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Bilayer Tablet: Important Dosage Forms

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ABSTRACT

Bilayer tablet is new era for the successful development of controlled release formulation and also provide a successful key for other drug delivery system. Bilayer tablet is made up of two layers in which one is immediate layer for initial dose and second layer is sustained layer for maintenance dose. Thus, bilayer tablet is useful for sequential release of two drugs in combination and is applicable for improved patient compliance and mainly for reduced toxicity. It is useful for both single and multiple dose therapy. The present article gives an idea about an introduction of bilayer tablet, various tablet presses, manufacturing process, GMP and quality requirements, and challenges in bilayer tablet and recent approach in bilayer tablet development.

Keywords: Controlled release, Bilayer tablet, Immediate layer, Sustained layer.

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INTRODUTION

Oral route of drug administration has wide acceptance up to 50 to 60% of total dosage form and is the most convenient and preferred route for systemic effects due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation.[1] The bilayer tablet is a concept utilized by Skpe Pharma PLC in their Geometrix tablet, which is composed of different layers.[6] Bilayer tablet is defined as, the solid oral dosage form, usually round, spherical, oval or biconcave in shape and consists of one or more than one medicament designed in two layer systems which can be suitable for combination therapy and biphasic release therapy.[2]The drug release pattern of each layer depends upon its formulation. Drug release can be rendered almost unidirectional if the drug is incorporated in upper non adhesive layer and its delivery occurs into the whole oral cavity.[3] Bilayer is useful for both development of immediate and sustained release formulation. These two layers are composed together by granulation and compression method. Coloring the separate layers provides many possibilities for unique tablet identity. [1] Various problems associated with the formulation of bilayer tablet such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between two layers, reduced yield. To overcome these problems, development and production of quality bilayer tablets need to be carried out on purpose built tablet presses. [1] In the recent years ,pharmaceutical drug product manufacturer have oriented their product development activities to fixed dose combinations (FDCs) for treatments like type 2 diabetes, hypertension, pain and HIV/AIDS. [16, 17, 18, 19, 20]

Need of Bilayer Tablets[4]

or the administration of fixed dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery system such as chewing devices and floating tablets for gastro retentive drug delivery. Controlling the delivery rate of either single or two different active pharmaceutical ingredients. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/ erodible barriers for modified release. To separate incompatible Active pharmaceutical ingredient from each other to control the release of API from one layer by utilizing the functional property of the other layer(such as osmotic property).

Challenges in the Bilayer Tablet Manufacturing[1]

1) Delamination: Tablets falls apart when the two halves of the tablet do not bond completely. The two granulation layers should adhere when compressed.

2) Cross-Contamination: When the granulation of the first layer intermingles with the granulation of second layer or vice versa, cross contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross-contamination.

3) Production yield: To prevent cross-contamination dust collection is required which leads to losses. Thus, bilayer tablets have lower yield than single layer tablets.

4)Cost: Bilayer tableting is more expensive than single layer tableting for several reasons:

a) The tablet press costs more.

b) The presses generally runs more slowly in bilayer mode

c) Development of two compatible granulations is must, which means more time spent on formulation development analysis and validation.

These factors if not well controlled/ optimized in one way or another will impact the bilayer compression 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 and process. [1]

Advantages[2,5]

Cost is lesser than as compared to other dosage form.

Greater chemical and microbiological stability.

Easy to swallow with least tendency for hang up.

Suitable for large scale production.

They are unit dosage form and often the greatest dose precision and least contact variability.[5]

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.[2]

Disadvantages[7]

Some drug resists compression into dense compacts owing to amorphous nature.

Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.

Difficult to swallow in case of children and unconscious patients.

Drugs with poor solubility, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate that will still provide adequate or full drug bioavailability.

Quality and GMP Requirements[5,13]

To produce 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 constituent the bilayer tablet. Providing sufficient tablet hardness.

Preventing cross contamination between the two layers.

Producing a clear visual separation between the two layers.

High yield and individual control of the two layers.

