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BILAYER: A REVIEW

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ABSTRACT

Bilayer tablet is great suiting for sequential arrival of two medicaments and it is also capable of partitioning the two contrario substances. It is also suited for sustain release tablets in which one layer is immediate release layer and another is sustain release layer. The foremost objective of the controlled drug delivery system is to minimize the dosing recurrence. The elementary point of modified drug release formulations is to improve a therapeutic regimen by providing prolonged and continuous action for predetermined time period providing greater safety, efficacy and precision. The present article provides a review on the bilayer tablet technology,various tablet press used and its evaluation.

KEYWORDS: Bilayer tablet, Sustained release, immediate release layer.

INTRODUCTION[1,2]

The majority of the formulations available today are taken orally. It means this route of administration is most commonly used all over the world and most of the researchers are pulled in towards this class of formulation. The foremost objective of the controlled drug delivery system is to minimize the dosing recurrence. The elementary point of modified drug release formulations is to improve a therapeutic regimen by providing prolonged and continuous action for predetermined time period providing greater safety, efficacy and precision. Bilayer tablet is the new age for the affluent development of modified drug release formulation. Bilayer tablet may be better than those routine utilized dosage forms. Bilayer tablet is great suiting for sequential arrival of two medicaments and it is also capable of partitioning the two contrario substances. It is also suited for sustain release tablets in which one layer is immediate release layer and another is sustain release layer.

Need of Bilayer Tablet[3]

- To modulate the delivery rate of two or more different active pharmaceutical ingredients.
- To formulate the fixed dose combination of different APIs, increase the product life cycle.
- To modify the total surface area available for API layer either by sandwiching with one or more inactive layers in order to attain swellable/erodible barriers for modified release.

Advantages of Bilayer Tablet[1, 4]

- Less expensive previously, value concerning illustration contrasted with different measurement structure.
- Substantial physical, chemical and microbiological steadiness as compared to other dosage form.
- Unpleasant stench and bad taste can be conceal by using various coating technique.
- Ideal for mass scale production.
- Lighter and compact.
- Versatile and Functional concept
- Recognition of product is straightforward and rapid necessitating no auxiliary steps when employing an embossed and/ or monogrammed punch face.

Disadvantage of Bilayer Tablet[5]

- Drugs having bitter taste, drugs with unpleasant stench or drugs that are oxygen sensitive might require coating.
- Children and unconscious patient may find difficult to swallow it.
- Drugs hosting poor wettability, poor release profile are difficult to formulate.
- Cross tainting might occur between two layers.
- Capping
- Several drugs refrain compression due to amorphous nature, low density character.

Challenges in Bilayer Manufacturing[1, 6]

In spite of the aforementioned merits of the bilayer tablets, there are several complication associated with the mechanism and compression of bilayer tablets that have been reported in the literature in recent years.

- Cross contamination: When the granules of one layer blend/mix with the granules of other layer, cross contamination occurs. It may repress the purpose of the bilayer tablet.

- Delamination: Tablet separates aside when they the two parts of the gadget do not bond with each other.
- Cost: Bilayer tablet is more expensive as compared to the traditional dosage forms.
- Production yield: Bilayer tablet have a lesser yield than single layer tablet.

Types of Bilayer Tablets[7,8]

The term bilayered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous).

Homogenous Type

Bilayer tablets are preferred when the release profiles of the drugs are different from one another.

Bilayer tablets allows for designing and modulating the dissolution and release characteristics. 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.

VARIOUS TECHNIQUES FOR BILAYER TABLET[1,2,9,10,11]

a) EN SO TROL TECHNOLOGY: To increase solubility to a magnitude or to formulate optimized medication dosage form Shire laboratory utilized an coordinated methodology to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technology.

b) Bilayer and trilayer OROS push pull technology: This framework is utilized for the solubility issue Alza developed the L-OROS system where a drug is embedded in a lipid soft gel in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semipermeable membrane, penetrated for passage opening.

c) OROS® push pull technology: This technique comprises of two or more layers among which one or more layer need aid basically of the pill and other layers comprise of push layer.

