An Emerging Trend of Elegant Bilayer Tablets as Floating Tablets – A Review

K. Satish Kumar[1], Dr. K.Srikanth[2]
[1]*Research Scholar, Bir Tikendrajit University*
[2]*Research Supervisor, Bir Tikendrajit University*

Abstract-Over a past few decades, around 90% drugs have been formulated for the purpose of oral delivery. Oral ingestion is the most convenient and commonly employed route of drug delivery, due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. Due to these properties oral dosage form has gained much attention and became the popular class of formulation worldwide. Bilayer tablets do offer a definite advantage over conventional release formulations of the same drug. So as to overcome the problems associated with the conventional dosage form, there arose an interest in developing the controlled drug delivery system in the form of bilayer tablets. Now a day the use of bilayer tablets has been increased in the pharmaceutical industry. Bilayer tablet technology is a new emerging era, in the pharmaceutical industry. Bilayer tablet is the novel technology for the development of controlled release formulation and developing a combination of two or more active pharmaceutical (API) ingredients in a single dosage form. Bilayer tablet technology can be a crucial role for development of controlled release in order to give a successful drug delivery and can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (Immediate and Controlled Release in Single Tablet). Drugs which are formulated in the form of biphasic system have different biological applications such as analgesic, antipyretic, antiallergenic, coronary vasodilators, antihypertensive and anti-histaminic. Oral route of administration involve oral controlled drug delivery which aims to deliver drug for an extended period of time which provide good bioavailability and makes the dosage form reproducible. The system gets many difficulties due to physiological problems like absorption window is narrow for some drugs and alteration in emptying time of stomach and drugs has stability issues in intestine. To overcome these difficulties GRDDS is designed which provide oral controlled sustained dosage form as it delivers the drug at slow rate in systemic circulation and maintains effective plasma concentration because drug is retained in stomach for a prolonged period of time as compare to conventional oral dosage form. Floating drug delivery system (FDDS) belongs to the group of gastro-retentive drug delivery system (GRDDS). These dosage forms are designed to achieve prolong gastric residence time in sustained release manner. Incorporation of drug in GRDDS, shows improve bioavailability, enhance solubility of drug that are less soluble in high pH environment. By flotation mechanism controlled gastric retention of solid dosage form can be achieved. Bilayer floating drug delivery system shows the unique combination of bilayer with floating mechanism. It shows successful development of controlled release formulation. Bilayer floating tablet provide both immediate as well as sustained release layer formulation. An attempt has been made in the review to introduce FDDS, Floating bilayer, its mechanism, different technologies required for its preparation, summarize its characterization and *in -vivo* success of GRDDS. The objective of this review article is to ensure that to reduce the frequency of dosing and drugs are available to its citizen are not only safe and effective, but are also properly manufactured and packaged to meet the established quality target product profile over it shelf life.

Key Words: Bilayer tablets, API, Formulation, Controlled release, frequency of dosing, Floating drug delivery system, Release Pattern, Characterization and *In-vivo* success of GRDDS.

INTRODUCTION

Pharmaceutical tablet is the dominant dosage form for drug delivery, occupying two-thirds of the global market. Generally, they are produced by compressing dry powder blends consisting of a number of components with different functionalities in a die. It is technically difficult to ensure that a tablet possesses both a certain mechanical strength and a low packing density, so that it is sufficiently strong to maintain its integrity during handling and transport and also weak enough to satisfy the dispersion and dissolution

requirements[1][2][3]. An ideal drug delivery system is such that provides the required drug amount within a short duration and also maintains the steady level of drug concentration throughout the dosing period[4]. However, any conventional dosage form behaves as per its type which can be either immediate release or sustained release. Furthermore, the drugs with shorter half life should be administered multiple times to maintain required drug level. Controlled drug delivery system has been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms[5][2].

Need of Developing Bilayer Tablets:

- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property)[7-9].
- For the purpose of developing novel drug delivery system such as buccal/Mucoadhesive delivery system and floating tablets for gastro retentive drug delivery system. It helps in controlling drug delivery rate of single or two APIs[10].
- The preparation of bilayer tablets is used to provide systems for the administration of drugs which are incompatible and to provide controlled release tablet preparations with surrounding multiple swelling layers[11][12].
- In case of drugs having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Analytical work may be simplified by separating of the layer prior to assay.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance[1315].

