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REVIEW ARTICLE

A REVIEW 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, DUROS technology.

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, 5, 6, 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 dose dumping and failure to achieve site specific drug delivery.[10] 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.[11, 12]

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BILAYER TABLETS:

Figure 1 A: Single Layer Tablet

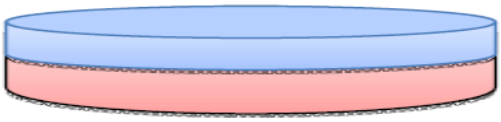

Figure 2 B: Bilayer Tablet

THE GOAL TO DESIGNING BILAYER TABLETS: [13, 14, 15]

- Controlling the delivery rate of either single or two different API'S.
- 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).
- For the administration of fixed dose combinations of drugs, Prolong the drug product life cycle**,** buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- 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.
- 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. 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 a controlled release, 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.

ADVANTAGES OF BILAYER TABLET DOSAGE FORM: [16, 17, 18]

1. Bilayer tablets can be designed in such manner as to modify release as either of the layers can be kept as extended and the other as immediate release.
2. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
3. Separation of incompatible components.
4. Prospective use of single entity feed granules.
5. Greatest chemical and microbial stability over all oral dosage form.
6. Objectionable odour and bitter taste can be masked by coating technique.
7. Bilayer execution with optional single - layer conversion kit.
8. Low cost compared to all other dosage form.
9. Offer greatest precision and least content uniformity.
10. Easy to swallow with least hang up problems.
11. Flexible concept.
12. Suitable for large scale production.
13. Lighter and compact.
14. Patient compliance is improved leading to improve drug regimen efficiency.
15. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and least content variability.
16. Patient compliance is improved fewer daily dose are required compared to traditional delivery system.

DISADVANTAGES OF BILAYER TABLET DOSAGE FORM:

1. 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.
2. Difficult to swallow in case of children and unconscious patients.
3. Adds complexity and bilayer rotary presses are expensive.
4. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
5. Cross contamination between the layers.
6. Insufficient hardness, layer separation, reduced yield.
7. Imprecise individual layer weight control.

GENERAL PROPERTIES OF BILAYER TABLET DOSAGE FORM: [19]

1. It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.

2. It should have graceful product identity free of defects like chips, cracks, discoloration and contamination.
3. Must have a chemical stability shelf life, so as not to fallow alteration of the medicinal agents.
4. The bilayer tablet must release drug in a expectable and reproducible manner.
5. It should have physical and chemical stability.

VARIOUS TECHNIQUES FOR PREPARATION OF BILAYER TABLETS:

EN SO TROL TECHNOLOGY: [8, 16]

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 enhancer into controlled release technologies.

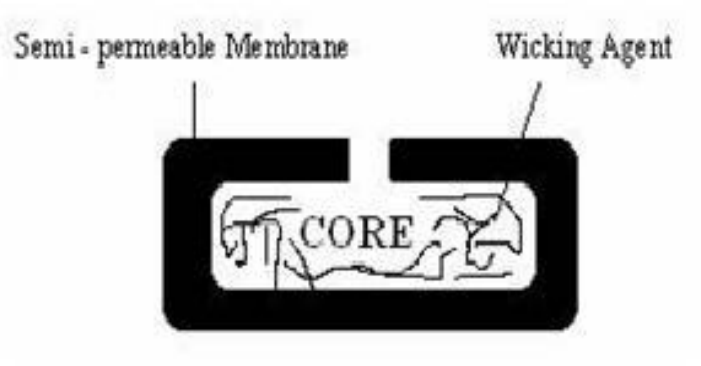

Figure 1: EN SO TROL Technologies

OROS® PUSH PULL TECHNOLOGY:[8]

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 (Fig.3). 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.