The medication layer primarily comprise of drug along with two or more distinct agents. So this drug layer comprises of drug which is in poorly soluble structures. There is further inclusion of suspending agent and osmotic agent. A semi permeable membrane surrounds that tablet core.

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

Benefits offered by the DUREDAS™ technology include

1) Bilayer tableting innovation.
2) Tailored release rate of two medication components.
3) Capability of two different Controlled Release Formulations joined.
4) Ability for immediate release and sustain release components in same tablet.
5) Unit dose tablet.

e) PRODAS or programmable oral drug absorption system

PRODAS is a mutliparticulate drug delivery technology that is basically based on the encapsulation of sustain release minitablets in the size range of 1.5 to 4 mm in diameter. This technology represents a mix of multiparticulate and hydrophilic matrix tablet technologies and thus provide the fancied arrival rates. These considerations may comprise immediate release delayed release and / or controlled release minitablets. In addition to controlled release absorption over a predetermined period. PRODAS technology additional empowers on targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitablets formulated with different ingredients.

f) GEMINEX TECHNOLOGY

In this drug delivery system at diverse times more than one drug can be delivered. This technology primarily increases the therapeutic efficacy of the drug by reducing its side effects. It is beneficial both to industry as well as to patient as in single tablet it delivers the drug at different rates.

g) ERODIBLE MOLDED MULTILAYER TABLET

Egalet erodible molded tablets in an erosion based system. It is beneficial in delivering zero order or sustain release with least effect from the gastrointestinal environment. Egalet erodible molded multilayered tablets are developed by injection moulding egalet technology consists of a coat and a matrix. Drug release is superintend through the gradual erosion of the matrix part. The mode and rate of release are designed and engineered by altering the matrix the coat and the geometry to achieve by altering the matrix the coat, the geometry to attain either a zero order release or a delayed. For a zero order, a drug is scattered through the matrix. The coat is biodegradable but has low water permeability to prevent its penetration. The matrix tends to erode when in contact with available water. The erosion of the matrix is due to GI fluids and initiated by gut movements in the GI tract. The drug release is mediated almost completely by erosion because the dosage form is designed to slowdown the water diffusion into the matrix. It is definitely more desirable for drugs with chemical and physical stability issues after contacting with water. Egalet delivery technology is developed based on standard plastic injection molulding to ensure accuracy, reproducibility and low production cost.

Table 1: Technology used for different layer tablets[1]

Company Name	Name of Technology	Approach
Skye Pharma	Geomatrix Technology	One or two impermeable polymeric coating applied on one Or both bases of the core tablet
Accu-Break pharmaceutical s, Inc.	Accu-Break Technology: Accu-B &Accu-T bilayer or tri-layer tablet technology	Suitable for FDCs combination, easily divided, and ability to separate IR from CR and to take appropriate half tablets And the free layer drug does not affect drug release
Alza Corporation	OROS push pull technology, Bilayer or trilayer core	Consists of one push layer and 1 or more drug layer, osmotic agent & water swellable polymer
Flamel Technologies	Flame Micro pump Technology	Permits DR and ER drug delivery system Permits DR and ER drug delivery system
Elan Drug Technologies	DUREDAS Dual Release Drug Absorption System	Immediate and sustained release rates of drug

VARIOUS ASPECTS OF BILAYER TABLET[12]

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 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.

INTRA GASTRIC BILAYERED FLOATING TABLETS

These are also compressed tablet and contain two layers i.e. Immediate release layer and 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.

PREPARATION OF BILAYER TABLET[13,14]

Bilayer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included.

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 for formulator 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 1 was found to be major factor influencing tablet delamination.

5) DIFFERENT TYPES OF BILAYER TABLET PRESSES[13]

A) PICCOLA BILAYER

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

B) ROTAB BILAYER

a) Software

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

b) Working

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

c) R and D modified technique

R and D modified RoTab Bilayer is featured with measuring points on which there are graphical visualization and evaluation are possible. There is an additional alarm function on which punch tightness is controlled. Anytime upgration is possible which is R and D Plus.

d) R and D Plus.

