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A REVIEW ON BILAYER TABLETS

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ABSTRACT

Bilayer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Controlled release dosage forms have been extensively used to improve therapy with several important drugs. Use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper nonadhesive layer its delivery occurs into the whole oral cavity.

KEYWORDS: Bilayer tablet, GMP requirement for bi-layer tablets, various tablet presses, RoTotab push technology and DUROS technology.

I. INTRODUCTION:

Day-by-day's various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy. From last few years, interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation [1].

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose [2].

From various current methods for treating illness and diseases, chemotherapy (treatment with drugs) is the most frequently used technique. It has the broad range of applications over the greatest variety of disease states and is frequently the preferred treatment method. For many decades, treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers [3].

However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms 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[4].

Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed However, these drug delivery devices are mechanically complicated to design/manufacture and

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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 [5].

The main aim of the article is the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose.

II. RATIONALE BEHIND FORMULATION OF BI-LAYER TABLET:

1. Controlling the delivery rate of either single or two different APIs.
2. 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).
3. To adapt 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 controlled release [6].

III. ADVANTAGES OF BILAYER TABLETS [6]

1. Ease of accurate dosing and low content variability
2. Good physical and chemical stability
3. Competitive unit production costs
4. High level of patient acceptability
5. High convenience
6. Easy to package and ship
7. Simple to identify
8. Convenience of self administration.
9. Product identification is easy
10. Fewer daily doses are required compared to traditional delivery system.

IV.DISADVANTAGES OF BILAYERD TABLETS

1. Difficult to swallow in case of children and unconscious patients.
2. Add complexity and bi-layer tablet presses are expensive.
3. Insufficient hardness, layer separation, reduced yield.
4. Inaccurate individual layer weight control.
5. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
6. There should be compatibility between the two active ingredients [7].

V. APPLICATIONS:

1. Bi-layer tablets are mainly used in combination therapy.
2. Bi-layer tablets are used to deliver the loading dose and maintenance dose of the same or different drug.
3. Bi-layer tablets are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug
4. Bi-layer tablets are used to deliver the two different drugs having different release profile [7].

VI. Types of Bilayer Tablet.

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 extended release manner.

Heterogeneous Type

Bilayer tablet is suitable for sequential release oftwo drugs in combination, separate two incompatible substances [8].

VII. CHARECTERISTICS OF PRECOMPRESSED BILAYER TABLETS: [9].

Particle Size Distribution

The particle size distribution was measured using sieving method

1. **Photo-Microscope Study**

   Photo-microscope image of TGG and GG was taken (X 450 magnifications) by photomicroscope.
2. **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.
3. **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.

VIII.VARIOUS TECHNIQUES OF BI-LAYER TABLET:

1. **Oros ® push pull technology.**

   This system consist of mainly two or three layer among which the one or more layer are necessary for 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 comprise 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.

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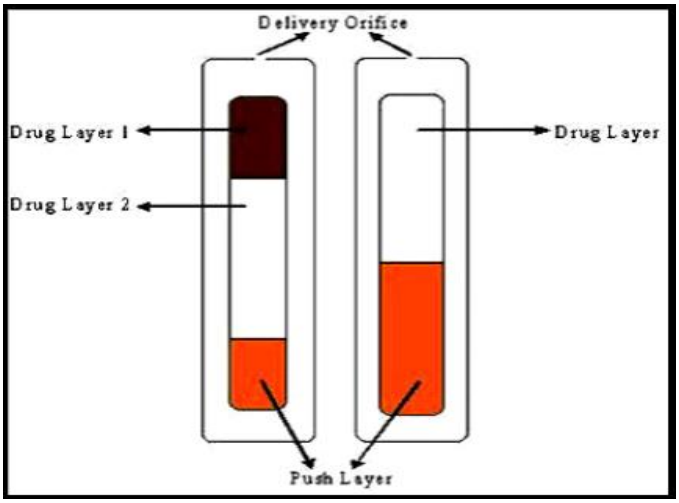

Fig. 1: Bilayer and trilayer ROS push pull technology

2. L-Orostm technology

This system used for the solubility concern 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 and then a semipermeable membrane, drilled with an exit orifice.

