Review Article

BILAYER TABLET

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ABSTRACT

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer tablet is better than the traditionally used mouthwash, sprays, gels. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bi-layer 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. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper nonadhesive layer its delivery occurs into the whole oral cavity.

Keywords: Bilayer tablet, RoTotab push technology, OROS® push pull technology, DUROS technology.

1) INTRODUCTION

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers.

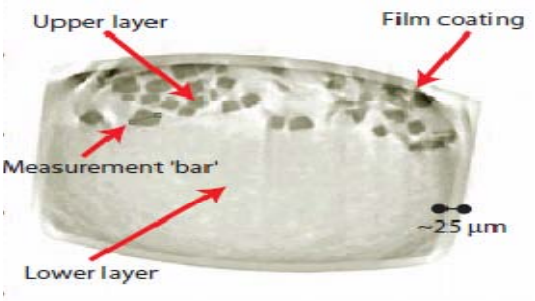

Figure 1: Conventional bilayer tablet structure.

There are clearly a number of issues of concern to the production of bilayered tablets. While the mechanical strength of layered tablets has been observed not to be a controlling factor in drug release the determination of this property could be beneficial in understanding the adhesion between various layers and provide an improved characterization of the systems. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bi-layer 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 preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Control release systems that have been proposed for providing controlled release formulations showing how the different designs can be used to control the drug release profile such as constant, delayed pulsatile and multi modal release profiles.[2] Several different geometries are described and to prepare these by compression will require various strategies.

2) VARIOUS TECHNIQUES FOR BILAYER TABLET

2.1) OROS® push pull technology[3]

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

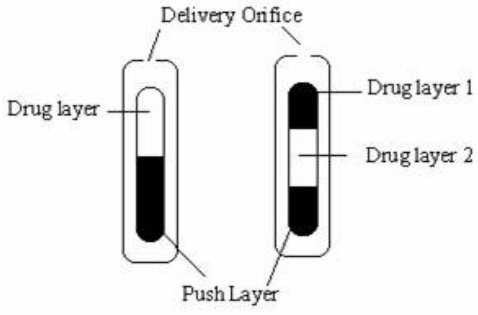

Figure 2: Bilayer and trilayer OROS Push pull technology

2.2) L-OROS tm technology.[3]

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

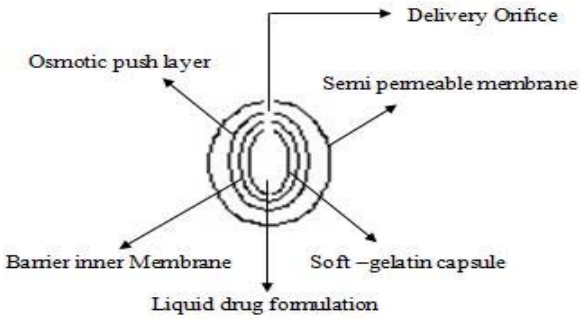

Figure 3: L – OROS tm technology

2.3) EN SO TROL technology.[3]

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

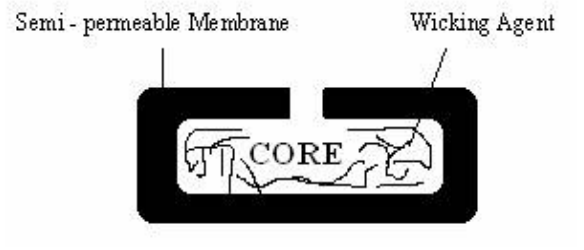

Figure 4: EN SO TROL Technology

2.4) DUROS technology[4]

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

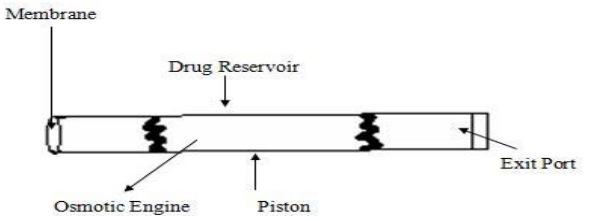

Figure 5

2.5) Elan drug technologies' Dual release drug delivery system

(DUREDAS™ Technology) is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tabletting process can provide an immediate-release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

2.5.1) Benefits offered by the DUREDAS™ technology include:

1) Bilayer tabletting technology.

2) Tailored release rate of two drug components.

3) Capability of two different CR formulations combined.

4) Capability for immediate release and modified release components in one tablet

5) Unit dose tablet presentation

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bilayer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bilayer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics. In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.

3) RoTab BILAYER5

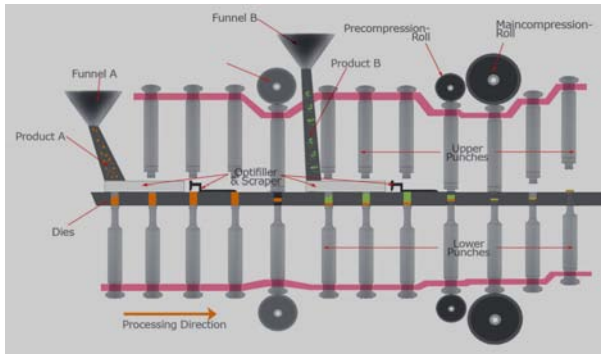

Figure 6: RoTab Bilayer

3.1) 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.

3.2) Basic technique

Software package for prevailing use of RoTab Bilayer in production mode. Operation with 15" touch-screen display, by automatical dosing regulation by compression force and adjustment o die table and Optifiller speed. Optional independent hardness regulation available.