Approaches/Aspects in Bilayer Technology[6]

Floating Drug Delivery System (FDDS): From the formulation and technological point of view, the floating drug delivery system isconsiderably easy and logical approach in the development of Gastro retentive forms (GRDDs). Approaches to Design Floating Drug Delivery System: The following approaches have been used for the design of floating dosage forms of single and multiple systems.

Intra-gastric bilayer floating tablets

These are also compressed tablet as shown in figure and contain two layers that are immediate layer and sustained layer.[15] (figure 1). Multiple unit type floating pills: This system consists of sustained release pills as 'seeds' surrounded by double layer. The inner layer consists of effervescent agent while the outer layer is swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and forms swollen pills like balloons which float as they have lower density.

Raft forming system.

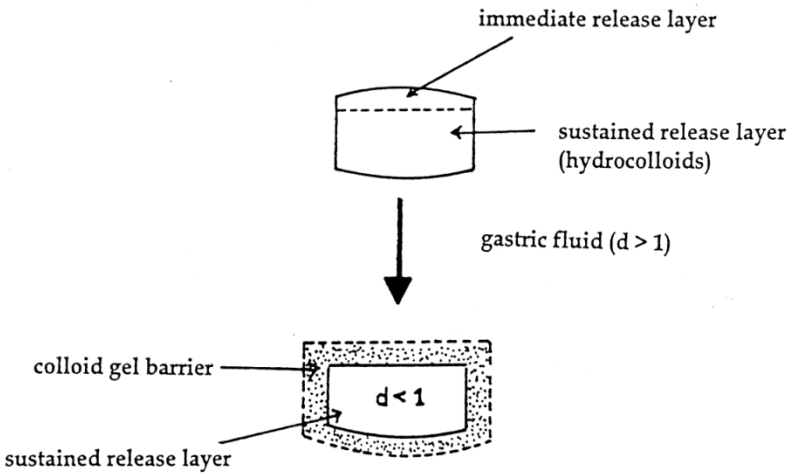

Figure 1:Intra-Gastric Floating Bilayer Tablet [15]

Technology

OROS® Push Pull Technology: (**Osmotic-controlled release oral delivery system)**

This system consists of mainly two or three layers among which the one or more layer is essential of the drug and other layer is 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 semipermeable membrane surrounds the tablet.(figure 2)

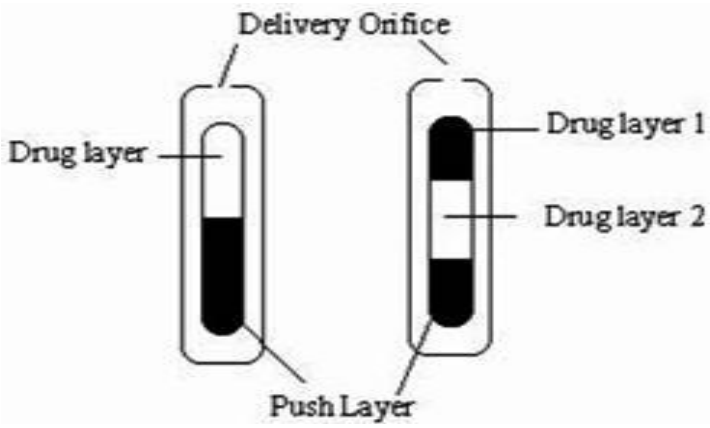

Figure 2: OROS Push Pull Technology of Bilayer and Trilayer Tablet Preparation [2]

L-OROS® Technology

The L-OROS® system was designed to provide continuous delivery of liquid drug formulations and improve bioavailability of the drugs .L-OROS system consists of two types that is soft gelatin capsule (softcap^{TM}) and hard gelatin capsule (Hardcap^{TM}).Both have a drug layer, barrier layer and push layer surrounded by a semipermeable membrane with a delivery orifice. The L-OROS hard cap system was designed to accommodate more viscous suspension with higher drug loading than soft cap design.[3, 21] (Figure 3)

