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Fundamentals and Potentials of Bilayer Tablet Technology

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ABSTRACT

Bilayer tablet has become the concept of increased interest within the pharmaceutical industry because a variety of reasons such as patent extension, reduce capital investment, marketing to name a few. In recent years, a growing interest has developed in designing a drug delivery system that consists of an immediate release component (IR) to extended-release dosages. 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 a loading dose and the second layer is the maintenance dose. General tablet manufacturing principles remain the same, there is much more to consider because making bilayer-layer tablets involves multiple often incompatible products, additional equipment, and many formulation and operation challenges. To overcome the shortcomings of a single-layered tablet approach like a bi-layered tablet (immediate and sustained release) can be satisfactorily used. This review explains the fundamentals of the bilayer tablet system along with the various techniques for their preparation, types of bilayer tablet presses, GMP requirements, challenges involved in bilayer tablet manufacturing, critical formulation aspects, and evaluation.

INTRODUCTION:

There are various routes to deliver drugs into the body such as oral (through swallowing), parenteral (through injection), transdermal (through the skin), pulmonary (through inhalation)[1,7,8,9]. There are phenomenal advances in the inhalable, transdermal, injectable, and other routes of administration, then also oral drug delivery remains to be the choice of a preferred one. Moreover, if the oral route is not feasible, pharmaceutical companies will invent resources in making it feasible rather than using an alternative drug system[1,2]. The oral route is the most commonly employed because of its ease of administration, pain avoidance, and accurate dosing flexibility in formulations along with better patient compliance[9,28,29]. Oral administration has 50 to 60% of acceptance of total dosage forms [1,3,4,5]. The oral drug delivery market is the largest drug delivery market amongst orally administered dosage forms. Tablets and capsules are the preferred class of products out of the tablets have several benefits over the other dosage form[1,4,5]. The productivity of oral drug delivery is influenced by several parameters like gastric emptying, the gastrointestinal transit time of dosage form and release of API from the dosage form, and the site of absorption of drugs.

Conventional dosage forms result in a broad range of fluctuations in plasma drug concentration level, unpleasant toxicity, alteration in the concentration of drugs in the bloodstream as well as in tissues [6,7,10,15]. Factors such as recurring dosing and uncertain absorption led to the theory of sustain or control drug delivery systems. The rationales behind designing such a delivery system are reducing the frequency of dosing, providing a uniform drug delivery system, and enhancing the effectiveness of the drug by localizing it at the site of action. The goal behind the development of a sustained drug delivery system is to assure safety, efficacy, and better patient compliance.[7,10,11,12,13,14,15,22,24]

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry for successful development of controlled release formulation along with various features to provide successful drug delivery[15,18,19,20,21,27]. Bilayer tablets are suitable to avoid chemical incompatibilities between APIs by physical separation and enabling the development of dual drug release profiles (IR with ER)[10,17,18,19,23]. In the bilayer system, the immediate release layer acts as a loading dose and the sustained release layer maintains the therapeutic plasma drug concentration for an extended period

[6,10,11,12,1315,16,17,24,26,30]. It has been observed that the release of the drug cannot be influenced by alteration in the mechanical strength. Thus, bilayer tablet has different drug aspects for analgesics, anti-inflammatory, anti-diabetic and anti-hypertensive[17,29]. Hence, several pharmaceutical companies are currently developing bilayer tablets, for a variety of reasons: patent extension, to reduce capital investment, marketing to name a few.[6,7,15,17,24,25]

Types and Classes of Tablet[7,14,31,33]

Table No. 1: Types and classes of Tablets

1. Oral Tablets for Ingestion	**2. Tablets Used In the Oral Cavity**
I. Standard compressed tablets	I. Buccal tablets
II. Multiple compressed tablets :	II. Sublingual tablets
	III. Troches and lozenges
a) Layered tablets b) Compression coated tablets c) Inlay tablets	IV. Dental cones
III. Modified release tablets	**3. Tablets Administered By Other Routes**
IV. Delayed action tablets	I. Implantation tablets
V. Targeted tablets :	II. Vaginal tablets
	4. Tablets Used To Prepare Solution
a) Floating tablets b) Colon targeted tablets	I. Effervescent tablets
VI. Chewable tablets	II. Dispersible tablets
	III. Hypodermic tablets
	IV. Tablet triturates

Concept of Layer Tablet

Layer tablet consists of two to three layers of granulation compressed together. Since the edges of each layer are exposed, they have a sandwich-like appearance. This kind of dosage form has the unique advantage of separating two incompatible API with an inert barrier of separation in between them. Layer tablets are designed for a variety of reasons as follows:

✓ Introducing a single API with biphasic drug release profile is possible with this or SR preparation with IR quantity in one layer and then slowly release portion with remaining layer can be produced.

✓ With the use of multilayer tablet delivery of either single or two different APIs can be controlled.[7,25,41]

✓ To administer fixed-dose combinations of different APIs.[7,25,42]

✓ In fabricating novel drug delivery systems like chewing device[7,43] buccal delivery systems[7,16], floating tablets for gastro retentive drug delivery.[7,25,34,47]

❖ **Rationales for Development of Bilayered Tablet.**[15,35,36]

1. For administration of various multiple APIs in fixed-dose combination, lengthen the life cycle of drug product, mucoadhesive drug delivery system, to make up with novel drug delivery systems like floating tablets and chewing devices for gastro retentive drug delivery.

2. Drug delivery rate is controlled with either a single or two unlike active pharmaceutical ingredient(s).

3. To alter the surface area available for API layer either by stuffing with one or two layers of actives to attain swellable or erodible barriers for control release.

4. To separate incompatible Active pharmaceutical ingredients (APIs) from each other, To control API release from one layer by taking advantage of functional properties of another layer (like- Diffusion, Osmotic property).

Ideal Characteristics [15,17,38,46,48,49]

1. A bilayer tablet should be free from defects such as cracks, chips, discoloration, contamination and it should possess an elegant product identity.[13]

2. It should have enough mechanical strength to resist mechanical shocks during its production, packing, shipping, dispensing.

3. It must have shelf life along with chemical stability.[20,37,39,40]

4. A tablet must release the drug in a presumed and reproducible manner.

5. It must possess physical stability to nurture its physical attributes over time.

Advantages of Bilayered Tablet

1. Offers maximum precision along with least content variability.[7,15,24,46,47,50,51]

2. Improved patient compliance in comparison with traditional systems since the fewer daily dose is sufficient to achieve a desired therapeutic effect.

3. Suitable for scale up. [7,24,30, 46,47]

4. Cost is lower including production, storage, transport, dispensing, and other health system costs. [7,17,24, 46,47]

5. Suitable concept for preventing direct contact between two drugs thereby enhances the efficacy of the combination of two drugs.

6. Objectionable odor and taste masking can be done by adopting coating technology.[17,24,30]

7. Offers the greatest physical, chemical, and microbial stability over all other oral dosage forms. [7,17, 46,47]

8. Better patient compliance leading to improved drug regimen efficiency.[32]

Limitations of Bilayered Tablet [6]

1. Involves chances of cross-contamination between the layers.[7,20]

2. Some API's resist the compression due to low density character and amorphous nature.[7,10,14,17,20,32, 45,49,52]

3. Drugs with poor wetting and slow dissolution properties are difficult to formulate.[10,14,49]

4. Bilayer rotary presses are expensive to add on the complexity.[7,20,32,45,52]

5. Multiple factors need to be taken into consideration while formulating such as the force of compression, compaction, deformation characteristics of materials, process parameters like the choice of lubricant, tensile strength, presence of coating.

