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A THEORETICAL PROSPECTIVE OF BILAYER MATRIX TABLETS

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ABSTRACT

Among the different controlled release dosage forms used for oral delivery, bilayer tableting technology has gained popularity in recent times, as it offers several advantages over conventional tablets. Since the last few decades pharmaceutical industry has shown more interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (monolithic or bilayer tablet) due to increased patient convenience and compliance. A bilayer tablet is one of the most acceptable options to avoid physical and chemical incompatibilities between APIs by physical separation and enable the development of biphasic drug release profiles (immediate release with sustained release). Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also may contains one drug for biphasic release in which one layer is immediate release as initial loading dose and second layer is maintenance dose in sustained manner. Several pharmaceutical companies are currently developing bi-layer tablets due to variety of reasons; patent compliance, therapeutic benefits and reduces cost of treatment. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains the development and production of quality bilayer tablets by overcoming common problems associated with it, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc.

Key words: Bilayer tablets, Biphasic release, immediate release, Sustained release, matrix tablets, Floating tablet

INTRODUCTION:

Bilayer tableting technology has gained popularity in recent times, as bilayer tablets offer several advantages over conventional tablets. Conventional dosage form usually produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

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The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.[1] The bilayer tablet concept has long been utilized to formulate biphasic release of drugs. Such a bilayer tablet contains a first release layer and a sustain release layer. The first releasing layer leads to rapid release of the drug, so as to reach high serum concentration in a short period of time that is called as loading dose. The sustain release layer of the bilayer tablet releases the drug for prolonged period of time to maintain the effective concentration of drug within the therapeutic index.[2] This release pattern is required for successful treatment in many therapies, primarily when

maximum relief needs to be achieved as soon as possible, and is followed by a sustained release phase to avoid repeated drug administration. So bilayer matrix tablet containing a single drug having one layer as fast release layer and another as sustained release layer will be beneficial for the chronic disease like asthma, diabetes, hypertension and inflammation that require immediate effect as well as maintenance therapy.[3]

Floating bilayer tablet

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Floatation of drug delivery system in the drug can be achieved by incorporating floating chamber filled with vacuum, air or inert gas from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also require keeping the dosage form.[4] The bilayer tablet is a concept utilized by Skye Pharma PLC in their geomatrix tablet, which is composed of two different layers. The system allows the incorporation of more than one drug into a single 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 controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers. Gastroretensive drug delivery systems were designed to prolong the residence time of drug in the GIT and this approaches can be utilised for preparation of bilayer tablet containing an immediate release layer and a sustained release layer.[5]

Reasons for design of multilayer tablet dosage forms[6]

- To separate incompatible active pharmaceutical ingredient (APIs) from each other and to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property, vapour pressure, electromagnetic force, sonophoresis etc).
- To control the delivery rate of either single or two different active pharmaceutical ingredient(s). In those cases one layer is usually fast release layer and another layer is controlled release layer.
- To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery.

Benefits of bilayer dosage forms over conventional tablets[7]

- Bilayer tablet may contain two drugs for synergistic effects for single disease (pain, fever etc) or for control of two different diseases attacking at a time (e.g diabetics and hypertension).
- Bilayer tablets are superior to repeat action products; where one layer provides the initial dose, rapidly disintegration in the stomach, the other layer are insoluble in gastric media but are released in the intestinal environment.
- Bilayer tablets can be used to mitigate the side effects that takes place due to use of another drug (e.g use of Diclofenac sodium usually causes peptic ulcer that can be prevented by use antiulcer drug by designing a bilayer tablet).
- Patient convenience is improved because fewer daily doses are required compared to traditional systems.
- Patient compliance is enhanced leading to improved drug regimen efficacy.
- Separate physically or chemically incompatible ingredients.

Advantages of the bilayer tablet dosage form[8]

They are unit dosage form having two layers containing a single drug for biphasic release or two drugs and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

- Overall cost is lower compared to repeat dosing of single oral dosage form.
- More than one drug can be incorporated in single dosage form.
- Lighter and compact.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.

Disadvantages of the bilayer tablet dosage form[9]

- Difficult to control the weight of individual layer.
- Chance of cross contamination between the layers.
- Insufficient hardness.
- Reduced yield.
- Adds complexity and bilayer rotary presses are expensive.