General properties of Bilayer Tablet[16]

1. A bi-layer tablet should posses an elegant product identity and should be free of defects like crackschips, contamination and discoloration.
2. Must have sufficient strength which will handle mechanical shock during its production.
3. It must have the chemical and physical stability tomaintain its physical attributes over time.
4. Must have a chemical stability shelf-life.

Applications[17-19]

1. Bi-layer tablets are suitable for sequential release of two drugs in combination.
2. It is improved technology to overcome the shortcoming of the single layered 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.

Advantages of Bilayer Tablet Over The Other Conventional Tablet [13][14][15]

1. This formulation can be used to separate two incompatible substances.
2. When the two different layers of the tablet contain two different drugs, then the tablet can be easily used in combination therapy.
3. It makes possible Extended-release preparations with the immediate-release quantity in one and the slow release portion in the second layer.
4. Two-layer tablet require less material than compression coated tablets, weight less, and may be thinner.
5. The weight of each layer can be accurately controlled, in the contrast to putting one drug of a combination product in a sugar coating.
6. For chronic condition requiring repeated dosing.
7. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bilayer Tablet[13][14][15]

- ✓ One of the major challenges in bilayer formulation is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- ✓ If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- ✓ 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.
- ✓ Administration of sustained release bilayer tablet does not permit the prompt termination of therapy.

- ✓ The physician has a less flexibility on adjusting the dose regimens.

Bilayer Tablet [20-22]

Bilayer tablets are efficient for sequential and simultaneous release of two different API's. In this two layers are immediate release and second one is sustained release. Bilayer tablet is suitable form to deliver two drugs at one time without any dynamic and pharmacological interaction with each other. The bilayer tablet containing subunits that may be either the same drug (homogeneous) or different drugs (heterogeneous).

A. Homogenous Type:

Bilayer tablets are mainly referred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution profile and release rate characteristics. Bilayer tablets are formulating with one layer of drug for immediate release while second layer designed to release drug in the extended release manner.

B. Heterogeneous Type:

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

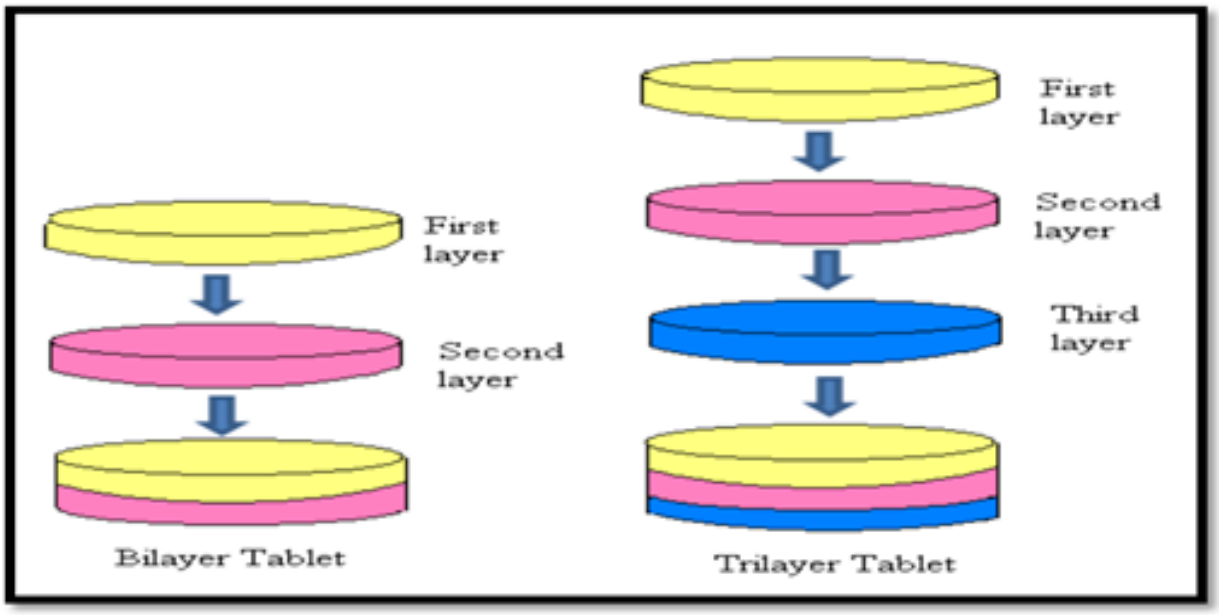

Figure - 1: Types of Multi-layered tablet.