6. Difficult to control the individual layer weight.[32]

7. Reduced yield, insufficient hardness, layer separation.[7,45,52]

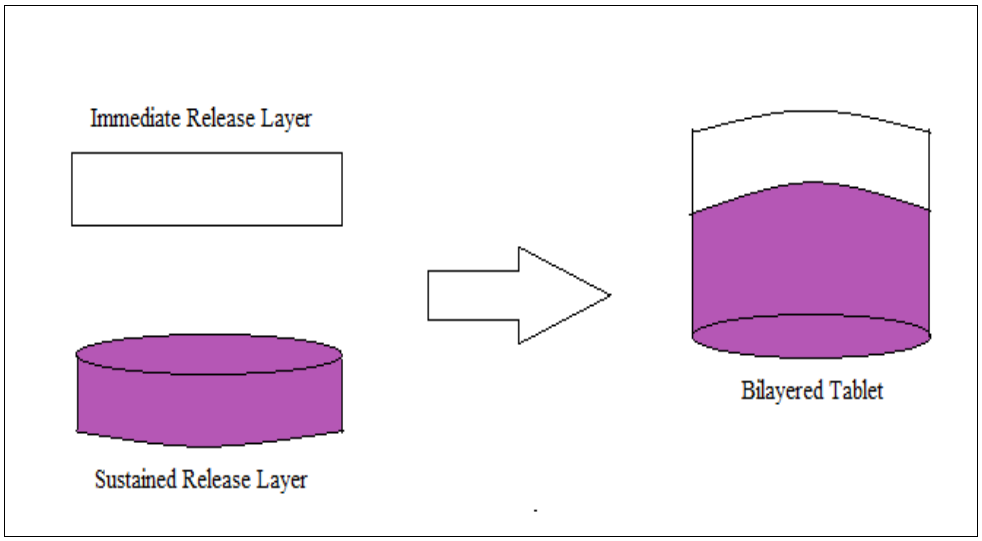
8. Difficult to swallow for pediatrics and unconscious patients.[7,10,14,17,20,32,45,49,52]

TYPES OF BILAYER TABLET

Bilayer tablet is suitable to deliver two drugs at a time without any pharmacological interaction. The tablet having subunits can be either of the same drug (Homogeneous) or different drugs (Heterogeneous)[5,30,53,54].

a) Homogeneous type: These are favored when the drug shows a dual release profile. They are designed in such a way that the immediate release layer acts as a loading dose and the sustained release layer acts as a maintenance dose.

b) Heterogeneous type: These are preferred when two incompatible substances are combined in a single dosage form separated from each other. Two drugs providing sequential release in combination are of this type.



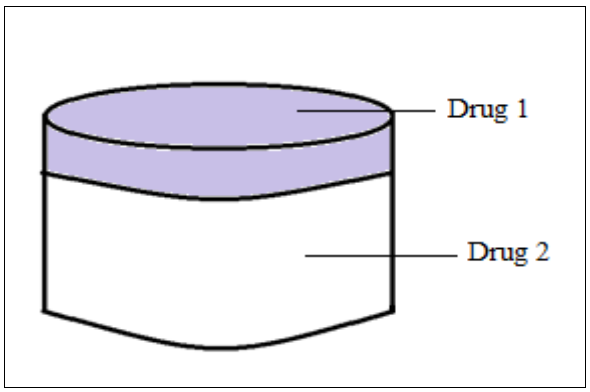


Figure No. 1: Bilayer Tablets (the same drug with different release pattern) homogeneous)

MECHANISM OF DRUG RELEASE [32]

Bilayer tablet has a matrix core containing active drug and modulating layers or barriers in it having the ability to erode. These layers act by limiting the surface available for drug release. Thus, the interaction between active solute and dissolution medium is delayed, along with this solvent penetration rate is controlled and core is preserved for some duration. Hence, the Burst effect can be achieved in the desired range and constant drug release can be maintained. After this phase due to barrier erosion surface available for drug release increases and there is a decrease in delivery rate due to the saturation effect. Various dissolution patterns can be achieved such as pulsatile, extended-release for different drugs by varying the formulation of layers.

METHOD OF PREPARATION [14,17,30,55,56,57,58]

Bilayer tablets are prepared with one layer of the drug for immediate release with the second layer designed to release the 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 to minimize the area of contact between two layers.

1. Compaction

To produce an adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be a difficult task for the for emulator to achieve these conditions, especially in the 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 the material involves both compressibility and consolidation.

2. Compression

It is defined as a reduction in bulk volume by eliminating voids and bringing particles into closer contact.

3. Consolidation

It is the property of the material in which there is increased mechanical strength due to inter-particulate interaction (bonding). The compression force on layer one was found to be a major factor influencing tablets delaminating.

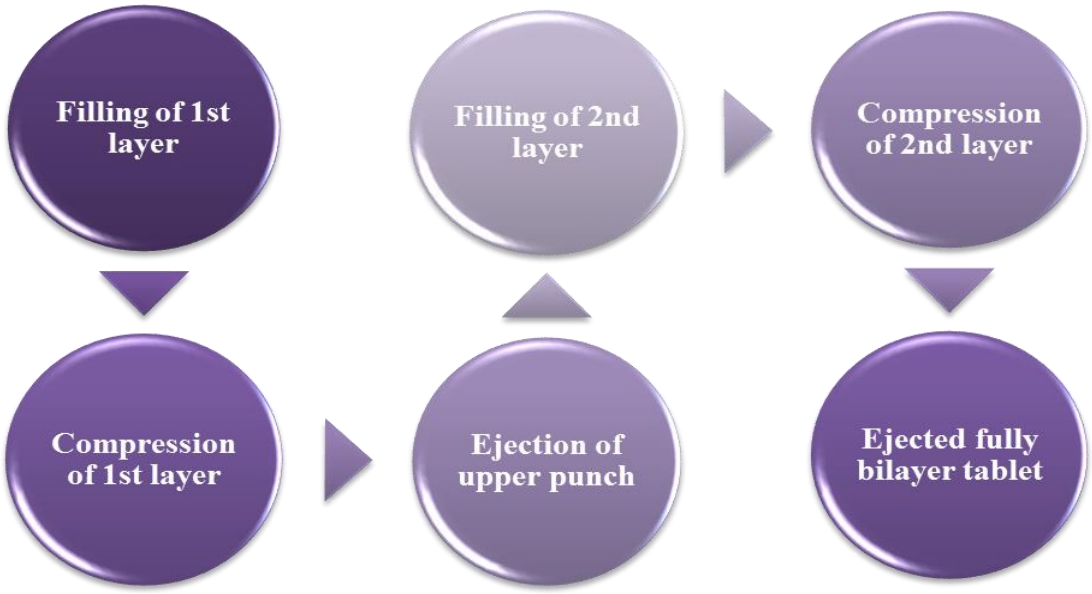


Figure No. 2: Compression cycle for Bilayer tablet

CHALLENGES IN BILAYER MANUFACTURING[17]

1. **Delamination**: Tablet descend when two layers do not bond completely, granules of both layers should have adhered during compression.

2. **Cross Contamination**: When the granulations of one layer intermix with granules of another layer cross-contamination occur. To prevent proper dust collection becomes necessary.

3. **Production Yield**: Proper dust collection ensures the prevention of cross-contamination but it leads to losses. Hence, bilayer tablets have a lower yield as compare to single-layer tablet.

4. **Cost:** Bilayer Tableting is costly than single-layer tablets for the following reasons.

a) Bilayer rotary presses are expensive.

b) Press generally runs slowly in bilayer mode.

c) Granules of both the layers should be compatible, eventually, formulation development analysis and validation become a time-consuming process.

These parameters if not optimized properly will affect bilayer compression and quality aspects of the tablet. Thus, it becomes necessary to enable the design of robust products and processes.

GMP REQUIREMENTS [6,7,14,17,24,32,52,59,60,61-64]

To produce a quality bi-layer tablet, in a validated and GMP-way, the chosen press must be capable of:

1.Preventing capping and separation of the two individual layers that constitute the bi-layer tablet,

2.Providing sufficient tablet hardness.

3.Preventing cross-contamination between the two layers.

4.Producing a distinct separation between the two layers & give a high yield.