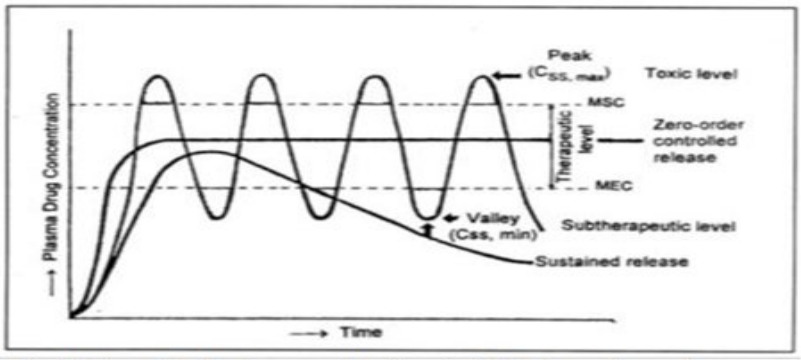

Fig 1: Plasma level release profile of controlled release dosage form

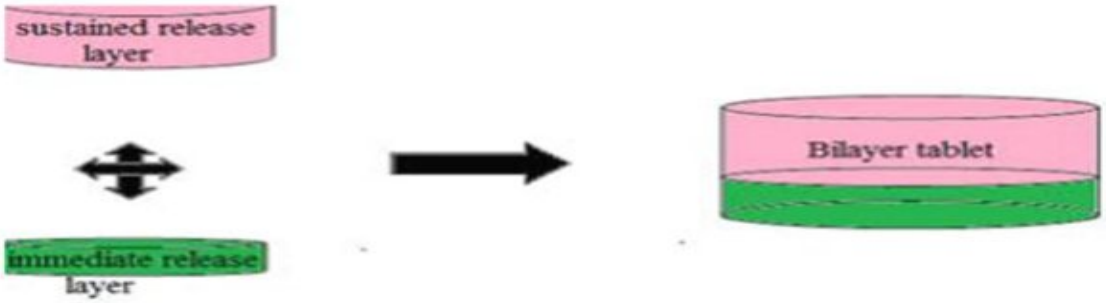

Fig 2: Schematic diagram of bilayer sustained release matrix tablet

Fig 3: Schematic representation of homogeneous type bilayer tablet

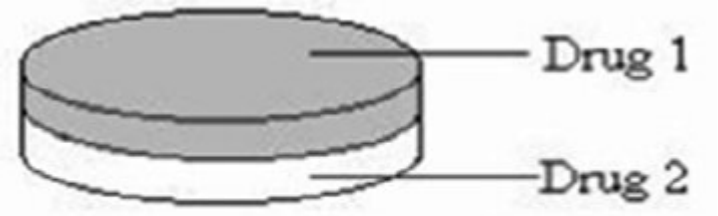

Fig 4: Heterogenous type bilayer matrix tablet

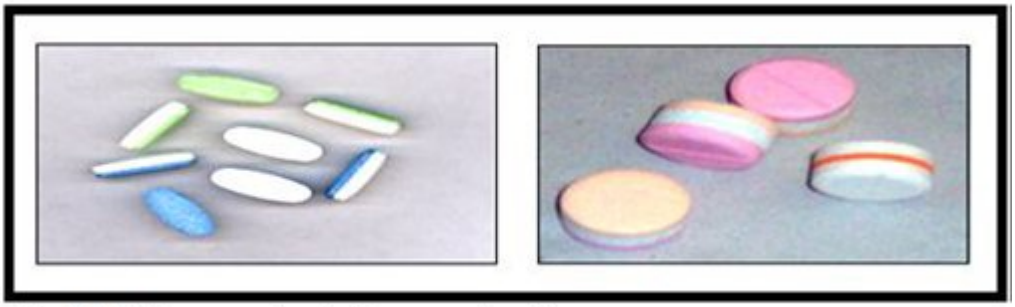

Fig 5: Multilayer sustained release matrix tablet

General properties of bilayer tablet dosage forms[10]

- A bilayer tablet should have elegant product identity with free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time.
- The bilayer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

TYPES OF BILAYER TABLETS

The bilayer tablets can be classified into two categories based on the subunits that it contains in two layers. They may be either the homogeneous (same) type or heterogeneous (different) type.[11]

Homogenous type

Such type of bilayer tablets is preferred when the release profiles of the same drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Homogeneous type bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner.

Heterogeneous type

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

Advantages

They are used as an extension of a conventional technology

- Ability to combine different release rate. IR and SR in the same tablet for chronic condition requiring repeated dosing.
- Promoting patient convenience and compliance because fewer daily doses are required compared to traditional delivery system.

APPROACHES FOR LAYERED TABLETS

1. Multi Layered tablets – two to three component systems.
2. Compression coated tablets – tablet within a tablet.
3. Inlay tablet – coat partially surrounding the core.

Multilayered tablets (Bi, Tri)

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and they are incompatible, the best option for the formulation pharmacist would be to formulate multilayered tablet. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different colour to produce a distinctive looking tablet.[12]

Compression coated tablets

This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet and prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.[13]

Inlay tablets

This is a type of layered tablet in which instead of the core tablet being completely surrounded by coating, top surface is completely exposed. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet.[14]To reduce capital investment quite often existing but modified tablet presses are used to develop and produce such tablets. The development and production of quality bilayer tablets needs to be carried out on purpose-built tablet presses to overcome common bilayer problems. Using a modified tablet press may therefore not be your best approach to producing a quality bilayer tablet under GMP conditions. Especially when in addition high production output is required.[15]

BILAYER TABLETS: QUALITY AND GMP REQUIREMENTS

To produce a quality bilayer tablet, in a validated and GMP way, it is important that the selected press is capable of preventing capping and separation of the two individual layers that constitute the bilayer tablet.[16]

Ideal properties for bilayer tablet press

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet
- Providing sufficient tablet hardness and high yield.
- Preventing cross contamination between the two layers

