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A Review on Bilayer Tablets

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Abstract:

Bilayer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of the successful drug delivery system. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles like the immediate release with extended release. Bilayer tablet is a very different aspect of anti-inflammatory and analgesic. Bi-layer tablet is suitable for sequential release of two drugs in combination 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 short coming of the single layered tablet. There are various applications of the player tablet, it consists of monolithic partially coated or multilayered matrices.

Keywords: Bilayer tablets, Preparation, Characterization, Various presses.

INTRODUCTION

On the basis of these considerations, we have proposed a bilayer tablet, in which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is an controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer .Multi-layer tablet dosage forms were designed for variety of reasons; to control the delivery rate of either single or two different active pharmaceutical ingredients (API), to separate incompatible APIs 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), 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 administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers. However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. Therefore, the major problem, that has to be overcome, is to understand in detail the sources of these problems in micro- and macroscales and to develop remedies to solve them during solid dosage delivery design.

ISSN: 3107-6513

APPLICATIONS

- Bi-layer tablet is suitable for sequential release of two drugs in combination.
- Separate Two Incompatible Substances.
- Sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.
- Promoting Patient Convenience and Compliance
- Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet
- Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- Bilayer tablets are used for bilayer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.
- Bilayer tablets are used to deliver the two different drugs having different release profiles.

Advantages:

- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Cost is lower compared to all other oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallowing with least tendency for hang-up.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages:

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating

Ideal Characteristics:

- It should be elegant & free from chipping, cracking, decontamination.
- It ought to have adequate quality to with stand mechanical shock during its tablet formulation process.

Need of Bilayer Tablets:

- To modify the total surface available for API layer either by sandwiching with one or two in active layers in order to achieve swellable/erodible barriers for modified release
- For the administration of fixed dose combination of different API prolong the drug product life cycle buccal/mucoadhesive delivery system; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery
- To separate incompatible modified Active pharmaceutical ingredient (APIs) 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).
- Controlling the delivery rate of either single or two different active pharmaceutical ingredients

TYPES OF BILAYER TABLETS

1.Single sided tablet press.
2.Double sided tablet press
3.Bilayer tablet press with displacement monitoring
4.Multilayer compression basics.

ISSN: 3107-6513

1.Singlesided Tablet press

Fig1: Single Sided Tablet Press

Various types of bilayer 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 in gravity fed or force fed with a different powder, producing the 2 individual layers of the tablet. When the dye passes under the feeder, it is at first loaded with the first layer of powder followed by the second-layer powder then the entire tablet is compressed in one or two step. The two layers in the dye mix slightly at their interface and in most cases bond sufficiently so that no layer separation occurs when the tablet is produced this is the simplest way of producing a bilayer tablet.

Limitations

- No weight monitoring or control of the individual layers.
- No distinct visual separation between the 2 layers.
- Dwell time due to the small compression roller possible deaeration resulting capping in poor and hardness problems

2.Double sided tablet presses

Fig 2: Double Sided Tablet Press

Most of the double side tablet press, which automates production control use the compression force to monitor and control the weight of the tablet weights. The effective compression force exerted on each individual tablet with the help of the compression system at the main compression of the layer. This system helps into reject out the tolerance tablets and correct the dies fill depth when required.

ADVANTAGES

- Low compression force exerted on the first layer to avoid chapping and separation of the individual layer.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between two layers.
- A clear visual separation between the two layers.
- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Maximized yield.
- Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet.

Limitations

- Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during a final compression.
- Bonding is too restricted if the first layer is compressed at a high compression force.
- The low compression force required when compressing the first layer,unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with compression measurement.

3. Bi Layer Tablets Presses with Displacement

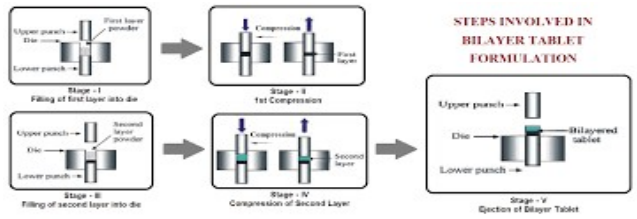

Fig3: Bilayer Tablets Presses with Displacement

ISSN: 3107-6513

The principle of bilayer tablet press is fundamentally different from the principle of compression force. In this case the accuracy increases withreduced compression force. At higher production speed the risk of capping and separation increases, but can be reduced by sufficient dwell time a tall four compression stages.

Advantages

- Displacement weight monitoring /control for accurate independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid chapping and separation of the 2 individual layers.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed
- Maximum prevention of cross contamination between the layers.
- A clear visual separation of the layers.
- Maximized yield.