5.Producing High yield, accurate, and individual weight control of the two layers

VARIOUS TYPES OF BILAYER TABLET PRESSES[7,14,17,24,30]

1. Single-Sided Tablet Press.

2. Double-Sided Tablet Press.

3. Bilayer Tablet Presses With Displacement Monitoring**.**

1. Single-sided press[65]

The simplest design is a single-sided press with both chambers of the double feeder separated from one another. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. 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 whole tablet is compressed in one or two (pre and main-compression) steps. The two layers within the die mix slightly at their interface and in most cases bond sufficiently so that no layer-separation occurs when the tablet is produced.

Dwell time: It is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major parameter in producing a quality tablet, especially when compressing a difficult formulation.

Compression Force: Many bilayer formulations require a primary layer compression force of 100 daN to retain the capacity to bond with the second layer. Above 100daN, this

ability could be lost and bonding between both layers might not be sufficient, leading to the low hardness of the bilayer tablet and separation of the two layers.

Limitations:[65-68]

1. No weight monitoring/control of the individual layers.

2. No distinct visual separation between the two layers.

3. Very short first layer-dwell time because of small compression roller, possibly leading to poor de-aeration, capping, and hardness problems.

4. Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

2. Double-sided tablet press[25,65]

It is one among the simplest system of tablet press to eliminate the restrictions of the single-sided press thus; a double-sided tablet press is preferred over a single-sided press. It offers a private fill station, pre-compression, and main compression for every layer. In this, the bi-layer tablet will undergo 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 tablet or layer is measured by the system at the main compression of the layer. This measured peak compression force is that the signal employed by the system to reject out of tolerance tablet and proper the die fill depth when mandatory.[25,46]

Advantages[17,24,25]

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 primary and secondary layer to provide sufficient hardness at maximum turret speed.

4. Maximum prevention of cross-contamination between two layers.

5. A clear visual separation between the two layers.

6. Maximized yield.

Limitations

1. The separation of the two individual layers is due to insufficient bonding between the two layers during the final compression of the bi-layer tablet.

2. Correct bonding is merely obtained when the primary layer is compressed at a low compression force so that this layer can interact with the second layer during final compression.

3. Most of the double-sided tablet presses are provided with an automated controller for monitoring compression force and control tablet weight, but the compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

4. 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 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. This double-sided tablet press has been specifically designed and developed for the production of quality bilayer tablets and provides:

Advantages:

1. Weight monitoring/control for accurate and independent weight control of the individual layers.

2. The low compression force is applied on the primary layer to avoid capping and separation of the two individual layers.

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 the two layers.

5. The clear visual separation between the two layers and maximized yield.

VARIOUS TECHNIQUES FOR BILAYER TABLET[6,10,14,24,30,69,71,72]

1. OROS ® push-pull technology[17,59]

This system consists of mainly two or three layers among which the one or more layer is essential of the drug and another layer consist of push layer. The drug layer mainly comprises the drug along with two or more different agents. So this Drug - The layer consists of a drug that is poorly-soluble form. There is a further addition to suspending agent and osmotic agent. A semi-permeable membrane surrounds the tablet core. The drug layer is poorly soluble. Suspending agent and the osmotic agent may be added further. A semi-permeable layer separates the tablet core from surrounding.

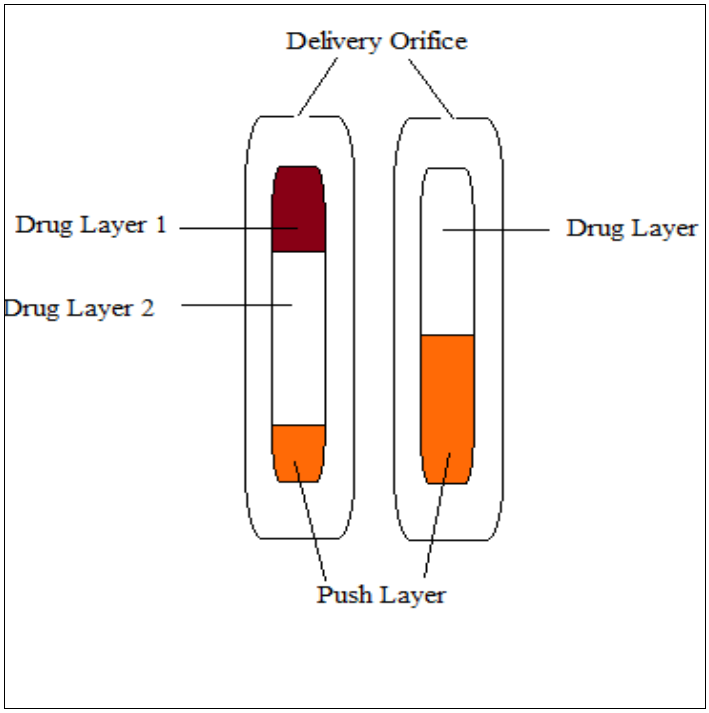


Figure No. 3: OROS ® push-pull technology

2.L-OROS technology [17,69]

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, then osmotic push layer and then a semi-permeable membrane, drilled with an exit orifice.

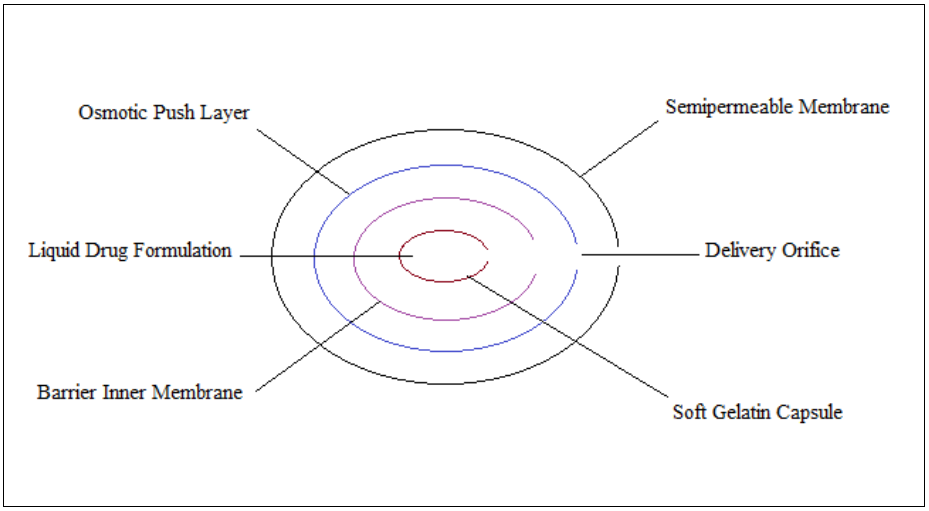


Figure No. 4: L–OROS TM Technology

3. EN SO TROL Technology[17,70]

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

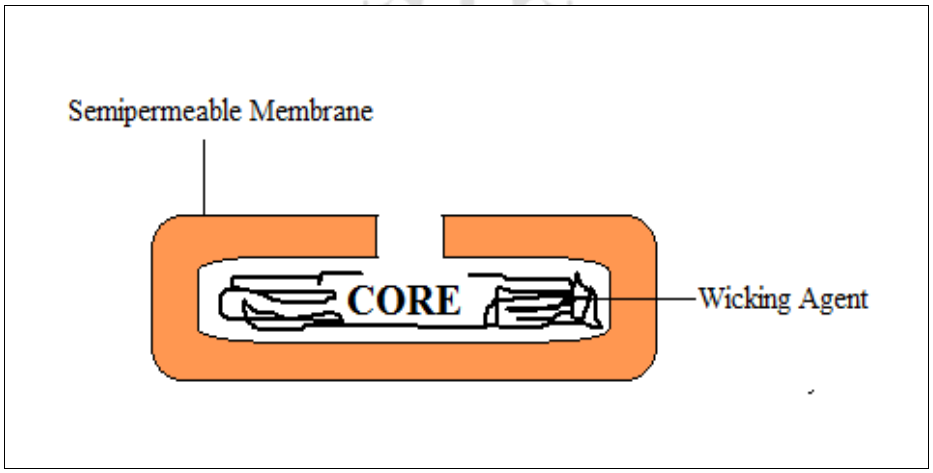


Figure No. 5: EN SO TROL technology

APPROACHES OF BILAYER TABLET [6,14,17,30]

1. Floating Drug Delivery system

These are designed to possess a low density and hence float on gastric contents after administration until the system either disintegrates or the device absorbs fluid to the extent where its density is such that it loses buoyancy and may pass more easily from the stomach with a wave of Motility liable for gastric emptying. The bilayer tablet is constructed in such a

fashion that, one layer gives the immediate dosing of the drug which provides faster onset of action while another layer is meant as a floating layer that floats within the stomach.