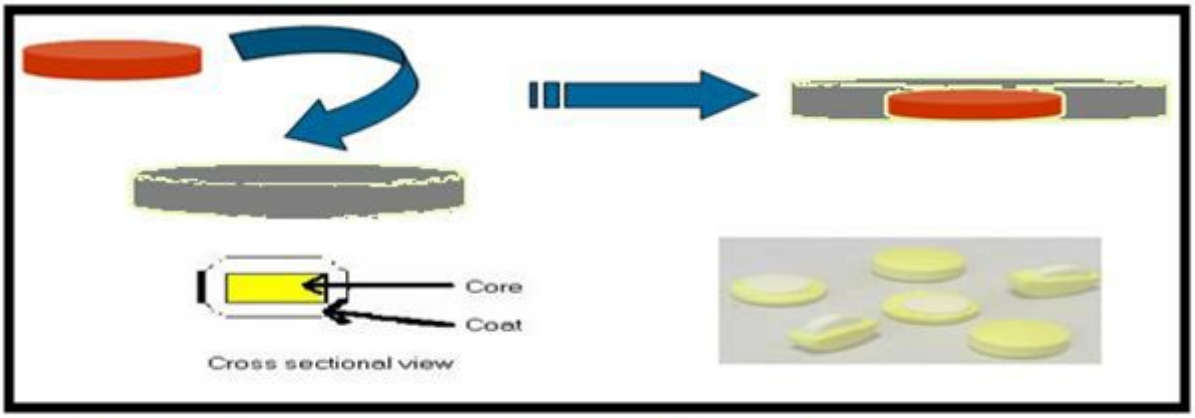

Fig 6: Schematic diagram of compression coated multilayer matrix tablet

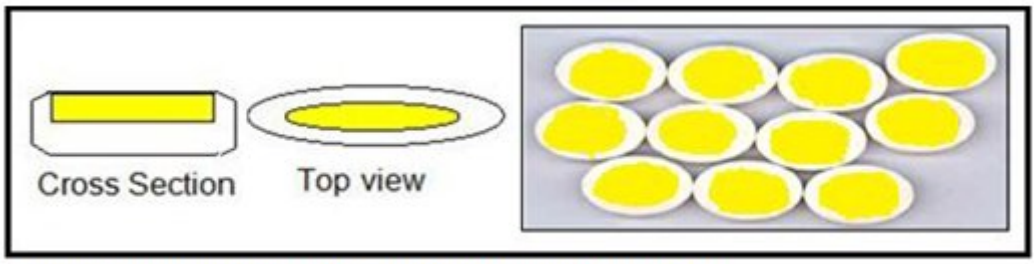

Fig 7: Schematic representation of inlay type bilayer tablet

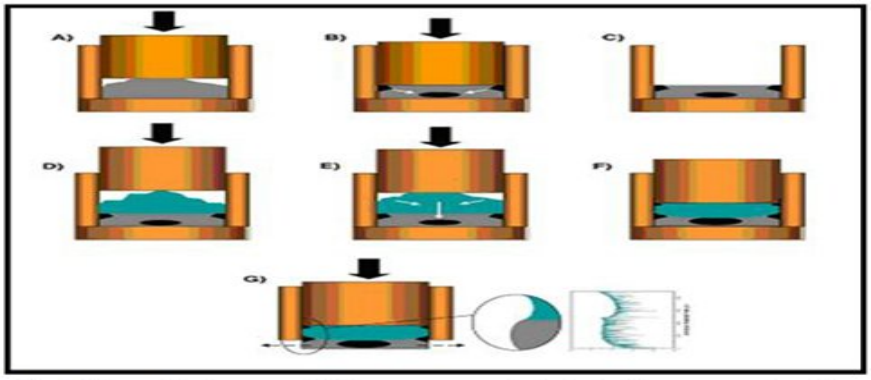

Fig 8:Schematic diagram of different stages of uniaxial tablet compaction of bilayer tablets

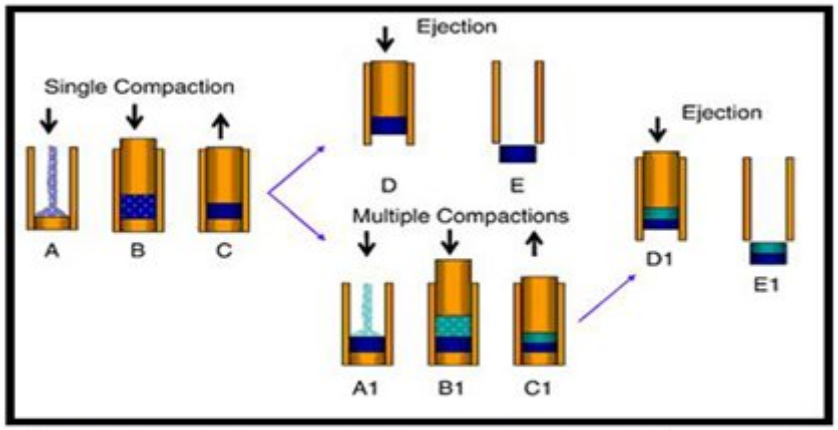

Fig 9: Schematic diagram showing manufacturing of bilayer matrix tablet utilising uniaxial compaction

BILAYER TABLET PRESS

The XM 12 bilayer tablet press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in 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 die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for small scale bilayer applications. The KORSCH XM 12 bilayer 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 offer unprecedented flexibility. The XM 12 Bilayer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooths surfaces that permit fast cleaning and changeover. The machine features a 5 KN tamping station, 40 KN precompression station, 80 KN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level.[17]

Small Scale bilayer tablet press

- 5 KN first layer tamping force.
- 40 KN precompression forces.
- 80 KN main compression force.
- Single layer conversion capability.