4.Multilayertabletcompressionmethod

Fig 4: Multilayer Tablet Compression Method

Presses can be designed specifically for multi layer compression or a standard double press can be converted for multipliers. The multilayer tablet concept has been long utilized to develop sustained release formulations such tablets have fast releasing layer and may contain players or triple layers to sustain the drug release from the tablet. The pharmacokinetics advantage relies on the fact that drug release from fast releasing granules leads to sudden rise in blood concentration, however the blood level is maintained at a steady state as the drug is released from the sustained granules immediate dosing and other layer with bio adhesive property. immediate dosing and other layer with bio adhesive property.

MANUFACTURE OF MULTILAYER TABLETS

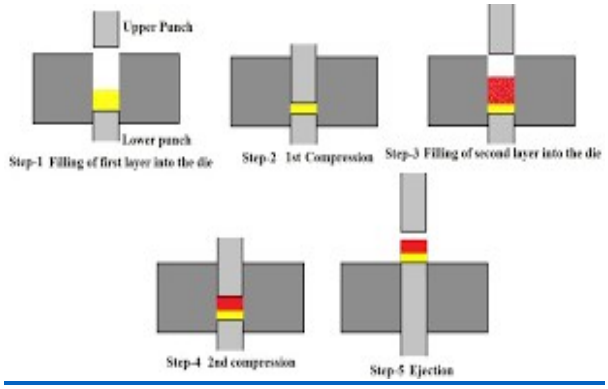

Fig 5: multiple layer tablets

- The manufacture of multilayer tablets has been successful for over 50 years2. 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 dosing3.
- However, despite this, a considerable amount of expertise is still required to formulate these tablets and to ensure consistent manufacture to satisfy regulatory requirements .One problem that causes great concern is the delamination of layered tablets5, 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, coherensolid bodie
- 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 tablets6. Bilayered tablets have proven to be effective in delivering drugs that require a loading dose followed by a maintenance dose7

ISSN: 3107-6513

- Commonly, in bi layered 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 trac
- 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 super disintegrant in the rapid release layers of various formulations, while the polymers Eudragit® RL, Eudragit® RS and EC were utilized in the sustained release layer
- 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
- The same concept has been demonstrated in a patent by Kim and co-workers where the system provided release of two drugs in different manner
- 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 glimepiride9. This further emphasizes the positive function of these systems in treating chronic conditions such as hypertension and diabetes. Nirmal and co workers developed a bi layered 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.
- 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 concurrently10. This bi layered system design may thus be valuable for future application in the successful treatment of hypertension.

VARIOUS TECHNIQUES FOR BILAYER TABLET

1.OROS push pulls Technology

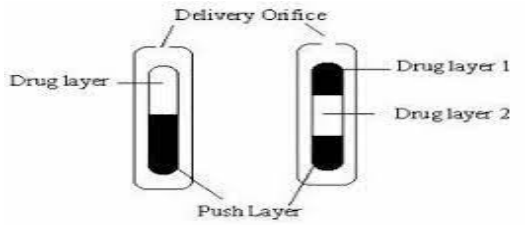

Fig 6: Oros Push Pulls Technology

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. 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. 5: Bilayer and tri layer OROS push pull technology

2.L-OROSTM Technology

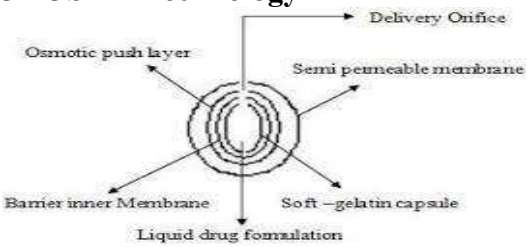

Fig 7: L-Orostm Technology

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, than osmotic push layer and

ISSN: 3107-6513

then a semi permeable membrane, drilled with an exit orifice.

3. EN SO TROL Technology

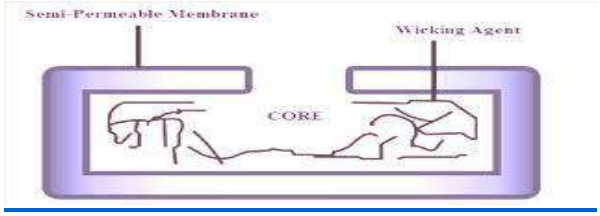

Fig 8 : En So Troll Technology

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 identifiedenhancer into controlled release technologies.

4.DUREDAS Technology

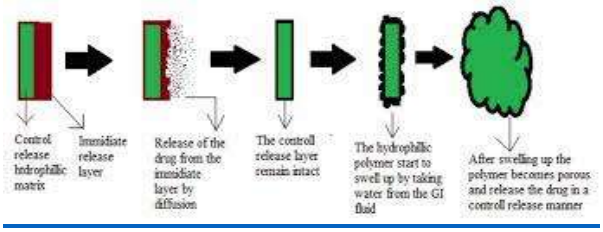

Fig 9: Dure Das Technology

This system is also known as 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 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 a combination of hydrophilic polymer

5. 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 release minute quantity of concentrated form in continues and consistent from over months or year.