2. Polymeric Bio-adhesive system

These are designed to imbibe fluid following 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 one layer with immediate dosing and the other layer with bioadhesive property.

3. Swelling system

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult. 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 the stomach. The simple bilayer tablet may contain an immediate-release layer with the other layer as extended-release or conventional release.

CRITICAL FORMULATION ASPECTS OF BILAYER TABLET

1) API and Excipients

Physicochemical properties of API and excipients are important for the successful manufacturing of bilayer tablets. Characteristics of layered tablets such as hardness, laminating tendency depend on qualitative and quantitative composition along with the tendency of deformation during compression of each layer of a tablet. While manufacturing the layer tablets flow properties, particle size distribution, Compression ability are the important parameters for assurance of accurate weight control of each layer of the tablet. Compression of the layer with a smaller drug dose is often recommended to achieve satisfying API content uniformity. In a bilayer tablet, 1:1 or 1:2 is the weight ratio of the layer is used. Sometimes 1:3 or 1:4 is also used but during developmental research layers, up to 1:6 have been formulated.

2) Granulation[81]

The procedure of forming or crystallizing into small particles is known as granulation. The size of the granules ranges between 0.2 to 4.0mm. This process combines one or more particles and forms granules which will allow tableting to be within required limits. In this way, a reproducible procedure is obtained which results in producing quality tablets. Granulation is performed to prevent segregation; it takes place because of differences in the density or size of the components of the powder mix. Generally, dense particles tend to settle down at bottom of the container, and fewer ones on the top because of their small size, non-uniform shape, or cohesive surface characteristics do not flow well. When such powder is converted into granules, they are larger and more uniform leads to improved flow properties. Some powders are difficult to compress but granules of the same powder are easy to compact. Ideal granules will have an equal distribution of all the components of powder mix in the accurate proportion in each granule. Two types of granulating methods are employed in the pharmaceutical industry.

✓ **Dry Granulation** [81,86-88]

This technique is employed when the product to be granulated is moisture or heat sensitive. In this, granules are formed without using the liquid solution. For this high shear mixer, a granulator is used. Initially, powder particles are aggregated under high pressure. It can be conducted under two processes, either a large tablet (slug) is produced in a heavy-duty tableting press, or powder is pressed between two rollers to produce a sheet of materials. When the tablet press is used for dry granulation, the powder may not have sufficient flow to feed the material uniformly into the die cavity, which leads to variation in the degree of densification thus roller compactor an auger feed system is used which ensures consistent delivery of powder between two pressure rollers. The powders are compacted into a ribbon or pellets and milled through a low shear mill before tablet compression.

✓ **Wet Granulation[81]**

In this, granules are produced with the addition of granulating fluid onto the powder bed which is under influence of an impeller (in a high shear granulator) or air (in a fluidized bed granulator). The granulating fluid must be volatile and non-toxic so that it can be easily evaporated. Typical granulating fluids are Water, Ethanol, and Isopropanol alone or in combination. These fluids can be aqueous or solvent-based. When the fluid is mixed with the

powder base it leads to aggregation of the primary powder particles to produce wet granules. When water is used as a granulating fluid it may not be strong enough to create and hold the bond between powder particles. In such cases liquid binder (pharmaceutical glue) such as Polyvinylpyrrolidone (PVP) dissolved in water or solvent added to this process. PVP forms a bond with powders and then solvent or water evaporates resulting in the formation of densely held mass which is then milled. This process leads to the formation of granules. This method can be very simple or complex depending on the final objective of the tablet, characteristics of the powder, and the available equipment. In the traditional process, wet mass is passed through a sieve to produce wet granules and then dried.[82-85]

✓ **Direct Compression** [81]

It is considered the easiest method since granulation is omitted. This procedure only involves powder blending, lubrication, and compaction. Usually, it is essential to use excipients precisely designed for direct compression and fabricated to provide the necessary flow and compaction properties. These substances are referred to as Filler-binders. The utility of this method may be limited by the dose of the drug to be tableted. The Amount of granulating fluid used, the temperature of the air during drying of the granules, time required for the massive step is considered important parameters during granulation of the therapeutically active substance. Impact of the factors is considered and response can be classified into four categories:

1. Properties of granules – example. Bulk density, tapped density, ability to flow, particle size distribution

2. Extensometric properties – example. Elasticity, plasticity, ejection strength, lubrication index, cohesion index

3. Physical characteristics – example. Thickness, hardness, friability, weight variation

4. Analytical tests – example. In vitro profile, Content Uniformity

3) The concentration of polymer:

The release of drugs from a tablet is dependent on the concentration of polymer. An increase in the polymer concentration usually reduces the dissolution rate of a tablet. These considerations do not affect the drug release in layered tablets, precisely in bimodal tablets, since the solubility of some polymers depends upon the pH of the surrounding medium. For

example. at pH 1.2 effect of decreasing amount of HPMC is not significant but at pH 6.8 and 7.4 drug release increases with a decrease in the amount of the polymer. This is because at low pH HPMC is insoluble. Hence, there is no effect on the breakdown of the polymer network. At high pH, less dense polymer dissolves quickly than a tight structure, which results in an increased drug release rate. Thus the concentration of polymer which is pH-sensitive need to be controlled more closely. Examples of such polymers are PEGs, Kollidon SR, Methocel K4 premium.

4) Concentration of Diluent:

Diluent has a great impact on the drug release rate because of solubility. Thus, diluents or fillers are used in the core of the tablet. Diluent when comes in a contact with the release medium, enhances the porosity of the polymer and ultimately affects the drug release rate. Thus the amount of polymer is adjusted according to the diluent to maintain constant tablet weight. Examples. Lactose, Starch 1500.

5) Effect of lubrication:[6]

The addition of lubricant has a key impact on interfacial strength. Ty et al. has observed that the effect of the amount of lubricant on strength of the bilayer tablet is more dominant for polymeric materials. The interfacial strength of the layered tablet reduces with an increase in the concentration of lubricant. It also reduces the roughness between adjacent layers and ultimately results in reducing the interaction between the layers. The absence of lubricant leads to a picking and sticking effect. Thus, spraying of the lubricant onto the dies and punches, instead of adding directly to the granules has been investigated to determine the effect of lubricant on the critical quality attributes of the tablet. This process has been called ‘External Lubrication’ in the literature. It has been observed that it increases the crushing strength of the tablet by 40%without prolonging the tablet disintegration. Thus external lubrication is the preferable approach though, this method has been shown to improve the production of a monolayer tablet it, can be potentially used to better understand the impact of lubricant on the quality attributes of bilayer tablet.

6) Interfacial strength:

Interfacial cracks produced by residual stresses are responsible for cracking, laminating, and fracturing of layered tablets. These changes are not observed immediately after the compacting process[9,89,90],. All these changes in the interface result in a reduction of

overall stiffness and increase brittleness in the tablet. The difference in Young's modulus between layers of the tablet causes the elastic mismatch and generates the radial stress which ultimately leads to delamination of the layered tablet[9,91-95]. Ko et al. observed that when brittle material such as lactose is used in both the layers of the tablet, the elastic mismatches between adjacent layers are reduced. If the material present in the first layer is more elastic, the tension present in the overall system weakens the strength of the tablet such tablets can lead to delamination.

