials and midrange production. The bilayer execution, single layer conversion kit and exchangeable turret offers, a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and change over.

Evaluation parameters of Bilayer tablet[30]

4. GENERAL APPEARANCE

The general appearance of a tablet, its visual identity and overall “elegance” is essential for consumer acceptance. It includes tablets size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape

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

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.

Weight Variation Test

For Weight Variation Test, twenty tablets are selected randomly and the average weight is calculated thereafter the Weight variation is calculated and weight variation is compared with IP standard.

Friability

Friability will be measured by taking randomly 10 tablets which is weighed and placed in a Friabilator (Roche Friabilator) and rotated at 25rpm for a period of 4 minutes. After resolution, the tablets can be dusted and weighed.

Hardness

The hardness of the tablet will be carved out using Monsanto type hardness tester. The hardness of the tablet in $Kg/cm^2$is measured.

5. *IN-VITRO* DISSOLUTION STUDIES

The bilayer formulations are subjected to *in-vitro* drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled.

Drug Release Kinetics

The bilayer tablet formulation, drug release profile to be assessed for release kinetics Zero order, First order, Higuchi, Koresmeyer Peppas, etc. and is used to obtain drug release mechanism. All the release kinetics is carried out by appropriate statistical analysis.

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