Bilayer application

The XM 12 features an exchangeable turret capability to permit a single machine to run all press tool sizes to provide maximum flexibility and versatility. An internal lift arm eliminates the cost and space requirement of a large external turret removal device.[18]

- Single layer conversion kit adds yet another dimension of flexibility.
- Single layer conversion.
- 30 Minute conversion time
- High speed single layer capability (120 RPM)

Advantages

- Flexible Concept.
- Bi-Layer execution with optional single-layer conversion kit.
- Exchangeable turret.
- Turret sizes for product development, scale-up, and mid-range production.
- Full production capability in a scale-up machine.
- Self-contained, fully portable design.
- Fast and Easy Changeover.
- Internal turret lift device for extreme simplicity in turret removal and installation.
- Clean compression zone with quick-disconnect design.

TYPES OF BILAYER TABLET PRESS

- Single sided tablet press.
- Double sided tablet press or “compression force” controlled tablet press.
- Bilayer tablet press with displacement monitoring.

Single sided tablet press

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or force fed with different powers, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.[19]

Limitations of single sided tablet press

- No weight monitoring/ control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor deaeration, capping and hardness problems. This may be corrected by reducing the turret- rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first layer tablet sampling and sample transport to a test unit for in line quality control and weight recalibration.[20]

Double sided tablet presses

A double sided press offers an individual fill station, precompression and main compression for each layer. In fact the bilayer tablet will go through four compression stages before being ejected from the press. Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when required.

Advantages

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

- Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between two layers.
- Maximized yield.

Limitations

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression. Bonding is too restricted if first layer is compressed at a high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". Most of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight. Compression force control system is always based on measurement of compression force at main compression but not at precompression.

Bilayer tablet press with displacement monitoring[19, 20]

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force. In fact the lower the precompression force, the more the monitoring control system and this ideal for good interlayer bonding of the bilayer tablet.

Advantages

- Weight monitoring/control for accurate and independent weight control of the individual layers.
- Low compression force extends on the first layer to avoid capping and separation of the two individual layers.
- 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 the two layers.

BILAYER COMPRESSION BASICS[18, 19]

A. Initial layer die filling and compaction.
B. Initial layer compaction showing the predominant stress transmission profile.
C. Density profile of initial layer before die filling of the final layer.
D. Final layer die filling and compaction.
E. Final layer compaction showing the predominant stress transmission profile.
F. Density profile of bilayer tablet before ejection.
G. Ejection of a bilayer tablet.

Dashed arrows show the postulated radial expansion due to energy dissipation. Black areas correspond to regions of localized high density. Arrows show the direction of the applied stress.

A. Die filling
B. Compression
C. Decompression
D. Lower punch removal and reapplication of load to the upper punch
E. Tablet fully ejected.

MANUFACTURING PROCESS OF BILAYER TABLET[19]

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's propensity for delamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of precompression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity.