7) Compression force and Adhesion strength;[81]

Compression force applied on a particular layer is crucial and has a significant impact on strength and interfacial attraction between layers hence; it contributes to the mechanical integrity of bilayer tablets [9,89,96-100]. Thus, it is necessary to adjust optimum compression force to achieve the tablet with desired properties. Lack of optimum compression force can leads to mismatching between the layers of plastic material and can result in delamination of tablets [91,93]. The compression pressure and punch speed affect the compatibility and resistance to compressibility into the die.[27] Generally, compression forces range between 2-18kN. The role of compression force for the first layer is to press the powder or granules to reduce the volume and creating a space for the second layer along with this it also smoothens the first layer surface.

In general, as the compression force increases, the tensile strength increases while surface roughness reduces. Surface smoothening increases the chances of delamination by limiting the intermolecular adherence between adjacent layers. Bilayer tablet having brittle material do not show delamination even if higher compressive force is applied to the first layer (example: 6kN)When polymers like methylcellulose are used in both the layers of the tablet and higher force is applied for the compression then there is a reduction in interfacial strength of the tablet. The level of the compression force applied to the first layer is the parameter to decide interfacial strength between layers. Kottala et al. discovered that the interfacial strength of the polymeric material used in a tablet depends upon the compression force applied to the second layer.

As per the research conducted by Akseli et al, In manetal and Karehill et al.

The minimum amount of force should be applied to the first layer so that, there will be sufficient surface roughness is developed which will increase the contact and adhesion

between adjacent layers. Moreover, to increase adhesion strength, Lubricant content and compression force should below to create a high compression force outer layer of the tablet. It is preferable to apply less pressure for the pre-compression or adjusting the compression zone in the die.

(For the second layer) it will reduce the risk of delamination or capping. Usage of one- or-two-way die will reduce air bubbles level during compression. turret speed significantly affects the strength of the tablet.

8) The hardness of the tablet:[6]

The resistance of tablets during storage, transportation, shipping, breakage, handling before usage depends upon their hardness. It is measured by Veego hardness tester and expressed as kg/cm square. It is determined in terms of tensile strength. As per fell and Newton, it is calculated by the formula

$$\sigma = 2P/\pi Dt$$

Where,

σ -Tensile strength (kg/cm square)

D - Diameter of tablet (cm)

t - Thickness of tablet (cm), P - Force applied to fracture

An increase in tensile strength reduces the tablet porosity which depends on compression. Compression of the lower weight layer is preferred over the weight of another layer because preserving the integrity of the second layer is difficult as compared to the first one. Kottala et al have produced bilayer tablets with methylcellulose and lactose in ratios 1:1, 1:3, and 3:1 concluded that used materials and neither their ratio can significantly affect the breaking force. Compatibility properties between sequences of layers can control interfacial roughness and ultimately interfacial strength. Akseli et al studied the effect of the sequence of a layer on mechanical strength. Initially, when the starch layer is compressed over methylcellulose significant reduction in surface roughness of methylcellulose is observed which ultimately leads to the lesser intermolecular attraction between two layers. After the reversal, the starch in the first layer and then compression of methylcellulose over it is characterized by comparatively higher tensile strength.

9) Coating:[6]

Multilayer tablets are often coated for several reasons such as to enhance elegance, to protect the cores from environmental conditions, to control the release profile. During product development tablets are exposed to compression loads, high temperature, and solvents. Thus, avoiding the delamination coating process is important. During the coating process, it is necessary to know the coefficients of thermal expansion of tablet layers and their effect on the integrity of the tablet. It has been observed that during coating of the tablet, cracks appeared on the surface of one layer of tablet within few minutes of coating, leaving the other intact. After testing, it was found that the coefficient of thermal expansion is significantly different for both layers. When the coating is performed individually for both the layers separately at temperatures 40-45° no cracking was found. To reduce cracking product was reformulated with each layer having nearly the same thermal expansion coefficient.

10) *In-vitro* Performance:[6]

The *In-vitro* dissolution requirement of the bilayer tablet will differ as per the dosage design and Physico-chemical properties of a drug in each layer. This variation imposes challenges in the development of dissolution methods for bilayers, especially if APIs with different water solubility are included in bilayer tablets. Rate of swelling, rate of water uptake are important aspects that need to be taken into consideration while developing the dissolution method.

Example. If the bilayer tablet aims to deliver two incompatible drugs then separation of these layers in dissolution may be of no significance since it would not have any effect on product performance (In- Vivo). However, if the bilayer tablet is a modified release product, having a feature to control the release rate of an API then the integrity of the layers in dissolution media is critical to the performance of the drug product (In- Vivo). Bilayer tablet consists of two water-insoluble APIs that need extensive use of simulated fluid for freshly prepared as well as for long-term stability samples. All the studies performed during dissolution method development must be included in the filling to support the final method which will be used for the release and stability of the drug product. Dissolution method development for limited water solubility is challenging than the highly water-soluble API. To evaluate the drug release performance of the bilayer drug product, well-established techniques can be used by understanding the solubility differences of APIs, use of appropriate surfactants, composition and volume of the dissolution media, pH, type of apparatus, and rate of agitation.

11) Stability:[6]

Stability studies are performed to ensure that the integrity of the drug product is preserved throughout the shelf life. In this drug products are observed closely and tested periodically. Bilayer tablets produced with two APIs in combination are convenient and simplify the treatment regimen. The use of combination two APIs or the same API with different release patterns optimizes the treatment and has shown better patient compliance. To achieve this objective the quality and performance of the tablet must be maintained over the expiration period.

The stability studies are performed as per ICH guidelines and supportive data is included in the filing during the product development phase. It is recommended that the applicant perform drug-drug, drug- excipient interaction, and effect of the manufacturing process, heat, humidity on the integrity of the bilayer, and drug release over the expiration period.

REGULATORY PERSECTIVE[32]

WHO has observed that there is an international trend of fixed-dose combination products in the market because of their simplicity in procurement and cost-effectiveness. Fixed-dose combinations (FDCs) hold a better prospect for the treatment of disorders such as tuberculosis and HIV. However, for regulatory authority, several factors are to be considered before the registration of the FDCs. Out of them prescription ethics and rationality of formulation are the most important parameters.

FDCs can relate with bilayer formulations since both of them refer to a drug product having two or more active ingredients in a pre-defined composition with a fixed ratio. As per WHO new fixed-ratio combination products are considered as new drugs in their own right. They are only acceptable when the dosage of each ingredient meets the requirement of a defined population group and the combination has proven advantage over single compounds administered separately in terms of therapeutic effect, safety, or compliance. They should not be treated as generic versions of single-component products.

As per ICH guidelines, protocols have been issued for testing and licensing criteria for fixed-dose combination products, bioavailability, and bioequivalence studies. Categories of FDCs approved in India are as follows.

Category I – Not marketed in India having one or more APIs, is a new drug and not approved in India.

Category II – Not marketed in India but the APIs are approved.

Category III – Marketed in India but some changes are sought.

The regulatory guidelines of FDCs can be applied for bilayer formulations. The field of bilayer tablets continuously developing new types of excipients or technology with more efficacious drug products having novel mechanisms for drug release.

EVALUATION [6,7,10,14,17,20,24,25]

1. Thickness

The thickness and diameter of tablets were important for uniformity of tablet size and were measured using venire caliper.

2. Hardness

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 within the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to interrupt the tablet when the force generated by a volute spring is applied diametrically to the tablet. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to interrupt the tablet. Hardness, which is now more appropriately called crushing strength determinations is made during tablet production and is utilized to determine the need for pressure adjustment on a tablet machine. If the tablet is just too hard, it does not disintegrate within the required period to meet the dissolution specifications; if it is too soft, it cannot withstand the handling during subsequent processing like coating or packaging and shipping operations. The force required to interrupt the tablet is measured in kilograms and crushing strength of 4 Kg is typically 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 a few sustained-release tablets are much harder (10 -20 kg). Tablet hardness is related to other tablet properties like 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. Stability Study (Temperature dependent): The bilayer tablets are packed in suitable packaging and stored under the subsequent conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after 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 work out the kinetics of degradation.