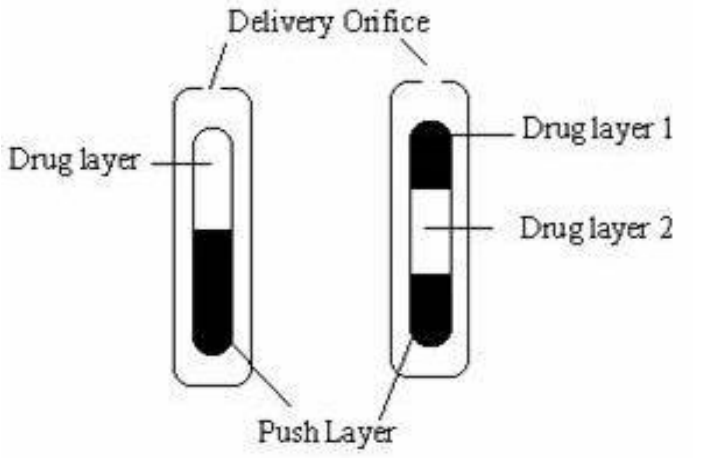

Figure 2: Bilayer and trilayer OROS Push pull technology.

L-OROS tm technology[18]

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 than a semi permeable membrane, drilled with an exit orifice (Fig.4).

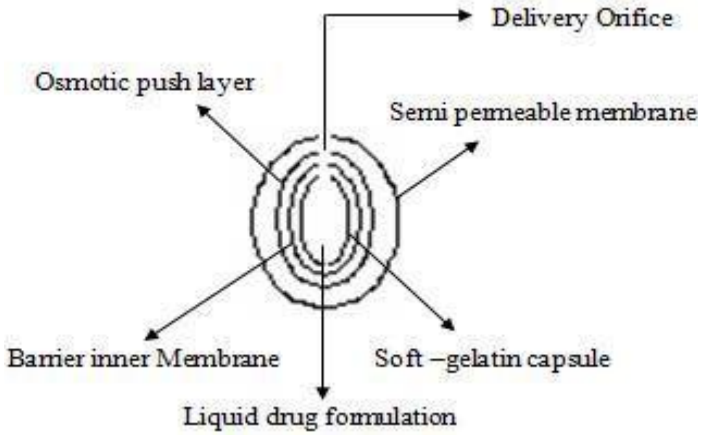

Figure 4: L – OROS tm technology.

DUROS TECHNOLOGY: [8, 18]

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 5).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 reglious minute quantity of concentrated form in continues and consistent from over months or Year.

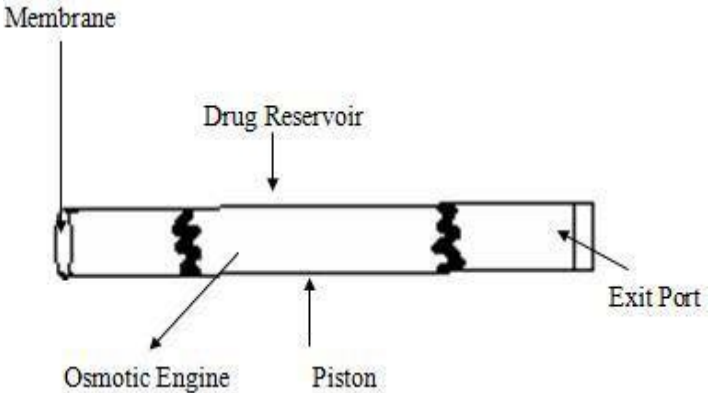

Figure 5: DUROS Technology

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 tab letting 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 polymers.

Benefits offered by the DUREDAS™ technology include:

- Bilayer tabletting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.
- Capability for immediate release and modified release components in one tablet.
- Unit dose, tablet presentation.

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bi-layer. Two different release rates can be achieved from each side. In this way greater prolongation of sustained release can be achieved. Typically an immediate release granulate is first compressed followed by the addition of a controlled release element which is compressed onto the initial tablet. This gives the characteristic bi-layer effect to the final dosage form. A further extension of the DUREDAS™ technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers and drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are possible. A number of combination products utilizing this technology approach have been evaluated. The DUREDAS™ technology was initially employed in the development of a number of OTC controlled release analgesics.

In this case a rapid release of analgesic is necessary for a fast onset of therapeutic effect. Hence one layer of the tablets is formulated as immediate releases granulate. By contrast, the second layer of the tablet, through use of hydrophilic polymers, releases drug in a Controlled manner. The controlled release is due to a combination of diffusion and erosion through the hydrophilic polymer matrix.