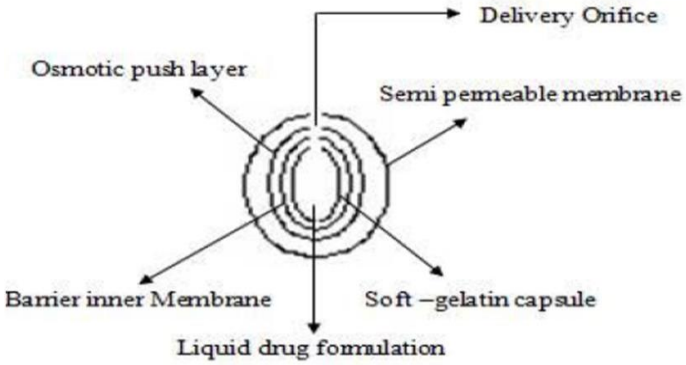

Figure 3: L-ORPS® Technology of Bilayer Tablet

ENSO 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 of the identified enhancer into controlled release technologies. (Figure 4)

Figure 4: ENSO Technology of Bilayer Tablet

DUREDAS$_{TM}$ Technology

DUREDAS or **DUAL RELEASE DRUG DELIVERY SYSTEM** (Elan Corporation)utilizes bilayer tablet technology, which has been specifically developed to provide two different release rates or dual release of drug from a single dosage forms. The tablets are prepared by two separate direct compression steps that combine an immediate release granulate (for rapid onset of action) and controlled release hydrophilic matrix complex within the tablet. The controlled release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix. [25] To expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continuous to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the DUREDAS technology is the production of the controlled release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each layer is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible.

Benefits offered by DUREDAS technology include:[25]

1) Bilayer tablet technology tailored release rate of two drug components capability of two different controlled release formulation combined.

2) Capability for immediate release and modified release components in one tablet.

3) Unit dose tablet presentation.

PRODAS Technology

PRODAS or Programmable Oral Drug Absorption System (Elan Corporation) is a multi-particulate drug delivery technology that is based on encapsulation of controlled release mini-

tablets in the size range of 1.5 to 4mm in diameter. This technology represents a combination of multi-particulate and the hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Mini-tabs lets with different release rates can be combined and incorporates into a single dosage form to provide the desired release rates. These combinations may include immediate release, delayed release, and / or controlled release mini-tablets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using mini-tablets formulated with different active ingredients. [7, 26]

GEMINIX Technology

Geminix is a dual drug delivery technology that can deliver one or more drugs at different times. The Geminix technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize side effects. The benefit of Geminix to the pharmaceutical industry, and ultimately to patients, is that two different actives or the same active can be delivered at differing rates in the single tablet. Pen west is actively applying its Geminix technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer and disorders of the central nervous system.[4, 30]

Manufacturing Process

Bilayer tablet can be prepared using method like direct compression, dry granulation, and wet granulation methods. Layers also prepared by combination of two methods.[12]

1. Preparation of granules

Bilayer tablets prepared with one layer of drug for immediate release and the second layer for sustained release. An immediate release layer of the tablet is prepared by using super disintegrating agents and wet granulation methods. A sustained release layer tablet is prepared by using swellable.[3, 27, 28] Polymers and non-aqueous granulation method. The tablet layers were made in order to achieve desired disintegration time, drug release, friability, thickness, and hardness. The steps involved in their preparation: sifting, mixing, preparation of binder, preparation of granules, drying, lubrication. Prepared granules were stored in a double lined polythene bags.[3,27,28].The manufacture of bilayer 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. 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.[22, 29, 31]

2. Bilayer compression Basics[13]

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 bilayer tablet.

Dwell time

Dwell time is defined as the time during which compression force is above 90percent of its peak value. Longer dwell times are a major factor introducing a quality tablet, especially when compressing a difficult formulation.[22]

Recent Development in the Field of Bilayer Tablets

The introduction of bilayer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit dosage form.[1]

Evaluation

General appearance

The general appearance of a tablet, its visual identity and overall elegance is essential for consumer acceptance. Includes in tablet shape. Size, color, presence or absence of an odor taste surface texture physical flaws and consistency and legibility of any identifying marking.[5]

Tablet thickness and size

Thickness and diameter measured using vernier caliper.[6,14,15]

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 is measured by Monsanto hardness tester.[6,14,15] The force required to break the tablet is measured in kilogram and crushing strength 4kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness 4to 10 kg; however, hypodermic and chewable tablets are usually much softer 3kg and some sustained release tablets are much harder 10-20kg. Tablet hardness has been associated with other tablet properties such as density and porosity.