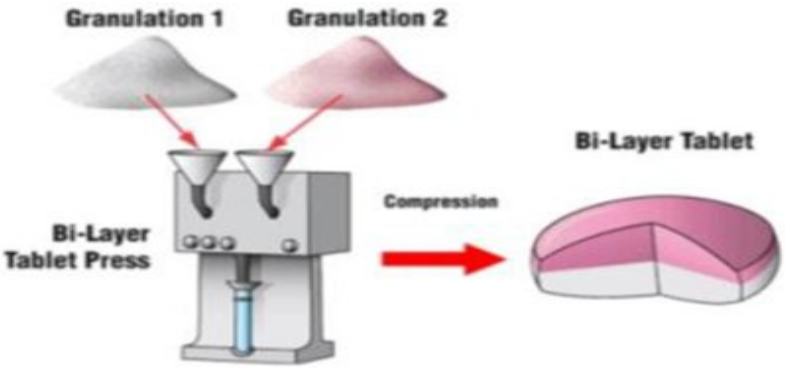

Fig 10: Schematic diagram of bilayer tablet press

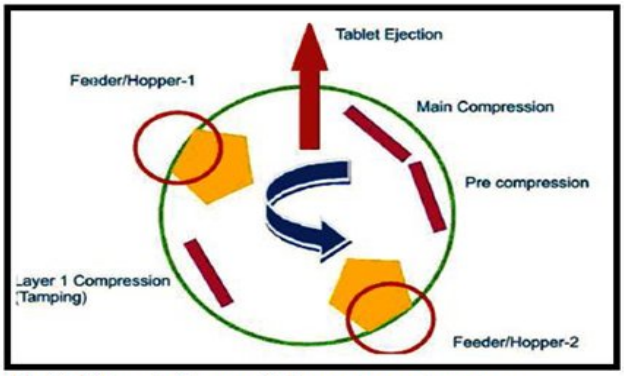

Fig 11: Schematic diagram of bilayer compression process

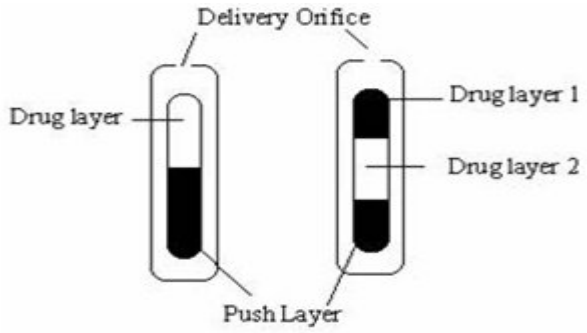

Fig 12: Bilayer and trilayer OROS push pull osmotic tablets

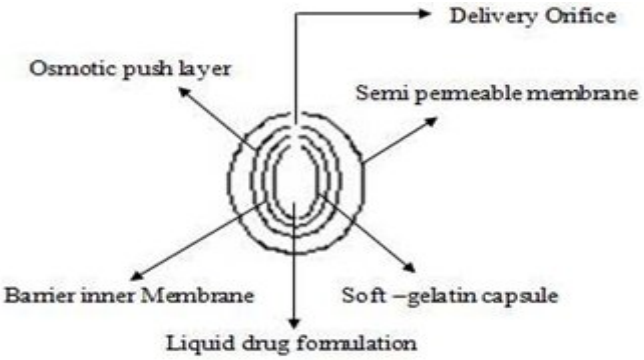

Fig 13: Schematic diagram of L-OROS bilayer tablet using TM technology

Compaction

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression

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

Consolidation

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

COMPRESSION FORCE FOR BILAYER TABLETS[20]

Since the material in the die cavity is compressed twice to produce a bilayer tablet, compressed first with layer one followed by both the layers, the compression force affects the interfacial interaction and adhesion between the two layers. A certain amount of surface roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface and makes the adhesion weaker. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce crack on the first layer which could act as a stress concentrator and eventually making the tablet interface weaker. This may result in capping or delamination of the tablet along the interface either during manufacturing or immediately after the level of compression force used in the first layer compaction determines the degree of surface roughness of the first layer. The higher the first layer compression force, the lesser the surface roughness resulting in reduced adhesion with the second layer. Therefore, for a given final compression force the strength of interfacial adhesion decreases with the increasing first layer compression force. It implies that the extent of plastic/elastic deformation of the first layer has profound effect on the strength of the interface. Thus, understanding the interaction and adhesion behaviour between different layers composed of various ingredients with differing physicochemical properties during compaction is critical to understand the failure mechanisms of bilayer tablets. Understanding of material attributes of the excipients and API that undergoes compression and compaction is decisive in predicting the interaction.

Various techniques for bilayer tablet

OROS push pull technology

This system consists of mainly two or three layers among which the one or more layer is essential of the drug and other layer consist of push layer (Fig.12). 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.

L-OROS TM technology

This system used for the solubility issue. Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer followed by a semipermeable membrane, drilled with an exit orifice (Fig 13).

EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies (Fig 14).

DUROS technology

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 15).This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continuous and consistent form over months or year.

DUREDAS technology

DUREDAS or dual release drug absorption system (Elan Corporation) utilizes bilayer tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by 2 separate direct compression steps that combine and immediate release granulate and a controlled release hydrophilic matrix complex within one tablet. The controlled release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in controlled manner.

