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A REVIEW ARTICLE ON BILAYER TABLETS

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ABSTRACT
Over the past 30 years stated that the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. 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.

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INTRODUCTION
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[1]. 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 [2, 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 [4-7]. Conventional dosage form are accused of repetitive dosing and unpredictable absorption window that cause wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor therapeutic efficiency[8]. This dynamic such as repetitive dosing and irratic absorption led to the concept of controlled drug delivery systems. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers[9]. The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. But often this controlles drug delivery system fails to achieve the stated advantages due to lack of releasing the initial bolus dose dumping and failure to achieve site specific drug delivery. Immediate release drug delivery system is intended to disintegrate rapidly, and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increase incidence of side effects.

Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, we have proposed a bilayer tablet (Table No.1, Figure No.1 and 2).

ADVANTAGES
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.

DISADVANTAGES
There should be compatibility between the two active ingredients.

Types of Bilayer Tablets
The term bilayered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous)[5].

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.

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 (X 450 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 and r are the height and radius of the powder cone.

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 $37\pm1°C$ 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 ð3Þ.

Compressibility

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

$$C = 100 \times (1-ÞB/ÞT).$$

Hausnser's Ratio

It is calculated by the formula,

H= Bulk density/Tapped density

Where B is the freely settled bulk density of the powder is the tapped density of the Powder.

EVALUATION OF SUSTAIN RELEASE BILAYER TABLET

Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire calliper.

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.

Friability

Friability is the measure of tablet strength. 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] $\times100$.

Uniformity of Weight

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. standards.

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 propensity 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 precompression 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 attributes of the tablet16. For instance, the extent of compact densification and resistance to

compressibility within the die cavity was impacted by compaction pressure and the punch velocity.

Evaluation of Bilayer Tablets[7]

General Appearance

The general appearance of a tablet, its visual identity and 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.

Size and Shape

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

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.

Weight variation

Standard procedures are followed as described in the official books.

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.

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 have 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.

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.

Table No.1: Commercially marketed bilayer tablets[9]

| 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.
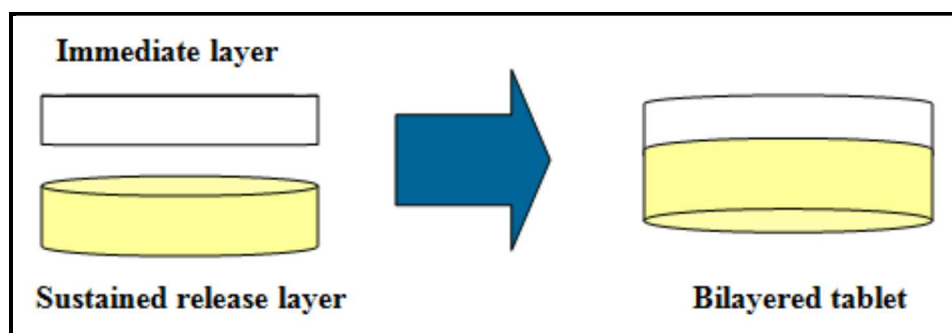
Figure No.1: Bilayered tablet

Figure No.2: Bilayered tablet with two drugs

CONCLUSION

Bi-layer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate (e.g. IR and ER) can be incorporated in a single unit. 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. To develop a dynamic bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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