Hardness generally increases with normal storage of tablets and depends on the shape; chemical properties, binding agent and pressure applied during compression .other tester used to checked tablet hardness are strong-cubb tester. Pfizer tester, Erweka tester, and Schleuniger tester.[25]

Friability

Friability is the measure of tablet strength. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable. Normally, when capping occurs, friability values are not calculated .It is usually measured by Roche friabilater. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4minutes of this treatment or 100 revolutions. The tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability is expressed in percentage as:

$$\%friability = 1(loss\ in\ weight \div intial\ weight) \times 100$$

Stability study(temperature dependent): The bilayer tablets are packed in a suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period 15 days and analyzed for a physical characterization (visual defects. hardness, friability and dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation.[5]

Characterization of Bilayer Tablet [6]

Particle size distribution

The particle size distribution was measured using sieving method.

Angle of repose

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

$$tan\emptyset = h/r$$

Where, h and r are the height and radius of the powder.

Moisture sorption capacity:1g of disintegrate uniformly distributed in petridish and kept in stability chamber at 37 ± 1℃and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

Density

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

$$LBD\ weight\ of\ the\ powder\ = volume\ of\ packing \sigma 2\rho$$

$$T\text{BD weight of the powder} = \text{tapped volume of the packing } \sigma 3\rho$$

Compressibility

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

$$C = 100 \times (1 - \frac{\rho b}{\rho t})$$

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 apparatus I at 100rpm, 37 ± 0.5℃, and pH 1.2 buffer (900ml)(that is 0.1N HCL)for 2hours,since the average gastric emptying time is about 2hours.The dissolution medium was replaced with 6.8 phosphate buffer (900ml)and experiment continued for another 10 hours. At different time intervals, 5ml of the sample were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV Spectrophotometer using multicomponent mode of analysis. [8]

Uniformity of weight

Twenty tablets are randomly selected and weighed individually. The average weight is determined then% deviation from the average weight is calculated.