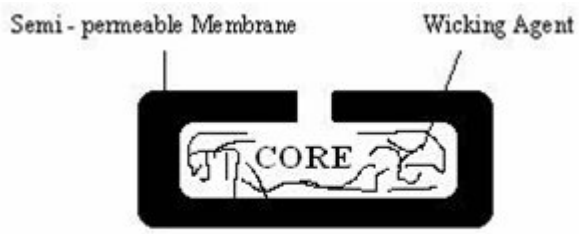

Fig 14: Bilayer tablet by EN SO TROL technology

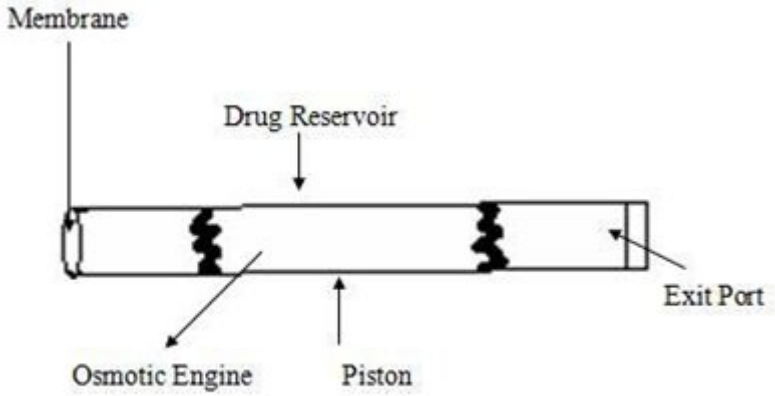

Fig 15: Multilayer tablets through DUROS technology

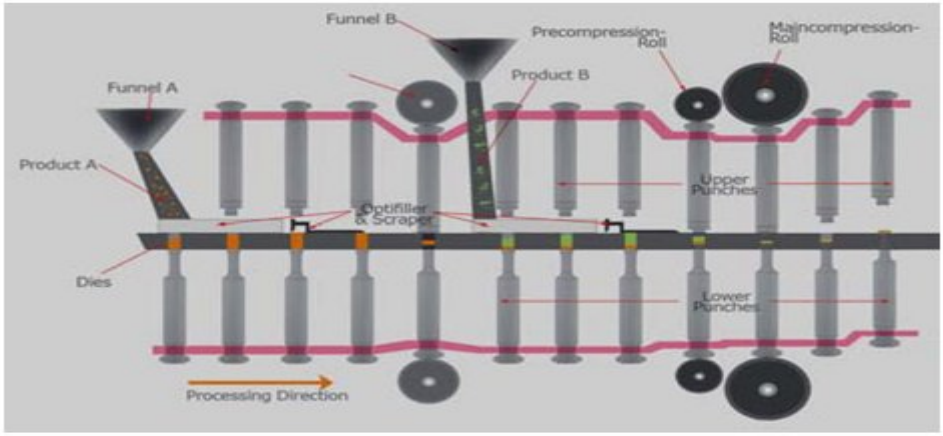

Fig 16: Schematic diagram of RoTab bilayer

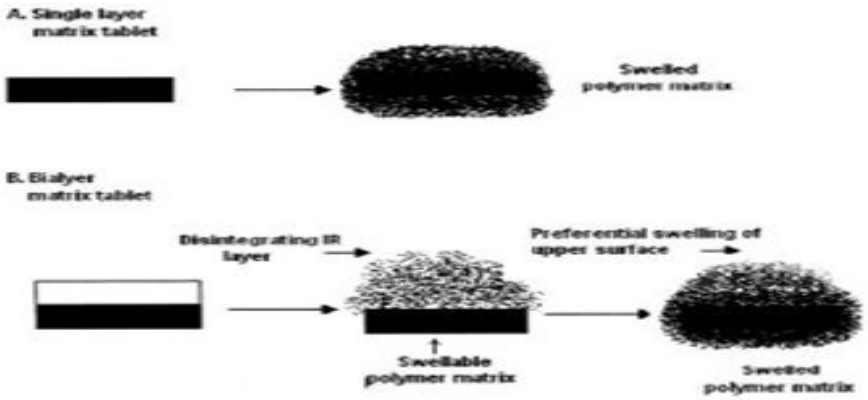

Fig 17: Schematic diagram of release pattern of bilayer floating tablets

Benefits offered by the DUREDAS technology

- Bilayer tablet technology.
- Tailored release rate of two drug components
- Capability of two different controlled release formulations combined
- Capability for immediate release and modified release components in one tablet.
- Unit dose, tablet presentation.

A further extension of the DUREDAS technology is the production of controlled release combination dosage forms. Where by two different drugs are incorporated into the different layers and the drug release of each is controlled to minimize therapeutic effect of the combination. Again both immediate release and controlled release combination of the two drugs are feasible.

ROTAB BILAYER[21]

Software

This software is modular designed and can be upgraded with additional functions at any time. An advanced industrial PC-system with 15" touch-screen guarantees precise results and fast graphical evaluations. The wide range of instrumentations allows a nearly perfect simulation of production machines in laboratory scale.

Basic Technique

Software package for prevailing use of RoTab bilayer in production mode is operation with 15" touch-screen display, by automatically dosing regulation by compression force and adjustment die table and optifiller speed. Optional independent hardness regulator is also available.

R&D modified technique

Basic package for galenical R&D on the RoTab bilayer contains evaluation and graphical visualization of instrumented measuring points, as compression 1st layer pre main compression and ejection force on a 15" touch screen display. Punch tightness control can be selected as an additional alarm function. Upgrade to R&D Plus is possible at any time.

R&D Plus

Contains all functions of Basic and R&D plus the possibility to evaluate and visualize the following special instrumentations on the 15" touch-screen display punch tightness control, tablet scraper force and display of force displacement. With R&D Plus the RoTab bilayer sets new standards in tableting technology.

Table 1: Various parameter of RoTab bilayer

Technical data RoTab Bilayer	B-20	D-16	B/D-8	Flex Adapt X-16
Maximum tablet diameter	16mm	25mm	16/25mm	bis25mm
No of punch stations	20	16	8/8	16
Tools (EU Standard)	B-30.16*	D-38.1*	B/D	BBS/BB/B/D
Maximum fill depth 1st layer	20mm			
Maximum fill depth 2nd layer	10mm			
Maximum initial compression 1st layer	10kN			
Maximum precompression	10kN			
Maximum main compression	60(80)kN			
Penetration range upper punch	2-4mm			
Maximum capacity in tabs/h	18-48000**	14,4-38400**	7,2-19200**	14,4-38400**
Power supply	3.5kW			
Weight	950kg			
Measurement in mm (L x H x W)	1465 x 1950 x 800			

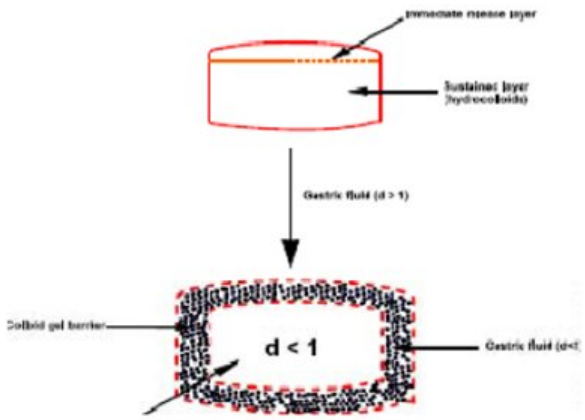

Fig 18: Intragrastic bilayer floating tablet

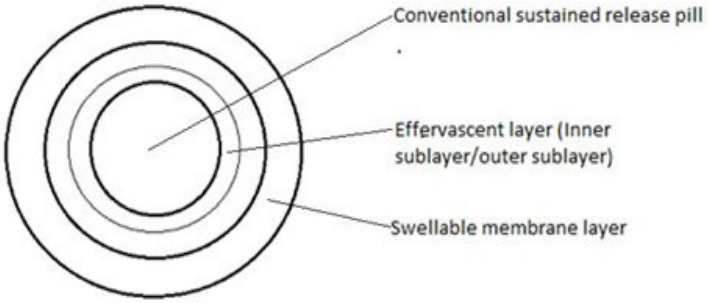

Fig 19: Multiple units of oral FDDS

VARIOUS ASPECTS OF BILAYER TABLETS[22]

