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BILAYER TABLET: A REVIEW

Balaji G*, Gnana Prakash K, Suresh Karudumpala, Venkatesh B

Department of pharmaceutics, Ratnam institute of pharmacy, Nellore, Andhra Pradesh, India.

ABSTRACT

Over the past 30 years as the expense and complications involved in marketing new drug entities have increased with concomitant recognition of the therapeutic advantages of controlled drug delivery systems. Bi-layer tablet is new era for the successful development of controlled release formulation and its consists of monolithic partially coated and multilayered matrices. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for controlled release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablet technology has improved to overcome the shortcoming of the single layered tablet. Several pharmaceutical companies are interested to developing bilayer tablets for a variety of reasons : patent extension, increase of therapeutic efficacy and to reduce capital investment. This article explains about different techniques of bilayer tablet and why the development and production of quality bilayer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, lack of proper bonding of two layers, stress due to high suppression force degrades certain active ingredients, chance of increase in impurities,.etc.

Keywords : Bilayer tablet, OROS® push pull technology, DUREDAS™ Technology, OYSTER Manesty bilayer tablet press, KAMBERT bilayer tablet press, layer-separation, cross-contamination between the layers.

INTRODUCTION

Oral route is the most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, oral route remain preferred mode. Usually conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The primary objective of Bilayer tablets is to ensure safety and improve efficacy of drugs as well as patient compliance. Bilayer tablets concept has long been utilized to develop both immediate release and sustained release formulation. The drug release pattern of each layer depends upon its formulation. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug is incorporated in the upper non-adhesive layer and its delivery occurs into the whole oral cavity.[1-3]

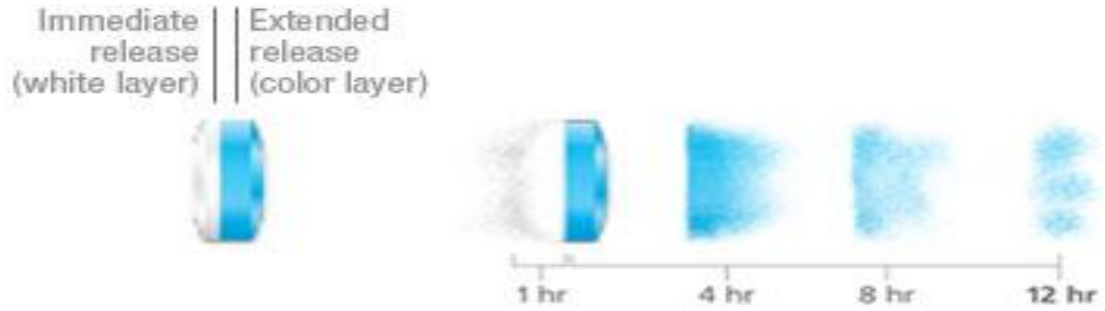

Figure 1: Drug release mechanism of a bilayered tablet comprising an Immediate release & a Sustained release layer

There are clearly a number of issues concern to the production of bilayer tablets. The adjacent compacted layers of a bilayer tablet are bonded together by mechanical means, understanding what influences the stress state, the mechanical properties of each layer and the resultant bilayer tablet and compression parameters along with specialized techniques to predict failure as a function of layer properties and compression conditions are primordial to successfully developing bilayer tablets.

NECESSITY OF BILAYER TABLETS

1. For the administration of fixed dose combination of different APIs, prolong the drug product shelf life, buccal or mucoadhesive drug delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.[3]
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s).
3. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve or erodible barriers for modified release.

4. 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, osmatic property).

ADVANTAGES

1. Bilayer execution with optional single layer conversion kit.[3]
2. Cost is lower when compared to other oral dosage forms.
3. Greatest chemical and microbial stability.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible concept.
6. 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.
7. Easy to swallowing with least tendency for hang-up.

DISADVANTAGES

1. Some drugs do not resist compression into dense compacts, owing to amorphous nature, low density character.[4]
2. Bitter drugs, unpleasant odour drugs, oxygen sensitive drugs may require encapsulation or coating.
3. Drugs with poor wetting, slow dissolution properties may be difficult to formulate or manufacture as a bilayer tablet.

VARIOUS TECHNIQUES INVOLVED IN FORMULATION

OROS® push pull technology[6-10]

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.