3.3) 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.

3.4) 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 tabletting technology.

Table 1: Various parameter of RoTab bilayer

Technical data RoTab Bilayer	B-20	D-16	B/D-8	Flex Adapt X-16
Max.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
Max.fill depth 1st layer	20mm			
Max.fill depth 2nd layer	10mm			
Max.initial compression 1st layer	10kN			
Max. precompression	10kN			
Max. main compression	60(80)kN			
Penetration range upper punch	2-4mm			
Max. 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			

4) BI-LAYER TABLET PRESS 6

The XM 12 Bi-Layer 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 Bi-layer Applications. The KORSCH XM 12 Bi-Layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and changeover.[7] 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.

4.1) Small-Scale bi-Layer

a) 5 KN First Layer Tamping Force.

b) 40 KN Precompression Force.

c) 80 KN Main Compression Force.

d) Single-Layer Conversion Capability.

4.2) Bi-layer application[8]

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.

a] single layer conversion kit adds yet another dimension of flexibility.

b] Single Layer Conversion.

c] 30 Minute Conversion Time.

d] High Speed Single-Layer Capability (120 RPM)

4.3) Advantages [9,10]

a) Flexible Concept.

b) Bi-Layer execution with optional single-layer conversion kit.

c) Exchangeable turret.

d) Turret sizes for product development, scale-up, and mid-range production.

e) Full production capability in a scale-up machine.

f) Self-contained, fully portable design.

g) Fast and Easy Changeover.

h) Internal turret lift device for extreme simplicity in turret removal and installation.

i) Clean compression zone with quick-disconnect design.

4.4) Bi-layer tablets: quality and GMP-requirements [11,12]

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

• Preventing capping and separation of the two individual layers that constitute the bi-layer tablet

• Providing sufficient tablet hardness

• Preventing cross-contamination between the two layers

• Producing a clear visual separation between the two layers

• High yield

• Accurate and individual weight control of the two layers these requirements seem obvious but are not as easily accomplished as this article aims to demonstrate

5) LIMITATIONS OF THE SINGLE SIDED PRESS BI-LAYER TABLETS

Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet.[13,14] 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 (two = pre- and main compression). The two layers in the die mix slightly at their interface and in most cases bond sufficiently. So that no layer-separation occurs when the tablet is produced.[15,16] This is the simplest way of producing a bilayer tablet. It undergoes certain limitation as follow.

• No weight monitoring/control of the individual Layers.

• No distinct visual separation between the two Layers.

• Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the 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 to eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, pre -compression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.[17,18]

6) VARIOUS ASPECTS OF BILAYER TABLET

6.1) Floating Drug Delivery Systems (FDDS) [22,23]

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive 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.

6.1.1) Intra gastric bilayered 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.

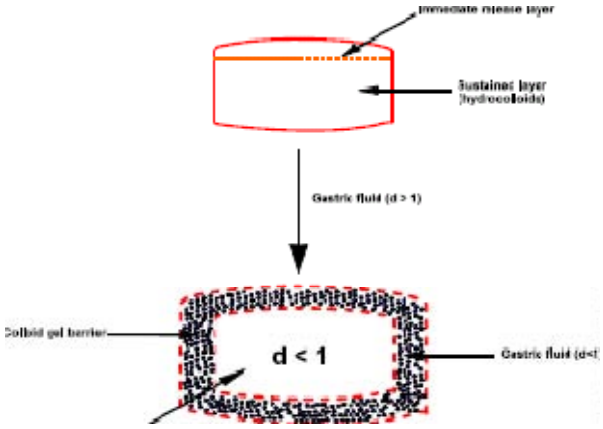

Figure 7: Intra gastric bilayer floating tablet.

6.1.2) 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.

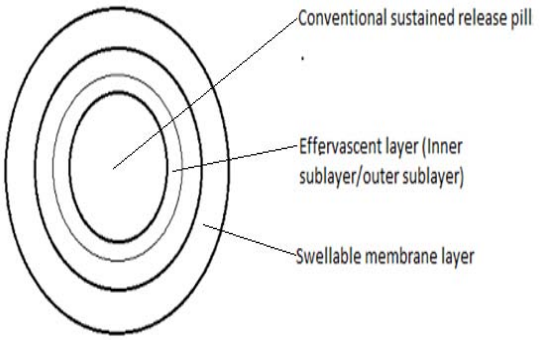

Figure 8: Multiple Units of Oral FDDS

7) CHARACTERIZATION OF BILAYER TABLET19,20

7.1) Particle size distribution

The particle size distribution was measured using sieving method

7.2) Photo-microscope Study

Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope

7.3) Angle of Repose

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\tan \Ø = h/r$$

where h and r are the height and radius of the powder cone.

7.4) Moisture Sorption Capacity

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

7.5) Density

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

LBD ¼ weight of the powder=volume of the packing ð2Þ

TBD ¼ weight of the powder=tapped volume of the packing ð3Þ

7.6) Compressibility

The compressibility index of the disintegrate was determined by Carr's compressibility index.

$$C = 100 \times (1 - \text{ÞB}/\text{ÞT})$$

8) EVALUATION OF SUSTAIN RELEASE BILAYER TABLET

8.1) Tablet Thickness and Size[20,21]

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire calliper

8.2) Tablet Hardness[20,21]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm2.

8.3) Friability[20,21]

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

8.4) Uniformity of weight

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. Bi-layer 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. Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines such as the Courtoy-R292F. Whenever high-quality bi-layer 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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