Floating drug delivery systems (FDDS)

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of gastroretentive dosage forms (GRDFs).

Approaches to design floating drug delivery system

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.

Intra gastric bilayer floating tablets

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

i) Immediate release layer and ii) Sustained release layer.

Multiple unit type floating pill

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 temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.

CHARACTERIZATION OF BILAYER TABLETS[22]

Particle size distribution

The particle size distribution was measured using sieving method.

Angle of Repose (θ)

Angle of repose is an important parameter that is used to find out the flow properties of granule and that is indicated as maximum angle possible between the surface of a pile of granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose is calculated by measuring the height and radius of the heap of granules formed.

$$\theta = \tan^{-1}\frac{h}{r}$$

Where θ was called as angle of repose, h and r were height and radius of the granule heap respectably. According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle "between" 25^0-30^0 indicates good flow. The angle "between" 30^0-40^0 indicates passable flow and angle greater than 40^0 indicates very poor flow.

Moisture sorption capacity

All granules have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of granules uniformly distributed in petridish and kept in stability chamber at 37±1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

Density

Both the bulk density (BD) and tapped density (TD) of granules are determined. The quantity of 2 gm of granules from each formula, previously lightly shaken to break any agglomerates formed; were introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second interval. The tappings were continued until no further changes in volume were noted. The process was continued thrice for each formulation and average was taken. Standard deviation was calculated for to know variation in the formulation. BD and TD of prepared granules were calculated using the following formulas.

$$BD = \frac{weight\ of\ the\ granule\ taken}{volume\ of\ the\ packing}$$

$$TD = \frac{weight\ of\ the\ granule\ taken}{tapped\ volume\ of\ the\ packing}$$

Compressibility Index (Carr's index)

The flow ability of granules can be evaluated by comparing the bulk density (BD) and tapped density (TD) of powder and the rate at which it packed down.

Compressibility index (Carr's index) of granule is calculated by following formula

$$Carr's\ index\ (\%) = \frac{TD-BD}{TD} \times 100$$

According to the specification the Carr's index values "between" 5-15 indicates excellent flow where as between 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable where as between 23-25 indicates poor flow. Between 33-38 indicates very poor flow and greater than 40 indicates extremely poor flow.

Hausner's ratio

The Hausner's ratios of granule are determined by following formula.

$$Hausner's\ ratio = \frac{TD}{BD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), where as greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, added glidant normally improves flow [9, 10].

EVALUATION OF SUSTAINED RELEASE BILAYER TABLETS[23]

Tablet thickness and size

Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo digital Thickness Gauge, Mitutoyo, Japan). Ten tablets bilayer matrix tablets from each formulation are randomly selected and used for thickness determination. The results are expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.

Tablet hardness

All the formulations bilayer matrix tablets are subjected to hardness measurement by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten tablets with known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 5-7 kg/cm^2 is considered as acceptable limit for bilayer matrix tablet.

Friability

Previously weighed ten bilayer matrix tablets from each batch are taken in Roche friabilator (Secor India). After100 revolutions of friabilator, tablets are recovered. The tablets are then made free from dust and the total remaining weight is recorded. Friability is calculated from the following formula.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

Where W_i and W_f are the initial and final weight of the tablets before and after friability test. For compress tablet that lose between 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.

Uniformity of weight

According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%. All formulated bilayer matrix tablets are evaluated for weight variation as per USP monograph. Twenty tablets are weighed collectively and individually using an electronic balance (Citizen CTG-302). The average weight and percent variation of each tablet is calculated.

Content uniformity

Twenty bilayer matrix tablets are taken and triturated to form powder and powder equivalent to one tablet is taken and dissolved in 100 ml of dissolution fluid and heated at 37 ^{0}C for 60 minutes with stirring. The solution is filtered, suitably diluted and the drug content is measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080). Each measurement is carried out in triplicate and the average drug content in the bilayer matrix tablets is calculated.

Swelling Index (*SI*)

The swelling behaviour of all formulations of bilayer tablet is measured by studying its weight gain in the dissolution medium under study. The swelling index of selected bilayer matrix tablets are determined by placing the tablets in the basket of dissolution apparatus maintaining dissolution medium at 37 ± 0.5ºC. After every one hour interval and upto 12 hour, each dissolution basket containing tablet is withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment is performed in triplicate for each time point. Swelling index is calculated by using the following formula.

$$Swelling\ Index\ (SI) = \frac{Wf - Wi}{Wi} \times 100$$

Where W_f and W_i is called as wet and dry weight of the tablet respectively.