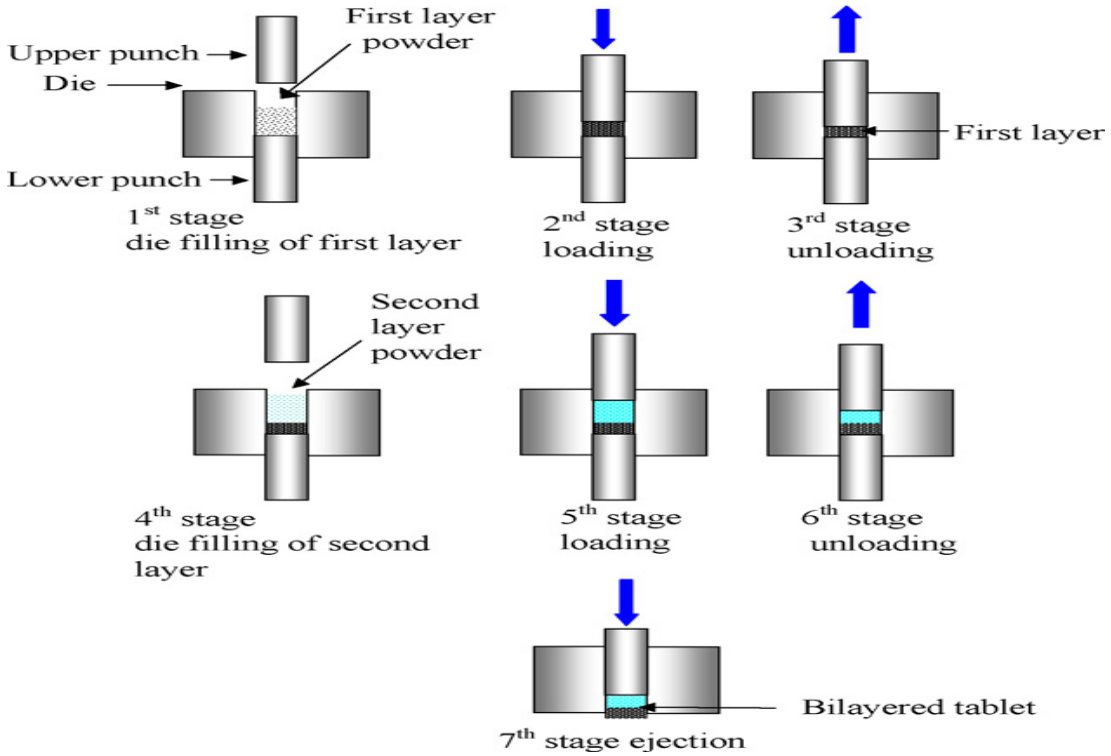

Figure 5: The Bilayered Tablet Uniaxial Die Compaction Cycle Used in This Work [23]

Table 1: Types of Bilayer Tablets [9, 10, 11]

Sr no	Type	Example
1	Modified release bilayer tablet	Metoclopramide HCl and Ibuprofen
2	Bilayer floating tablet	Rosiglitazone
3	Bilayer mucoadhesive tablet	Propranolol HCl

Table 2: Different Types of Tablet Presses [28]

Sr no	Type of press	Advantage	Disadvantage	Main feature
1	Single Sided	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	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	Simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity-or forced-feed with a different powder, thus producing the two individual layers of the tablet
2	Double Sided	The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of that layer.	Inherent to the principle of compression force monitoring	Offers an individual fill station, pre-compression and main-compression for each layer
3	Displacement Monitoring	weight monitoring/control for accurate and independent weight control of the individual layer	Table weight control using 'displacement' is based on the measurement of thickness variations under constant force and is measured at pre-compression	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-a clear visual separation between the two layers-maximized yield

Table 3:Marketed Preparation[31]

Sr no	Chemical name	Product name	Devloper
1	GLYCOMET®-GP2FORTE	Metformin hydrochloride,Glimiperide	USV Limited
2	ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd

3	DIAMICRON®XRMEX500	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd
4	NEWCOLD PLUS	Levocetrizine hydrochloride, Phenyl propanol amine, Paracetamol	Piramol Healthcare Ltd.
5	TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.
6	DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
7	TRIBET-1	Glimepiride, Pioglitazone hydrochloride, Metformin hydrochloride	Abbott Healthcare Pvt. Ltd.
8	PIOKIND®-M15	Pioglitazone, metformin hydrochloride	Psychotropic India Ltd
9	REVELOL®-AM 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.

Table 4: Patents on Bilayer Tablets[32, 33, 34, 35, 36]

Sr no	Author Name	Patent date	Patent no	Patent code	Work
1	AdmassuAbebe,Kyle Martin et al.	Dec 2012	US2013/0330406A1	US2013/0330406A1	Bilayer tablet formulation
2	Manabu Naktani,Kazutoshi Yokoyama et al.	May2008	US2008/0113023A1	US2008/0113023A1	Bilayer tablet comprising Telmisartan and Diuretic
3	David Francis Bain,DaleMunday et al.	May 2001	WO2001037814A1	WO2001037814A1	Bilayer tablet comprising Nicotine
4	Bharat PravinchandraMehta,Rajen Shah et al.	Jun 2006	US2006/0141037A1	US2006/0141037A1	Bilayer tablets of Oxcarbazepine for controlled drug delivery and process of preparation thereof
5	Friedal,Thomas Ochsenhausen et al	Nov 2012	EP2260833B1	EP2260833B1	Bilayer Pharmaceutical tablet comprising and Diuretic

Table 5: Recommended Long-Term and Accelerated Storage Condition [22]

Study	Storage condition	Minimum time period covered by data at submission
Long term	$25℃ \pm 2℃/60\%RH or\ 30℃ \pm 2℃/65\%RH \pm 5\%RH$	12months
Intermediate	$30℃ \pm 2℃/65\%RH \pm 5\%RH$	6months
Accelerated	$40℃ \pm 2℃/75\%RH \pm 5\%RH$	6months

CONCLUSION

Bilayer tablet is improving beneficial technology to overcome the shortcoming of the single layered tablet. Bilayer layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. 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-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 best solution.

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