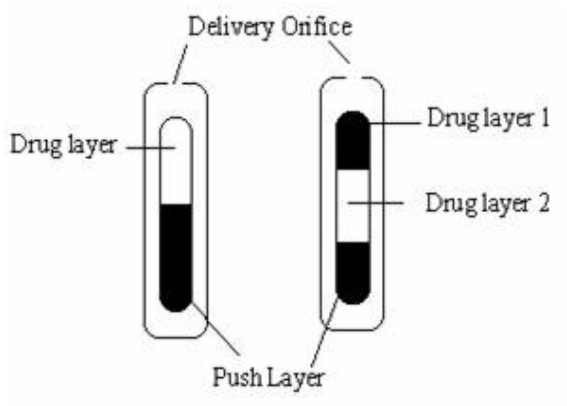

Figure 2: Bilayer and trilayer OROS push pull technology

L-OROS® technology

The L-Oros® system was designed to provide continuous delivery of liquid drug formulations and improve bioavailability of the drugs. L-Oros system consists of two types i.e., soft gelatin capsule (Softcap™) and hard gelatin capsule (Hardcap™). Both have a drug layer, barrier layer and a push layer surrounded by a semipermeable membrane with a delivery orifice. The L-Oros Hardcap system was designed to accommodate more viscous suspensions with higher drug loading than Softcap design.[13]

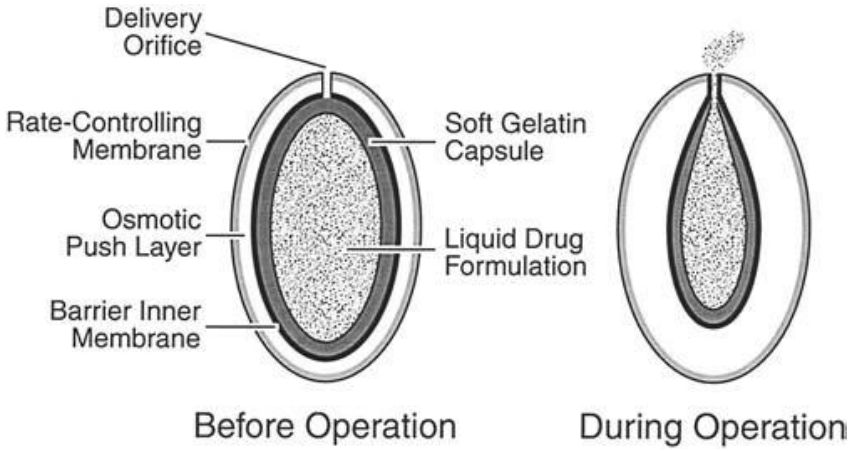

Figure 3: L-OROS® technology

EN SO TROL technology

Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled release technologies.[12]

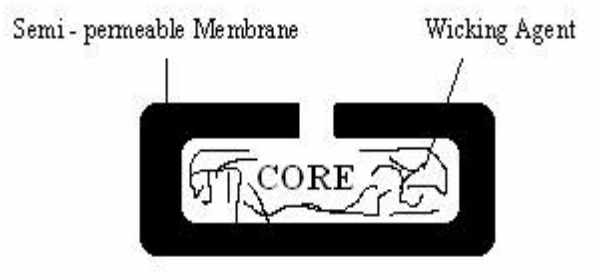

Figure 4: EN SO TROL Technology

DUREDAS™ technology

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct compression steps that combine an immediate release granulate (for rapid onset of action) and a controlled release hydrophilic matrix complex within one tablet. The controlled release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix.
To expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each layer is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible.[14]

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

DUROS technology

DUROS (Alza Corporation) is based on implant technology, which provides an alternative for the delivery of a wide range of therapeutic compounds, including 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. Following implantation, DUROS implants enable continuous, precise delivery of the therapeutic compound at rates as low as 1% of a drop of water per day. The cylinder is manufactured from titanium because of the material's tolerability to human tissue and its long use in medical devices such as implantable defibrillators and joint replacements. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time. Recently, Viadur (leuprolide acetate implant), which is based upon this technology, has been approved for once yearly palliative treatment of advanced prostate cancer.[15]