3. Size and Shape

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

4. Uniformity of weight

Weight variation test is done as per the standard procedure. Ten tablets each formulation is weighted using an electronic balance and the average weight is calculated.

5. Friability

Friction and shock are the majority of forces that often cause tablets to chip, cap or break. The friability test is closely associated with tablet hardness and is meant to gauge the power of the tablet to face up to abrasion in packaging, handling, and shipping. It is usually measured by the utilization of the Roche friabilator. Several tablets are weighed and placed within 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 is compared with the initial weight. The loss because of abrasion is a measure of the tablet friability and it is expressed as a percentage. A maximum weight loss of less than 1% of the load of the tablets being tested during the friability test is taken into an account generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values aren't calculated. A thick tablet may have less tendency to cap whereas thin tablets of huge diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss within the weight of the tablet is that the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = 1 - (\text{loss in weight} / \text{Initial weight}) \times 100.$$

6. Wetting time: Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to

the Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper.

The surface of the tablet is noted as a wetting time.

7. Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using the following equation,

$$R = 10 (Wa /Wb)$$

Where- Wb is the weight of tablet before water absorption & Wa is the weight of tablet after water absorption.

8. Dissolution Study: Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried 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 (900 ml) and the experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using the multi-component mode of analysis.

Applications [7,20,27,73,74]

1. Bi-layer tablets are suitable for the sequential release of two drugs together.

2. It is improved technology to beat the shortcoming of the regular tablet.

3. Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.

4. Bilayer tablets are used to deliver the two different drugs having different release profiles.

Table No. 2: Bilayer tablets Containing Two drugs in an individual layer[10,75-79]

Drugs		**Superdisintegrant used in Immediate-release layer (IR)**	**Polymer used in the sustained release layer (SR)**
1st layer	**2nd layer**		
Glimepiride	Metformin HCL	Sodium starch glycolate	HPMC K4M, sodium carboxymethyl cellulose
Valsartan	Metformin HCL	Crospovidone	HPMC K100M, sodium CMC, PVP K90

Table No. 3: Bilayer tablet containing the same drug in both layers (Biphasic Drug Delivery)[80]

Drug	**Superdisintegrant**	**Rate Retarding polymer**
Aceclofenac	Sodium starch glycolate	Eudragit RL 100
Propranolol Hydrochloride	Sodium starch glycolate	Ethylcellulose Eudragit RLPO, Eudragit RSPO
Guaifenesin	Sodium starch glycolate	Carbopole 934
Baclofen	Crosspovidone, Crosscarmellose	HPMC K4M

CONCLUSION:

Bilayer tablet technology is a concept that demonstrates technology for various applications such as quick/slow, bimodal, pulsatile delivery of active ingredients because it allows the precise modulation of the drug release process. Bilayer tablet quality and GMP requirements can vary widely. This explains why many different types of presses are being used to produce bilayer tablets, ranging from simple single-sided presses to highly sophisticated machines. Compression force-controlled press is limited when a quality bi-layer tablet needs to be produced in conjunction with accurate weight control of both layers. Low precompression forces are necessary to secure interlayer bonding. But at low forces, the compression force control system is not sufficiently sensitive and therefore lacks accuracy. The use of higher compression force may rapidly result in separation and Hardness problems when compressing bilayer tablets.

There are still several technological challenges that need to be overcome to produce a bilayer with equivalent reliability as found in monolayer tablets. The critical parameters in designing and manufacturing the bilayer tablet and heterogeneity of adjacent layers which has a significant effect on the properties of the individual layer and interfacial strength. To overcome these issues, pharmaceutical technology and manufacturers' are constantly evolving to develop new and improved techniques and methods.

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REFERENCES:

1. Swati Aggarwal, Navneet Syan, Pooja Mathur, Bi-Layer Tablet Technology - Opening New Ways in Drug Delivery Systems: An Overview, International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 4 (1) Jan– Mar 2013, Pg. 8-16
2. Furness G. Introduction. In: Oral Drug Delivery When You Find the Holy Grail. UK: ONdrug Delivery Ltd; 2007:3.
3. Dahiya A, Rohilla A, Rohilla S and Khan MU Gastroretentive dosage forms: Review on floating drug delivery systems. Int Res J Pharm 2011; 2(5):72-8.
4. Sharma A, Jain A, Purohit A, Jatav R and Sheorey RV. Formulation and evaluation of aceclofenac fast dissolving tablets. Int J Pharm & Life Sci 2011; 2 (4):681-6.
5. Rawlins E A. Bentley's textbook of pharmaceutics. 8th ed. London: Bailliere Tindall;1992:269
6. Rayaprolu Mounica, Junju Mohan Kumar, Voleti Vijaya Kumar, Sai Padmini Bolla, M. Pavani1, A New venture in drug delivery: Bilayered tablets review, International Journal of Research in Pharmaceutical and Nano Sciences 2(3), May-June 2013, 305 - 316.
7. Vishwakarma A. G., Mogal R. T., Pawar A. Y., Bi-Layer Tablet - A New Ways in Oral Drug Delivery System, International Journal of PharmTech Research, Vol.6, No.5, Sept-Oct 2014, pp. 1416-1428
8. Manjula, A., Selvam, P., Normal, R and Shakilabanu, S. In vitro evaluation studies of cross linked chitosan microspheres containing rabeprazole sodium. Int J Pharm Sci Res 2011, 2(6):1513-7.
9. Abdul, S., Poddar, S. S. A flexible technology for modified release of drugs: multi layered tablets. J. Control. Release 97 published 2004, 393–405.
10. Mehul Patel, Nihar Shah, A Sequential Review on Bilayer Tablets, Journal of pharmaceutical science and Bio scientific research (JPSBR), Volume 3, Issue 5: 2013 (163-169)
11. Yadav A and Jain Kumar D. Formulation development and invitro characterization of bilayer and floating bioadhesive tablets of propranolol hydrochloride. Asian Journal of Pharmacy and Life Science. 2011;1(1):2.
12. Singh KP and Kumar S. Bilayer and Floating Bioadhesive Tablets: Innovative Approach To Gastroretention. Journal of Drug Delivery and Therapeutics. 2011;1(1):32-35.
13. Kulkarni A and Bhatia M. Developments and Evaluation of Bilayer Floating Tablets of Atenolol and Lovastatin For Biphasic Release Profile, Iranian Journal of Pharmacy and Research. 2009; 8(1);15 -25
14. Manisha D. Bhadange1*, A. B. Darekar1, R B. Saudagar, Bi-layer tablet technology- opening new drug delivery system: An overview, World journal of pharmaceutical research, Volume 4, Issue 01, 529-548
15. R. Srihari, Patan Adamkhan, P. Siva Reddy, K. Sasikanth, B. Brahmaiah, Sreekanth Nama, An Emerging trends on bilayer tablets, International Journal of Innovative Drug Discovery, Vol 3, Issue 21, 2013,45-50
16. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bilayer tablet of Metoclopramide hydrochloride and Ibuprofen, AAPS Pharm Sci Tech, 9(3), 2008, 818-827.