Characterization of Bilayer Tablet:

Particle Size Distribution:

The particle size distribution was measured using sieving method

Photo-microscope study:

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

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 = Height
r = Radius of the powder cone

Moisture absorption 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

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 ð3

Compressibility:

The compressibility index of the disintegrate was determined compressibility index. C = 100 x (1-þb/þt)

EVALUATION OF BILAYER TABLET

1.General Appearance:

The general appearance of a tablet, its visual identity and over all elegance is essential for consumer acceptance. Includes in are tablets size, shape, colour presence or absence of an odor taste,

ISSN: 3107-6513

surface texture, physical flaws and consistency and legibility of any identifying marking.

2.Size and Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard.

3.Tablet thickness:

monitored and Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

4.Weight variation:

Weight variation is a frequently used term during tablet compression operation in pharmaceutical industries. As the name indicates Weight Variation is a defect in which weight differs from the defined ranges given by the official pharmacopoeias.

5.Friability:

Friction and shock are the forces that most often cause the tablets to chip, chop or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to with stand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6inches in each turn within the apparatus. After four minutes 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. The value is expressed as a percentage. 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 and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have fewer tendencies to cap where as thin tablets of large diameter, often show extensive cupping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of the tablet is the measure of variability and is expressed in percentage.

%Friability=1-(lossinweight/Initialweight)X100

6. Hardness

The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied to the tablet. The strong-Cobb Pfizer and apparatus which were later introduced measures the diametrically applied force required to break the tablet. Hardness, which is now more appropriately called crushing strength determinations are made during tablet production and are used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications, if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4to10 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 normals to rage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression.

Apparatus Used To Check Tablet Hardness

With time, various types of tablet testers were introduced for checking the hardness of tablets and some are given as follows,

- Monsanto Hardness Tester
- Strong Cobb Hardness Tester
- Pfizer Hardness Tester
- Erweka Hardness Tester

ISSN: 3107-6513

- Dr Scheluenger Pharmatron Hardness Tester
- Kraemer Elektronik's Hardness Tester

7.StabilityStudy

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guideline for accelerated studies.The tablets were withdrawn after a period of 15days and analyzed for physical characterizations Visualdefects, Hardness, Friability and Dissolution and drug content. The data obtained is fitted into first or derequations to determine the kinetics of degradation. Accelerated stability data are plotted according Arrhenius equation to determine the shelf life at 25°C.

1.TABLE NO.1; COMMERCIALLY MARKETED BILAYER TABLETS

S. No	Product Name	Chemical Name	Developer
1	ALPRAX PLUS	Sertraline, Alprazole	Torrent Pharmaceuticals Ltd.
2	Glycomet®-GP2Forte	Metformin hydrochloride, Glimepiride	USV Limited
3	DIAMICRON®XR MEX500	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. Ltd.
4	Newcold Plus	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramol Healthcare Ltd.
5	DIUCONTIN-K®20/250	Furosemide, Potassium chloride	T.C. Health Care Pvt. Ltd.
6	TRIOMUNE 30	Nevirapine, Lamivudine, Stavudine	Cipla Ltd.
7	PIOKIND®-M15	Pioglitazone, metformine hydrochloride	Psychotropics India Ltd.
8	Revelol®-Am 25/5	Metoprolol succinate, Amlodipine besilate	Ipca Laboratories Ltd.

Application:

• Separate two incompatible substances.

• Bilayer tablet is suitable for sequential release of two drug in combination.

• Bilayer tablet is used to deliver the loading dose and sustained dose of the same or different drugs.

• 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 short coming of the single layer tablet.

CONCLUSION

A bilayer tablet is a technologically advanced solution that addresses the shortcomings of a single-layered tablet. A bi-layer tablet can be used to segregate two substances that are incompatible, release two medications sequentially in tandem, or create a sustained release tablet where the first layer is the initial dose and the second layer is the maintenance dose. Tablets prepared in the multilayer form are utilised to give incompatible drug delivery methods and to provide control release tablet preparations through the employment of surrounding or multiple swelling layers. GMP regulations and the quality of bilayer tablets can differ greatly. This explains why a wide variety of presses, from straightforward single sided presses to extremely complex devices, are utilised to make bilayer tablets.

Bilayer tablet is improved beneficial technology to over come the short coming of the single layered tablet. There are various application of the bilayer 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 multilayer isused to provide systems for the administration of drugs, which are incompatible and to provide control 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 bilayer tablet, ranging from simple single-sided presses to highly sophisticated machines.

ISSN: 3107-6513

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