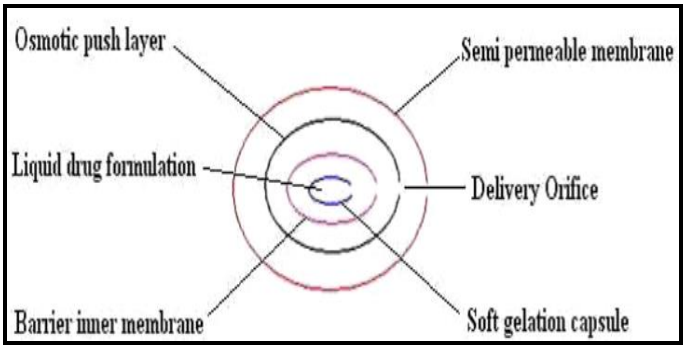

Fig. 2: L–OROSTM Technology

3. DUROS technology

DUROS (Alza Corporation) is based on implant technology, which provides an alternative of a wide range of therapeutic compounds, includes peptides, proteins and other bioactive macromolecules. These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year.

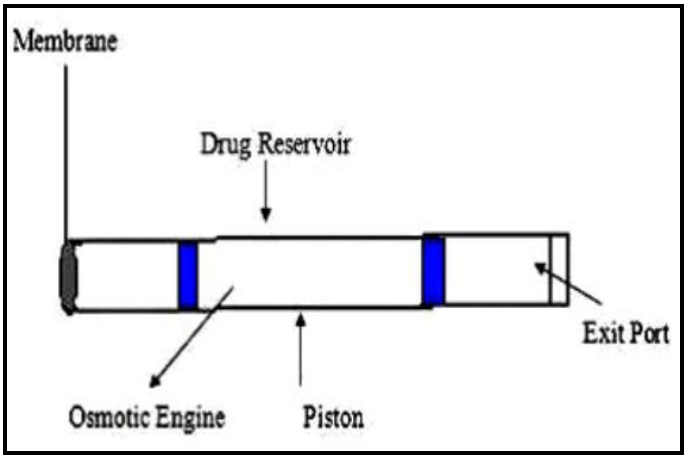

Fig. 3: DUROS Technology

4. EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory used an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies [10, 11].

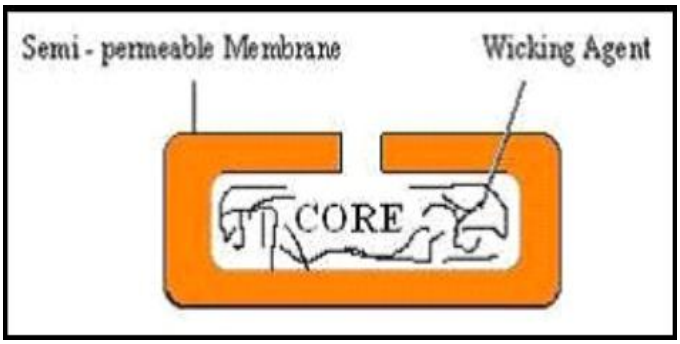

Fig. 4: EN SO TROL Technology

IX. MANUFACTURING PROCESS OF BILAYER TABLET

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. Thus, the tablet breaking force and the tablet's susceptibility for delamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality of the tablet. The extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity [11].

X. EVALUATION OF BILAYER TABLETS [12].

A. General Appearance

The general appearance of a tablet, its visual identityand overall-elegance is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking

B. Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

C. Tablet thickness

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.

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D. Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand 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 6 inches 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 less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress the loss in the weight of tablet is the measure of friability and is expressed in percentage as-

% Friability = 1- (loss in weight / Initial weight) X 100.

E. Hardness (Crushing strength)

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 diametrally to the tablet. The Strong-Cobb Pfizer and Schleuniger 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 4 Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kg; however, hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10 -20 kg). 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.

F. **Stability Study (Temperature dependent)**

The bilayer tablets are packed in 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 of 15 days and analyzed for 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 [12].

Table 1: Commercially marketed bilayer tablets [13, 14].

S. No	Product Name	Chemical Name	Developer
1	**ALPRAX PLUS**	Sertraline, Alprazolam	Torrent Pharmaceutcals Ltd.
2	**Glycomet®-GP2Forte**	Metformin hydrochloride, Glimepiride	USV Limited
3	**Newcold Plus**	Levocetrizine hydrochloride, Phenylpropanolamine, Paracetamol	Piramol Healthcare Ltd.
4	**DIAMICRON®XRMEX500**	Gliclazide, Metformin hydrochloride	Sedia® Pharmaceuticals (India) Pvt. 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.

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Fig. 5: Bilayered Tablets

XI. CONCLUSION:

Bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Bi-layer tablet quality and GMP-requirements can vary widely.

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