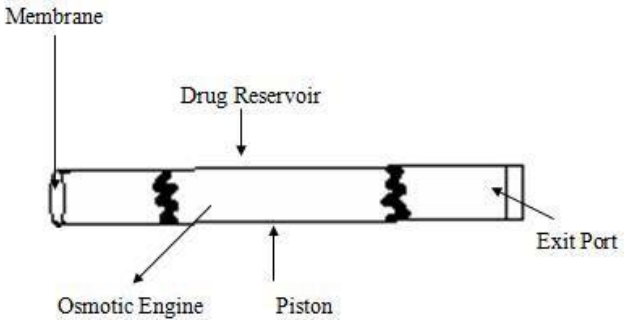

Figure 5: DUROS technology

PRODAS technology

PRODAS or Programmable Oral Drug Absorption System (Elan Corporation) is a multiparticulate drug delivery technology that is based on the encapsulation of controlled release minitablets in the size range of 1.5 to 4 mm in diameter. This technology represents a combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. Minitablets with different release rates can be combined and incorporated into a single dosage form to provide the desired release rates. These combinations may include immediate release, delayed release, and/or controlled release minitablets. In addition to controlled absorption over a specified period, PRODAS technology also enables targeted delivery of drug to specified sites of absorption throughout the GI tract. Combination products also are possible by using minitablets formulated with different active ingredients.[16]

GEMINEX technology

Geminex is a dual drug delivery technology that can deliver one or more drugs at different times. The Geminex technology controls the release rate of the two drugs to maximize their individual therapeutic effect and minimize side effects. The benefit of Geminex to the pharmaceutical industry, and ultimately to patients, is that two different actives or the same active can be delivered at differing rates in a single tablet. Penwest is actively applying its Geminex technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer and disorders of the central nervous system.[17]

BILAYER TABLETS: QUALITY AND GMP REQUIREMENTS

To produce a quality bilayer tablet, in a validated and GMP-way, it is important that the selected press is capable of:
• Preventing capping and separation of the two individual layers that constitute the bilayer tablet
• Providing sufficient tablet hardness
• Preventing cross-contamination between the two layers
• Producing a clear visual separation between the two layers
• High yield
• Accurate and individual weight control of the two layers

MANUFACTURING PROCESS
Preparation of granules

Bilayer tablets are prepared with one layer of drug for immeadiate release and the second layer of drug for extended release. An immeadiate release layer of the tablet was prepared by using super disintegrating agents and wet granulation method. A sustained release layer of the tablet was prepared by using swellable polymers and non-aqueous granulation method. The tablet layers were made in order to achieve desired disintegration time, drug release, friability, thickness, and hardness. The steps involved in their preparation: sifting, mixing, preparation of binder, preparation of granules, drying, lubrication. Prepared granules were stored in a double lined polythene bags.[12,18]

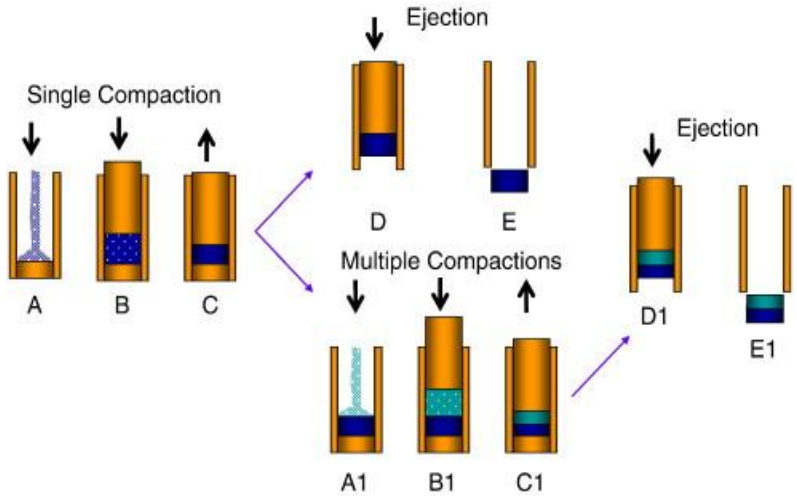

Figure 6: Schematic Diagram Showing The Manufacture Of Single And Bilayer Tablets Utilizing Uniaxial Compaction. A- Die Filling, B-Compression, C-Decompression, D- Lower Punch Removal And Reapplication Of Load To The Upper Punch, E-Tablet Fully Ejected. 1 Refers To The Final Compaction Conditions