MANUFACTURE OF MULTILAYER TABLETS

The manufacture of multilayer tablets has been successful for over 50 years[2]. New machine designs developed during the late 60s have made it possible to check the weight of individual layers by sampling without stopping the machine, providing in-process control facilities to ensure correct dosing[3]. However, despite this, a considerable amount of expertise is still required to formulate these tablets and to ensure consistent manufacture to satisfy regulatory requirements [4]. One problem that causes great concern is the delamination of layered tablets[5], which has become a more obvious problem with the increase in compression speed on modern high-speed rotary machines. The formulations used for each individual layer should be compressible and compactable on their own i.e. they should show satisfactory reduction in volume and form mechanically strong, coherent solid bodies. Under this assumption the interface between the layers should weld together during compaction and strong adhesion forces should hold the layers together after tablet ejection. However, this is not always the case, and as compressibility and compactability of the individual layers should not be the cause for delamination, other physical mechanisms need to be identified that can explain the problems with delamination that have hampered recent developments of layered tablets.

Bilayered tablets have proven to be effective in delivering drugs that require a loading dose followed by a maintenance dose[7]. Commonly, in bilayered systems, one layer contains a quantity of drug for conferring immediate release, while the second layer contains a quantity of drug for extended release. The rapid release layer disintegrates immediately after administration while the matrix layer remains intact during the passage of drug through the gastrointestinal tract. The matrix erodes in a controlled fashion in order to maintain blood levels. Two drugs may also be incorporated into this delivery system for variable release profiles. A bilayered tablet for the delivery of propranolol hydrochloride was developed by Patra and co-workers. These tablets were comprised of an immediate release layer and a sustained release layer. Sodium starch glycolate was employed as the superdisintegrant in the rapid release layers of various formulations, while the polymers Eudragit® RL, Eudragit® RS and EC were utilized in the sustained release layers. Drug release studies illustrated that there was an initial burst release that delivered the loading dose while the rest of the drug was released over 12 hours in a sustained manner [8]. The same concept has been demonstrated in a patent by Kim and co-workers where the system provided release of two drugs in different manners. The controlled release layer delivered metformin while the rapid release layer delivered glimepiride. The controlled release layer was made up of a mixture of hydrophobic and hydrophilic polymers, while the immediate release layer was composed of a disintegrant and glimepiride[9]. This further emphasizes the positive function of these systems in treating chronic conditions such as hypertension and diabetes.Nirmal and co- workers developed a bilayered tablet containing atorvastatin calcium for immediate release and nicotinic acid for extended release for the concurrent treatment of hypercholesterolemia. It has been shown that the combination of these two drugs results in an important reduction of low density lipoprotein cholesterol as well as desirable variations in high density lipoprotein cholesterol[10]. Methocel® K100M was employed as the polymeric matrix for nicotinic acid and the immediate release layer containing atorvastatin calcium was formulated using super disintegrant, croscarmellose sodium. Drug release studies were performed over 12 hours and the results indicated that these tablets were successful in delivering two types of drugs concurrently[10]. This bilayered system design may thus be valuable for future application in the successful treatment of hypertension.

VARIOUS TECHNIQUES FOR BILAYER TABLET

OROS® Push Pull Technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.1). 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.

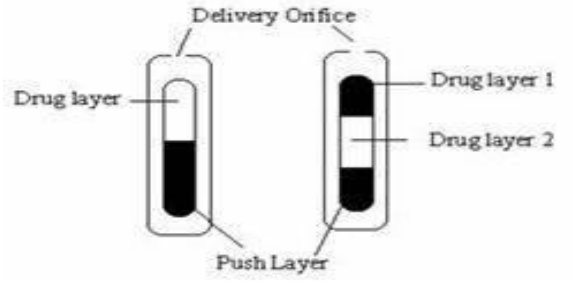

Fig. 1: Bilayer and Trilayer OROS Push pull Technology

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 semi permeable membrane, drilled with an exit orifice (Fig.2)[11].

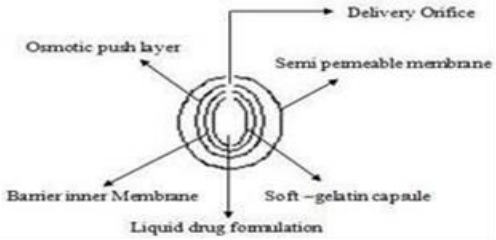

Fig 2: L – OROS tm technology

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.3)[11].