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

C) BILAYER TABLET PRESS

The Xm bilayer tablet press features a rectangle second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, which the main compression station will automatically compress, the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the dis table and completely eliminates any potential of cross contamination.

wipcon® solution available for potent for layer tablet press is a small scale press which is ideal for product development, scale up, clinical trials and midrange production. The bilayer execution, single layer conversion kit and exchangeable turret offers, a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and changeover the machine concept.

ADVANTAGES

Flexible concept.

Bilayer execution with optional single layer.

QUALITY AND GMP-REQUIREMENTS[15]

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

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

4. Producing a clear visual separation between the two layers
5. High yield Accurate and individual weight control of the two layers.

These requirements seem obvious but are not so easily accomplished.

EVALUATION OF BILAYER TABLET[16-17]

A) PARTICLE SIZE DISTRIBUTION

The particle size distribution was measured using sieving method.

B) PHOTON MICROSCOPE STUDY

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

C) 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.

D) 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.

E) 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

F) COMPRESSIBILTY

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

C = 100 x (1-ÞB/ÞT)

(Indian Pharmacopoeia, 1996; United States Pharmacopoeia, 2000:1944).

G) HAUSNERS RATIO

It is calculated by the formula, freely settled bulk density of the powder tapped density of the powder.

EVALUATION OF SUSTAIN RELEASE BILAYER TABLET

A) TABLET THICKNESS AND SIZE

Thickness and diameter of tablets were important for uniformity of tablet size.

Thickness and diameter was measured using venire caliper.

B) TABLET HARDNESS

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.

C) FRIABILITY

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.

D) 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.

E) DISSOLUTION STUDIES

Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and Intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5 ° C and pH 1.2 buffer (900 ml) (i.e. 0.1N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The

samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

F) Buoyancy Studies[18]

The time taken for dosage form to emerge on surface of medium is called floating lag time, duration of time by which the dosage form constantly emerges on surface of medium is called Total floating time (TFT).One tablet from each formulation batch is placed in USP type II dissolution apparatus containing 900 ml 0.1 N HCl dissolution medium using paddle at a rotational speed of 75 rpm. The temperature of medium is maintained at 37° ± 2°c. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium will be noted.

G) Stability Studies[19]

Stability study of the bilayer tablet can be evaluated as per ICH guidelines Q1C.

Table 2: Recommended Long Term and Accelerated Storage Conditions.

Study	Storage condition	Minimum Time Period
Long term	25°C±2°C / 60% RH ± 5% RH 30°C±2°C / 65% RH ± 5% RH	12 months
Intermediate	30°C±2°C / 65% RH ± 5% RH	6 months
Accelerated	40°C±2°C / 75% RH ± 5% RH	6 months

Drug Release Kinetics

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

Zero Order

Cumulative amount of drug released Vs time.

First Order

Log cumulative percentage of drug remaining Vs time.

Higucchi's

Cumulative percentage of drug released Vs Square root of time.

Korsmeyer's

Log cumulative percentage of drug released Vs log time.

FUTURE PROSPECTS

With respect to herbal Bilayer floating tablets.

Herbal drug delivery is the emerging trend in the pharmacy. Bilayer floating tablet is best choice for her-bal drug delivery. BFT have been designed which could release drug up to 12-24 hours. BFT of herbal drugs mainly improves the therapeutic effect of drug. Immediate and controlled release layer concept implemented to prolong drug(s) action. Some of herbal drugs that can be delivered as Bilayer floating tablets.

A. Ginger root (Zingiber officinale Rose) has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum and is also reported to have chemopreventative activity in animal models.

B. Turmeric Curcumin derived from turmeric has been shown to prevent gastric and colon cancers in rodents (Chakra-borty M et al., 2012).

C. Licorice In the recent study at the institute of medical microbi-ology and virology, Germany, researchers identified that licorice extract produced a potent effect against a strains of H.pylori (Chakraborty M et al., 2012).

4. Berberine Berberine has wide variety of activity against bacteria, viruses, fungi, protozoans, and helminthes (Chakrabor-ty M et al., 2012).

CONCLUSION

Bilayer tablet is beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. 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. Bilayer 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 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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