COMPRESSION PROCESS

The prepared granules of both the layers were compressed on a Double hopper Rotary Bilayer compression machine. Set the tablet hardness was 6-8kg/cm^2 and the thickness was 3.2 - 4.0mm. Both the prepared granules were come from two different hoppers into two different feed frames where they occupied the die cavity. The bottom layer was first compressed with lower pressure, which was then followed by filling of the die cavity by the upper layer granules. The final compression was done only after both the granules occupied the die cavity one on top of the other. The ejected tablets were collected and stored in poly-lined containers.

DIFFERENT TYPES OF BILAYER TABLET PRESS

OYSTAR Manesty BILAYER TABLET PRESS

Xpress® TABLET RANGE WITH mpower® – INTEGRATED TECHNOLOGY

OYSTAR Manesty's are highly successful Xpress® range of tablet compression machines consists of the Xpress® 300, Xpress® 500 and Xpress® 700.[11]

ADVANTAGES

- ✓ The new Xpress® range has been designed to facilitate batch production flexibility to run small, medium and large batch sizes on both single and double-sided presses.
- ✓ It is easy to use and at the same time provides excellent tableting results.
- ✓ With the introduction of a number of innovative features such as the stepped cabinet design and rapid product changeover these features allow customers to immediately access the upper and lower compression zones and reduce down time without the need to dismantle mechanical parts.

BENEFITS

- Quiet and vibration free operation
- 100KN compaction force capability for the first and second compression stages
- Soft start to avoid rejects at start of production
- Graduated feeder support pillar to allow easy and accurate feeder adjustment
- Novel effervescent and bilayer production
- Integrated turret removal system enables increased output and ability to change tooling configuration from B to D
- New compaction force measurements method introduced with mpower® control system provides fast and accurate reporting of data with predictive capabilities
- Compliant with cGAMP and FDA 21 CFR Part 11 guidelines

OYSTAR Manesty Xpress® 700

Figure 7: OYSTAR Manesty Xpress® 700

FEATURES AND BENEFITS

- ✓ Automatic weight control of each layer and complete segregation of different materials
- ✓ Special air jets to prevent cross contamination between layers
- ✓ A clearly defined demarcation line between layers.
- ✓ All sampling and setting of each layer's parameters are set via the control system.
- ✓ This conversion from a single layer version to a bi-layer version can be achieved quickly and easily.
- ✓ A single layer press can be converted to the bi-layer version at any time in the future by means of a retrofit conversion kit.
- ✓ High yields guaranteed

FASTER PRODUCT CHANGE OVER

Flexibility to produce different batch sizes efficiently is important in meeting current and future production demands. To assist in fulfilling this requirement, OYSTAR Manesty's Xpress® range offers an impressively fast turret exchange system. This tool free operation reduces product change over dramatically. The stepped cabinet design offers for the first time the possibility of accessing the upper and lower part of the compression zones without the need for tools. Access to the turret when removing punches and dies can be achieved in less than three minutes.

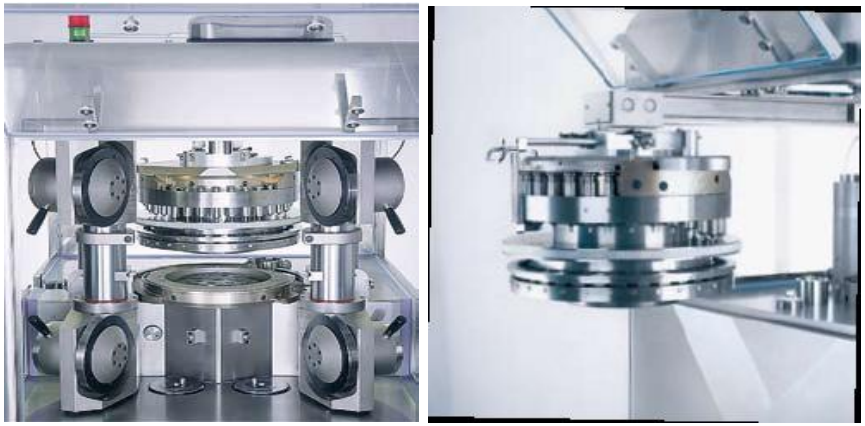

Figure 8: Xpress® 700 tool free turret removal system

Unique removable seal plates fitted as standard

This new feature significantly reduces the cleaning and the need to replace punch scraper seals. The upper and lower seals plates are made of stainless steel and can be fully immersed in water or placed in a washing machine.