17. C. Gopinath, V. Hima Bindu*, M. Nischala, An overview on bilayer tablet technology, Journal of Global Trends in Pharmaceutical Sciences, Volume 4, Issue 2, April- June 2013, pp. -1077-1085
18. Martindale, the Extra Pharmacopoeia, 31sted. The Pharmaceutical Press, London; 1996.p.936–937.
19. Shiyani B et al. Formulation and evaluation of bilayer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech 2008;9(3):818-27.Pranjal Kumar Singh et al, Sanjoo Kumar et al Bilayer and Floating Bioadhesive Tablets: Innovative approach to Gastroretention, Journal of Drug Delivery & Therapeutics; 2011, 1(1): 32-35
20. Shaikh Siraj Nawaj*, Patel Zuber, G. J. Khan, Patel M. Siddik and Khan Mujahed, Review on various aspects of Gastroretentive bilayer floating tablet, World Journal of Pharmaceutical research, Volume 6, Issue 12, 1146-1155
21. Kumari Roshani, Prabhudutta Panda, D.K. Vishwakarma, Navneet Kumar Verma. A brief review on bilayer floating tablet. International Journal of Advances in Pharmaceutics, 2017; 06(03): 70-78.
22. Nilawar, P.S., Wankhade, V.P., Badnag, D. B. An emerging trend on bilayer tablets. Int J Pharm & Pha Scie Res 2013; 3(1): 15-21
23. Chien, Y. W. Fundamentals of controlled-release of drug administration in: J. Swarbrick (Ed.), Novel Drug Delivery System Marcel Dekker, New York, 1982, pp. 465–574
24. Prasanna Kumar Desu, P. Likhitha1, S. K. Muneer, R. Lakshmi Prasanna, P. Venkateswara Rao, An emerging trend on bilayer tablets, World Journal of pharmacy and pharmaceutical sciences, Volume 6, Issue 12, 334-346
25. Rajiv Kumar, Parminder Nain, Jaspreet Kaur, Jasjeet Kaur Narang, Ravi Dhawan, Multilayer Tablet- The way of delivery of incompatible drugs, Journal of drug delivery research, Volume 5 Issue 1 2016
26. Krishnaiah YSR, Karthikeyan RS, Gouri Sankar V, Satyanarayana V. Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride. J Control Rel. 2002; 81(2): 45-56.
27. Yang L, Venkatesh G, Fassihi R. Compactionsimulator study of a novel triple-layer tablet matrix for industrial tableting. Int. J. Pharm. 1997; 152(1):45-52.
28. Al-Zoubi N, Malamataris S. Three-layer matrix tablets and simple approach of drug release programming. J Drug Del Sci Tech. 2008; 18(6):431-37.
29. P. Preetha; A. Srinivasa Rao; P. Pushpalatha, Biphasic drug delivery in controlled release formulations- A review, International Journal of Pharmacy and Technology, April-2015,Vol. 6,Issue No.4, 3046-3060
30. Ayush Garg, Amul Mishra, An overview on bilayer tablet dosage forms, International Journal of Research in Pharmacy and Pharmaceutical Sciences, Volume 5; Issue 1; 2020; Page No. 15-22
31. Aggarwal S, Syan N, Mathur P. Bi-layer tablet technology-opening new ways in drug delivery systems: An Overview. Int J Res Pharm and Biomedical Sciences. 2013; 4 (1):8-16.
32. Praveen Kumar Gaur, Shikha Mishra, Pradeep Prabhakaran, Snigdha Bhardwaj, Dinesh Puri, S. Sadish Kumar, Juhi Dubey, Anurag Verma, and Navneet Verma, Prospectives and Potentials of Bilayer Technology: A Novel Approach, Journal of Pharmaceutical Sciences and Pharmacology, Vol. 2, 1–14, 2015
33. Pujara ND, Gokani R, Paun J. Bilayer Tablet – An Emerging Trend. Int. J. Pharm. Res. Dev. 2012; 4(4): 102 – 111.
34. Hiten AP, Ajay Kumar T. A Novel approach of Bilayer Tablet technology: A Review. International Research Journal of pharmacy, 2012, 5-10.
35. Manidipta D. Bilayer Tableting Technology: An Overview, Journal of Pharmacy Research, 25(1), 2012, 310-314.
36. Martin A, Bustamante P, Chun A. Micromeritics in Physical Pharmacy-Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lippincott Williams and Wilkins, Baltimore, 2002, 446–448.
37. Rohan D. Deshpande, Gowda D V, Nawaz Mahammed and Deepak N. Maramwar. Bi-layer tablets- An emerging trend: a review, IJPSR, 2(10), 2011, 2534-2544.
38. Chandira RM, Palanisamy P, Jayakar B. Formulation and Evaluation of Bilayered Floating tablets of Metformin Hydrochloride. International Research Journal of Pharmacy, 2012; 3: 257-266.
39. Narendra C, Srinath MS, and Ganesh B. Optimization of Bilayer Floating Tablet containing Metoprolol Tartrate as a Model Drug for Gastric retention. AAPS Pharma Sci Tech, 2006; 7: 1-17.

40. Nirmal, J., Saisivam, S., Peddanna, C., Muralidharan, S., Nagarajan, M. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem. Pharm. Bull. 2008; 56: 1455–1458.
41. LaForce, C., Gentile, D. A., Skoner, D. P. A randomized, double-blind, parallel group, multicenter, placebo-controlled study of the safety and efficacy of extended-release guaifenesin/ pseudoephedrine
42. Maggi, L., Segale, L., Conti,S., Ochoa Machiste, E., Conte, U. Preparation and evaluation of release chara-cteristics of 3 Tab Gum, a novel chewing device. Eur J Pharm Sci. 2005;4: 487-493.
43. Park, C. R, Munday, D. L. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int J Pharm. 2002; 237: 215–226
44. Sungthongjeen, S., Sriamornsak, P., Puttipipatkhachorn, S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur. J. Pharm. Biopharm.2008;69:255–263.
45. Panchal, H. A, Tiwari, A. K. A Novel Approach of Bi-layer Tablet Technology- a review. IRJP. 2012:3(5):44-49.
46. Sowmya, C., Reddy, C. S., Tabasum, S.G., Varma, V. An overview on bi-layer tablets. IJPT.2012; 4 (2):2143-2156.
47. Shaikh TK, Gadhave MV and Jadhav SL. Different Techniques In Bilayer Tablets: A Review., International Journal of Universal Pharmacy And Life Sciences. 2012;1(1):1-8.
48. Nilawar SP, Wankhade PV and Badnag BD. International Journal of Pharmacy and Pharmaceutical Science Research. 2013;3(1);15.
49. Mohit ST, Ashish Kumar K, Shikha AD and Dishant G. Bi-Layer Tablets: An Emerging Trend, International Journal of Pharmaceutical & Biological Archives, 3(3), 2012, 499-506.
50. Kumar KK, Mahesh M, Sasikanth K. Design development and characterization of sustained release of Metformin hydrochloride and Gliclazide bilayered tablets by wet granulation method. Int J Biopharm, 1(2), 2010, 67-71
51. Deshpande, R. D, Gowda, D. V., Nawaz, M., Maramwar, D. N. Bi-layer tablets- An emerging trend: a review. IJPSR, 2011;2(10):2534-2544
52. Nagaraju R, Kaza R. Formulation and evaluation of bilayer sustained release tablet of salbutamol and theophylline. Int J Pharm Sci. Nanotech. 2009; 2(3): 638-46
53. Moiz, Prathima SM, Sadanandam M . Formulation and evaluation of bilayered tablets of montelukast and levocetrizine dihydrochloride Using natural and synthetic polymers. Int J Drug Deliv. 2011; 3(4):597-618.
54. Rudnic EM et al, Kottke et al MK Tablet dosage form.In Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd ed., vol 72. New York: Marcel Dekker Inc. p 369.
55. Breech AJ et al, Lucisano L J et al, Franz RM et al Investigation into substrate cracking of a film coated bilayered tablet. J. Pharm. Pharmacol. 1998; 40:282-283.
56. M.A. Kalam et al, M. Humayun et al, N. Parvez et al, S. Yadav et al, A. Garg et al, S. Amin et al ,Y. Sultana et al and A. Ali., Continental et al J. Pharmaceutical Sciences;2007,1: 30– 35
57. Li S.P. et al, Karth M.G. et al, Feld K.M. et al, Pendharkar C.M. et al, Willams R.O. et al, Evaluation of Bilayer tablet machines. A Case study. Drug Dev. Ind. Pharm. 1995; 21(5): 571 590.
58. Lechman L, Liberman HA, Kanig JL. The Theory and Practice of Pharmacy, 3rd Ed., Varghese Publishing House, Bombay, 1987, 430-453.
59. Robinson, J.R., Lee, V. H. Controlled Drug Delivery: Fundamentals and Applications 2nd Ed., Marcel Dekker, New York, 1987; p.4-36.
60. Bhandari, A., Bhatt, G.K., Kothiyal, P., Gosain, S. Bilayer tablet oral solid drug delivery system and challenges in the formulation: A Review. IJPRD. 2012;4(3) :29-44.
61. Patel, M., Sockan, G.N., Mani, K. T. Challenges in the formulation of bilayered tablets: A Review. IJPRD, 2(10), 2012, 30-42.
62. Shaikh, T. K., Gadhave, M.V., Jadhav, S.L., Gaikwad, D.D. Different techniques of bi-layer tablet: a review. Int J Uni Pharm & Life Sci.2012; 2(2):450-460.
63. Rudnic EM et al, Kottke et al MK Tablet dosage form. In Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd ed., vol 72. NewYork: Marcel Dekker Inc. p 369
64. Jan Vogeleer et al Bi-layer tablets - why special technology is required The Courtoy-R292F tablet press, designed for quality bi-layer tablets Niro Pharma Systems