ROTAB BILAYER:[23]

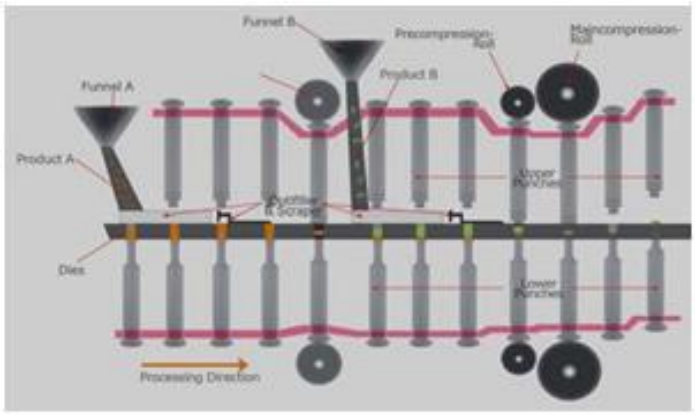

Figure 6: RoTab Machine

SOFTWARE:

This software is modular designed and can be upgraded with additional functions at any time. An advanced industrial PC-system with 15" touch-screen guarantees precise results and fast graphical evaluations. The wide range of instrumentations allows a nearly perfect simulation of production machines in laboratory scale.

BASIC TECHNIQUE:

Software package for prevailing use of RoTab Bilayer in production mode. Operation with 15" touch-screen display, by automatical dosing regulation by compression force and adjustment o die table and Optifiller speed. Optional independent hardness regulation Available.

R&D MODIFIED TECHNIQUE:

Basic package for galenical R&D on the RoTab Bilayer. Contains evaluation and graphical visualization of instrumented measuring points, as compression 1st layer pre main compression and ejection force on a 15" touch screen display. Punch tightness control can be selected as an additional alarm function. Upgrade to R&D Plus is possible at any time.

R&D PLUS:

Contains all functions of Basic and R&D plus the possibility to evaluate and visualize the following special instrumentations on the 15" touch-screen display Punch tightness control, tablet scraper force and display of force displacement. With R&D Plus the RoTab Bilayer sets new standards in tabletting technology.

BI-LAYER TABLET PRESS:

The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in 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 die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for Small-Scale Bi-layer Applications. The KORSCH XM 12 Bi- Layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press 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.7 The machine features a 5 KN tamping station, 40 KN precompression station, 80 KN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level.

SMALL-SCALE BI-LAYER:

a) 5 KN First Layer Tamping Force.
b) 40 KN Precompression Force.
c) 80 KN Main Compression Force.
d) Single-Layer Conversion Capability

BILAYERED TABLETS: QUALITY AND GMP REQUIREMENTS:[20, 21]

- To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bilayered tablet press is capable of: Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
- Providing sufficient tablet hardness.
- Preventing cross contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Precise and individual weight control of the two layers.

TYPES OF BI-LAYER TABLET PRESSES:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement.

(1) SINGLE SIDED TABLET PRESS:

The simplest design is the single sided press with both chambers of the double feeder separation from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first-layer powder followed by the second layer powder. Then the intact tablet is compressed in one or two steps.

LIMITATIONS OF THE SINGLE SIDED PRESS:

- 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 ensuing in poor deaeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the result of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

(2) DOUBLE SIDED TABLET PRESS OR "COMPRESSION FORCE" CONTROLLED TABLET PRESSES:

A double sided press offers an individual fill station, pre – compression and main compression for each layer. In fact the bi-layer tablet will go through four compression stages before being ejected from the press. Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when mandatory.

ADVANTAGES:

1. Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
2. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
3. Maximum prevention of cross contamination between two layers.
4. A clear visual separation between the two layers
5. Displacement weight monitoring for accurate and independent weight control of the individual layer.
6. Maximized yield.

LIMITATIONS:

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of bi-layer tablet. 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 final compression. Bonding is too restricted if 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 force measurement". Most of the double sided tablet presses with automated production control use compression force

to monitor and control tablet weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

(3) BILAYER TABLET PRESS WITH DISPLACEMENT:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement the control system sensitivity does not depend on the operation point. But depends on the applied precompression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet.

The upper pre-compression roller is attached to an air-piston which can move up and down in air cylinder. The air pressure in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system. This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller is pushed downwards against affixed stop.