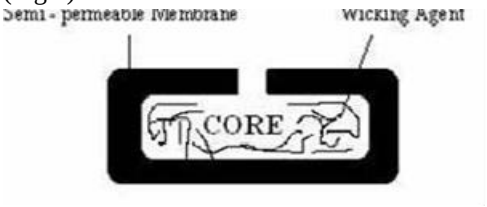

Fig 3: EN SO TROL Technology

DUROS Technology

The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or year (Fig.4).

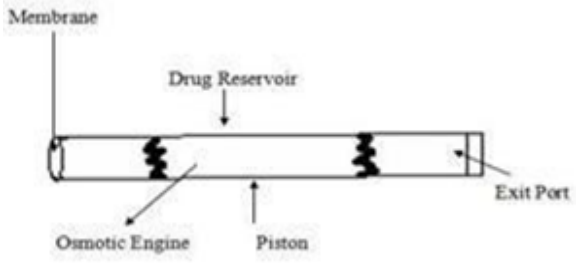

Fig 4: The DUROS Technology

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 immediaterelease 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.

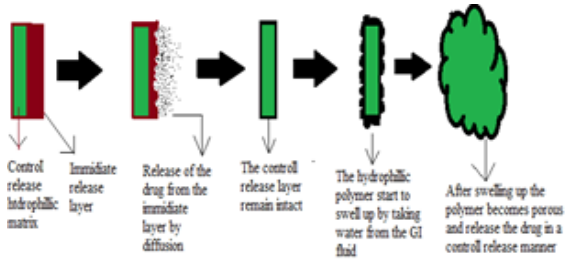

Fig - 5: DUREDAS Technology consists of control release and immediate release layer.

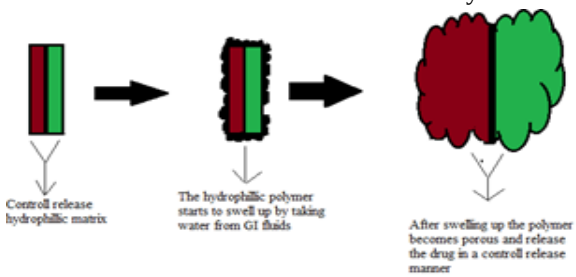

Fig - 6: DUREDAS Technology consist of two control release layers.

Benefits offered by DUREDAS™ Technology

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.

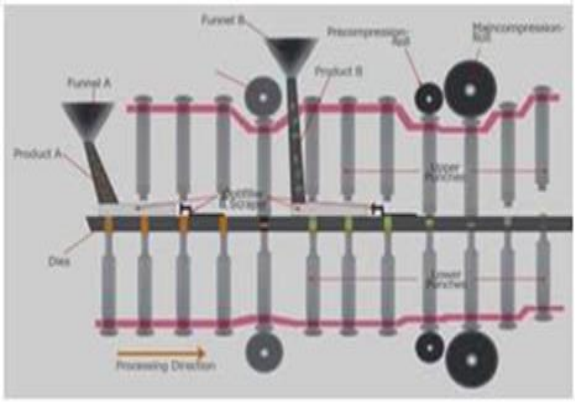

Fig 7: RoTab Bilayer instrumentations on the 15" touch-screen display Punch tightness control, tablet scraper force and display of force displacement. With RandD Plus the RoTab Bilayer sets new standards in tabletting technology.

BI-LAYER TABLET PRESS

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 crosscontamination. 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 [15].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[14].

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.

BI-LAYER APPLICATION[16]

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. 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.

RandD Modified Technique

Basic package for galenical RandD 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" touchscreen display. Punch tightness control can be selected as an additional alarm function. Upgrade to RandD Plus is possible at any time.

RandD Plus

Contains all functions of Basic and RandD plus the possibility to evaluate and visualize the following special. 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)

ADVANTAGES[17,18]

a)Flexible Concept.
b) Bi-Layer execution with optional single-layerconversion kit.
c) Exchangeable turret.
d) Turret sizes for product development, scale-up, andmid- 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 inturret removal and installation.
i) Clean compression zone with quick-disconnect design.

QUALITY AND GMP-REQUIREMENTS[19,20]

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, 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 obviousbut are not as easily accomplished as this article aims to demonstrate.
- 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.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. The manufacture of bi-layer tablets, produced by the sequential compaction of loose powder layers has recently become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. Bilayered tablets have proven to be effective in delivering drugs that require a loading dose followed by a maintenance dose

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