Stability study

The tablets of each formulation are packed in air tight bottles and subjected to accelerated stability studies according to ICH guidelines. The accelerated condition that was chosen for stability study at 40 ^{o}C ± 2 ^{o}C/ 75% ± 5% RH using humidity control oven NEC 210R10 (Newtronic Instruments, India) for 90 days. After that period the product is evaluated for friability, hardness, weight variation, thickness, drug content and in vitro release study.

Table 2: Storage condition according to ICH guidelines for stability studies of product

Study	Storage condition	Minimum time period covered by data at submission
Long term*	$25^0C\pm2^0C/60\%RH\pm5\%$ RH or $30^0C\pm2^0C/65\%RH\pm5\%$ RH	12 months
Intermediate**	$30^0C\pm2^0C/65\%RH\pm5\%$ RH	6 months
Accelerated	$40^0C\pm2^0C/75\%RH\pm5\%$ RH	6 months

Note: *It is upto the applicant to decide whether long term stability studies are to perform at $25^0C\pm2^0C/60\%RH\pm5\%$ RH or $30^0C\pm2^0C/65\%RH\pm5\%$ RH. **If $30^0C\pm2^0C/65\%RH\pm5\%$ RH is the long term condition, there is no intermediate condition.

Table 3: Bilayer tablets containing two different drugs in an individual layer

Sl. No.	Drug 1	Drug 2	Therapeutic benefits
1	Salbutamol	Theophylline	For treatment of Asthma
2	Metformin Hydrochloride	Pioglitazone	For treatment of Diabetics
3	Metformin Hydrochloride	Glimepiride	For treatment of Diabetics
4	Paracetamol	Diclofenac sodium	As analgesic and antipyretic
5	Metoprolol succinate	Amlodipine besylate	For treatment of hypertension
6	Diltiazem hydrochloride	Lovastatin	For treatment of hypertension and to reduce cholesterol level
7	Montelukast	Doxofylline	For treatment of Asthma
8	Montelukast	Levocetirizine	For treatment of Asthma associated with allergy

Table 4: Bilayer tablet containing same drug in an immediate release layer and sustained release layer

Drug	Fast release layer/ Backing membrane	Sustained release layer	Remarks
Indomethacin (floating tablet)	Ac-di-sol	HPMCK4M	Release the drug from fast release layer within 2 h and followed by sustained release upto 12 h. Reduce
Propropranolol HCl (Bucoadhesive tablet)	Ethyl cellulose (Backing membrane)	Sodium alginate and carbopol 971P	The formulation containing Sodium alginate and carbopol 971P in the ratio of 5:1 produce maximum drug release.
Guaifenesin (Matrix tablet)	Microcrystaline cellulose, Sodium starch glycolate	Metalose 90SH, Carbopol 934	Fast release of the drug (over 20%) within first half an hour and followed by sustained release for 12 h.
Atorvastatin calcium (Mucoadhesive buccal tablet)	Ethyl cellulose	Carbopol 934P, Sodium CMC, Hydroxyethyl cellulose, Sodium alginate	The optimised formulation performed 6h sustained release with desired therapeutic concentration.
Propanolol HCl (Matrix tablet)	Sodium starch glycolate	Ethyl cellulose, Eudragit RLPO and Eudragit RSPO	Over 30% of Propanolol HCl was released within 15 min and followed by sustained release for 12 h
Zolpidem tartarate (matrix tablet)	Cross carmellose sodium	HPMC K100M	Optimised formulation released more than 50% of drug within the first 30 min and remaining drug released could be extended upto 6 h
Verapamil HCl (floating matrix tablet)	Crosspovidone, sodium starch glycolate	HPMC K15M, HPMC K100M, Carbopol 971P	Immediate release layer get completely dissolved within 15-20 min and 30-45% drug released among the total dose followed by sustained release upto 12 h.

Table 5: Commercially available bilayer tablets

Product Name	API (Active pharmaceutical ingredient)	Manufacturer
ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceutical Ltd.
Glycomet-GP2Forte	Metformin Hydrochloride, Glimepiride	USV Limited
DIAMICRON XRMEX500	Gliclazide, Metformin hydrochloride	Sedia Pharmaceuticals (India) Pvt.Ltd.
DIUCONTIN-K 20/250	Furosemide, Potassium chloride	T.C Health care Pvt Ltd
TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd
PIOKIND-M15	Pioglitazone, Metformine hydrochloride	Psychotropics India Ltd
DOXOVENT-M	Doxofylline, Montelukast	Glenmark (Majesta)
Revelol-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.
Newcold Plus	Levocetrizine, Phenylpropanolamine, Paracetamol	Piramol Healthcare Ltd

CHALLENGES IN THE FORMULATION OF BILAYERED TABLETS

- Lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack driven by residual stresses in the tablet propagating a finite distance within the tablet and leads to delamination (layer-separation) which may not always be apparent immediately after compaction (e.g., during storage, packaging, shipping).
- If the compacted layers are too soft or too hard, they will not bond securely with each other which can lead to compromised mechanical integrity.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers. These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per sure (inefficient or uncontrolled process) 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.

CONCLUSION

Bilayer tablet is one of novel technology that overcomes many limitations associated with the single layered tablet. 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. To develop a dynamic bilayer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management. 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. Whenever high quality bilayer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution.

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