65. Abshagen U et al, Spo ¨rl-Radun S et al, First data on the effects and pharmacokinetics of isosorbide-5-mononitrate in normal man, Eur. J.Clin.Pharmacol.;1981; 19p.423–429.
66. Hutt V et al, Bonn R et al, Fritschi E et al, Jaeger H et al, Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide- 5- mononitrate preparation in healthy volunteers, Arzneim.-Forsch./Drug Res.;1995, p.142–145.
67. Patel Mehul, Ganesh et al, Nanjan Sockan et al, Challenges in the Formulation of Bilayered Tablets: A Review, International Journal of Pharma Research and Development, 2010, ISSN 0974 – 9446.
68. Aulton ME. Bilayer Tablets in Pharmaceutics, The Science of dosage form design, Churchill livingstone, 2nd ed, 2002, 414-418.
69. Fridrun P. Methods for the practical determination of the mechanical strength of tablets- From empiricism to science. International Journal of Pharmaceutics, 436, 2012, 214– 232
70. Science and Technologies [online]. [cited 2012 Available from URL: http://www.durect.com
71. Naisarg D. Pujara Ronak K. Gokani, Jalpa S. Paun. Bilayer tablet – An emerging trend ijprd, 2011; vol 4(04): June-2012 (102 - 111).
72. Sachin, S. K., Viraj, S.S., Prajkta, L.U., Baviskar, D.T. Bilayer Tablet. Int J Phar Sci Rev & Res. 2011; 9: 654-656.
73. Kumar, A. H., Kavitha, K., Kumar, S.A., Kumar, M. R., Singh, J. Novel Approach Of Bilayer Tablet Technology –A Review. Ijpcbs. 2013:3(3):887-893
74. Ashraful Islam S. M. A., Banu H., Saharaiar M. R., Bilayer Tablets of Paracetamol and Aceclofenac: Formulation and Evaluation, International Journal of Pharmacy and Technology, 2011, vol. 3(4), 3668-3681.
75. Naeem MA, Mahmood SA, Shhiq Z, Development and Evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen, Tropical
76. Dinda SC, Pattaynayak DP, Narayan UL, Design and Evaluation of A Fixed Dose Combination Formulation of Valsartan and Metformin HCl For Biphasic Drug Release: A Novel Approach To Increase Therapeutic Efficacy, International Journal Of Pharmaceutical Science and Technology, 6(1), 2011, 44-63.
77. Raghavendrarao NG, Yadav A, Kulkarni U, Formulation and Evaluation of Zero-order Release Glipizide Bilayer Matrix Tablets Using Natural and Synthetic Polymers, International Journal of Current Research, 2(1), 2010, 34-49.
78. Karwa P, Kasture PV, Tablets of Zolpidem Tartrate for Biphasic Drug Release, International Journal of Pharma Tech Research, 3(4), 2011, 1919-1929.
79. Anupam Sarma, Pulak Deb & Suvakanta Dash, Bilayer tablet and Duredas technology review, International Journal of Pharmacy and Biological Sciences, Volume 3 Issue 2, Apr-Jun,2013,554-563
80. Tomasz Blicharski, Katarzyna Swiader, Anna Serefko, Sylwia Kulczycka-Mamona, Michal Kolodziejczyk, Aleksandra Szopa,, Challenges in technology of bilayer and multi-layer tablets:a mini-review, Current Issues in Pharmacy and Medical Sciences, Vol. 32, No. 4, Pages 229-235
81. A. Niharika, D. K. Sarangi, D. Ghose, S. K. Mekap, R. Rana, Formulation evaluation of metoprolol succinate and hydrochlorothiazide bilayer tablets by wet granulation method, Research Journal of Lifesciences Bioinformatics pharmaceutical and chemical sciences, March-April 2018, 162-180
82. Vyas SP. et al. 2002
83. Huber HE et al., 1996
84. International Journal of Pharm Tech Research; Apr2009, Vol. 1 Issue 2, p159
85. Matrix type transdermal drug delivery systems of metoprolol tartrate: in vitro characterization. Aqil M, Sultana Y, Ali A.
86. Mukesh C. Gohel, Rajesh K. Parikh, Stavan A. Nagori, and Dilip G. Jena Fabrication of Modified Release Tablet Formulation of Metoprolol Succinate using Hydroxypropyl Methylcellulose and Xanthan Gum
87. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention C. Narendra, M. S. Srinath, and Ganesh Babu
88. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitino AM. Review of bilayer tablet technology. Int J Pharm. 2014;461(1-2):549-58.
89. Inman SJ, Briscoe BJ, Pitt KG. Topographic characterization of cellulose bilayered tablets interfaces. Chem Eng Res Dis. 2007;85(A7): 1005-12.

90. Anuar MS, Briscoe BJ. Interfacial elastic relaxation during the ejection of bi-layered tablets. Int J Pharm. 2010;387(1-2):42-7.
91. Busignies V, Mazel V, Diarra H, Tchoreloff P. Role of the elasticity of pharmaceutical materials on the interfacial mechanical strength of bilayer tablets. Int J Pharm. 2013;457(1):260-67.
92. Podczeck F. Theoretical and experimental investigations into the delamination tendencies of bilayer tablets. Int J Pharm. 2011; 408(1-2):102-12.
93. Podczeck F, Drake KR, Newton JM, Haririan I. The strength of bilayered tablets. Eur J Pharm Sci. 2006;29(5):361-6.
94. Podczeck F, Al-Muti E. The tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. Eur J Pharm Sci. 2010;41(3-4):483-8.
95. Danckwerts MP. Development of a zero-order release oral compressed tablet with potential for commercial tabletting production. Int J Pharm. 1994;112:34-45.
96. Akseli I, Abebe A, Sprockel O, Cuitino AM. Mechanistic characterization of bilayer tablet formulations. Powder Tech. 2013; 236:30-6.
97. Inman SJ, Briscoe BJ, Pitt KG. Topographic characterization of cellulose bilayered tablets interfaces. Chem Eng Res Dis. 2007;85(A7): 1005-12.
98. Kottala N, Abebe A, Sprockel O, Bergum J, Nikfar F, Cuitino AM. Evaluation of the performance characteristics of bilayer tablets: Part I. Impact of material properties and process parameters on the strength of bilayer tablets. AAPS Pharm Sci Tech. 2012;13(4):1236-42
99. Dietrich P, Bauer-Brandl A, Schubert R. Influence of tableting forces and lubricant concentration on the adhesion strength in complex layer tablets. Drug Dev Ind Pharm. 2000;26(7):745-54.
100. McGinity JW. Aqueous polymeric coatings for pharmaceutical dosage forms. New York: Marcel Dekker. 1997;549-70.