The lower pre-compression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower pre-compression determines the precompression height. At every pre-compression the upper punch hits the upper roller and is initially pushed downwards into the die. As the lower punch is pushed upwards by the lower roller the power is being compressed, while the exerted compression force increases. At a certain point the reaction force exerted by the power on the upper punch equals the force exerted by the air pressure on the piston. The punch has to continue its way under the roller because the torrent is spinning.

ADVANTAGES:

- Weight monitoring/control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

VARIOUS ASPECTS OF BILAYER TABLET:[22, 23]

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 as shown in figure and contain two layers i.e.
1. Immediate release layer and 2. Sustained release layer.

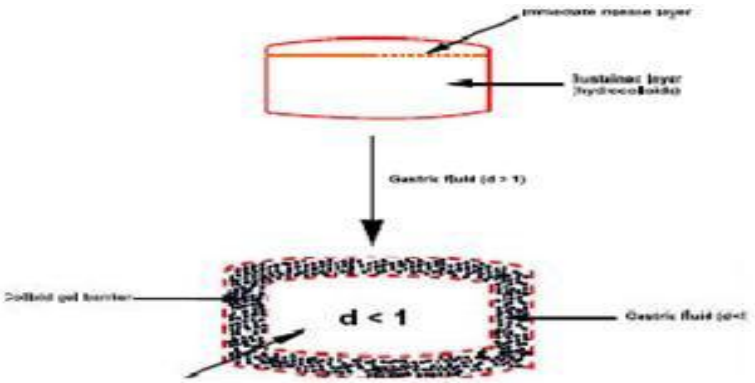

Figure 7: Intra Gastric Bilayered Floating Tablets:

MULTIPLE UNIT TYPE FLOATING PILLS:

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.

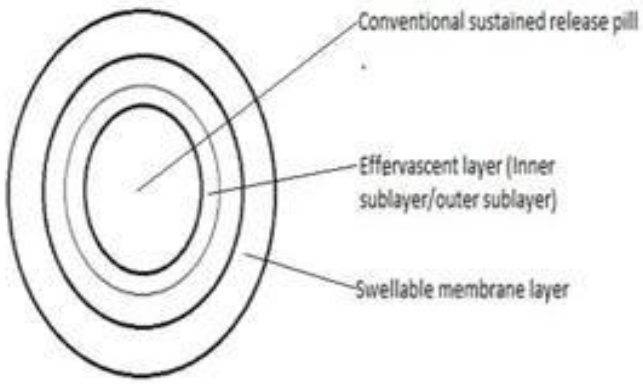

Figure 8: Multiple Unit Type Floating Pills:

CHARACTERIZATION OF BILAYER TABLET: [24, 25]

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 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±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 ð3Þ

COMPRESSIBILITY:

The compressibility index of the disintegrate was determined by Carr's compressibility index. C = 100 x (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/cm^2.

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] ×100

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.

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. 0.1 N 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.

ADVANCEMENT 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. Large number of work has been done in this field. Some of the recent findings are running.

Table 1: Tablet having Biphasic drug delivery system:

DRUG	PURPOSE OF STUDY	AUTHOR
Amlodipine Besilate and Metoprolol Succinct	Synergistic effect in Hypertension	Atram SC et al, 2009.[26]
Metformin HCl and Glimipiride	Synergistic effect in Diabetes	Pattanayak et al,2011.[27]
CefiximeTrihydrate and Dicloxacilline Sodium	Synergistic effect in bacterial infections	Kumar et al,2011.[28]
Losartan	Biphasic release profile	Hiremath et al 2010.[29]
Guaifenesin	Biphasic release profile	Kumar et al 2010.[30]
Tramadol and Acetamino-phen	Synergistic effect of drugs in pain	Naeem et al 2010.[31]
Propranolol HCl	Bimodal drug release	Patra et al 2007.[32]
Telmisartan & Hydrochlorthiazide	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan	Friedl et al 2009.[33]
Statin & Aspirin	To minimize interaction b/w two drugs and side effects due to aspirin	Ullah et al 2001.[34]
Telmisartan & Simvastatin	To minimize contact b/w Simvastatin & telmisartan	Kohlrausch et al 2006.[35]

CONCLUSION:

Bilayer tablet is improved beneficial technology to overcome the shortcoming of single layered tablet. Bilayer 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 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. 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. Bi-layer 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. Whenever high quality bi-layer 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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