Zero clearance feeder

The Zero Clearance feeder design has been proven to excel in maintaining consistent weight uniformity at a wide range of press operating speeds, whilst achieving yields well over 99%. This capability is maintained whether wet granulation or direct compression formulations are used.

Three paddle configurations offer the flexibility to tablet an extensive range of materials in the die. The feeder is mounted on a single column with calibrated height adjustment which allows the settings to be reproduced. Feeder gauges that measure the distance between the feeder and the die table are no longer required. A quick release mechanism ensures rapid removal for cleaning and significantly reduces set up time.

Figure 9: Various feed frames

mpower® CONTROL TECHNOLOGY

mpower® integrated control technology provides for the control and powered adjustment of all the main press parameters and acts as the means of communication to ancillary equipment. A user friendly windows 2000 based operator interface allows quick and intuitive operation and enables the press to be used with the minimum of specialist training.

FEATURES

- ✓ Flexible reporting
- ✓ Standard platform
- ✓ Highly configurable
- ✓ Single point of interface
- ✓ Recipe driven

TECHNICAL DATA

Xpress® 700	**49 stations**	**61 stations**	**73 stations**	**81 stations**
Die Type	D	B	BB	BBS
Maximum Tablet Diameter	25 mm	16 mm+	13 mm+	11 mm
Tablet output / hour Maximum	528,000	657,500	786,000	1,008,000
Max. 1st compression force	100 kN	100 kN	100 kN	100 kN
Max. 2nd compression force	100 kN	100 kN	100 kN	100 kN
Maximum filling depth	21 mm	18 mm	18 mm	18 mm

KAMBERT BILAYER TABLET PRESS FOR R&D

Kambert bilayer tablet press is designed to represent bilayer tablet production at a small scale, according to the needs of new product development. Kambert Expert Bi-layer press meets cGMP standards and can use type D or B tooling which allows the employment of the same punches used in production. For an appropriate adjustment in tablet production, there are totally independent systems for weight, height and hardness adjustment, both for the first and second layers. A PLC system having touch screen and software designed for easy development and production control including production rate and separately, the rate of the forced feeder.[19]

Figure 10: KAMBERT Bilayer Tablet Press

SPECIAL FEATURE

- ✓ Easy and quick assembly and dismantling of hoppers, feeders and dies for cleaning and production replacement purposes.
- ✓ Two product hoppers with paddle feeders.
- ✓ Easy access to the machine through removable doors, interconnected and equipped with safety switches.
- ✓ Independent vaccum ports for separate product recovery.
- ✓ Speed variation by inverter.
- ✓ Seals on lower punches.
- ✓ Central pillar drive system through an oil-immersed reduction gear box.

LIMITATIONS

Limitation in single sided 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 is gravity or forced fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps (two = pre and main compression). The two layers in the die mix slightly at their interface and in most cases bond

sufficiently so that no layer-separation occurs when the tablet is produced. This is the simplest way of producing a bilayer tablet. The limitations of such single sided press are...

- No weight monitoring/control of the individual layers
- No distinct visual separation between the two layers
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence 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.

Limitations of "compression force" - controlled double sided tablet presses

Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bilayer 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 of the tablet. Bonding is severely restricted if the first layer is compressed at a too-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 double sided tablet presses with automated production control use compression force to monitor and control tablet weight. Many bilayer formulations require a first layer compression force of less than 100daN in order to retain the ability to bond with the second layer. Above 100daN, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers. This basic problem, inherent to the principle of compression force monitoring is overcome by using a different weight monitoring system based upon **'**displacement**'**.

"Displacement measurement" as the alternative to "compression force measurement" has the advantage that accuracy increases with reduced compression force. At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at all four compression stages. Weight monitoring based upon 'displacement' also provides increased dwell time in addition to good bonding between the two layers, with improved and accurate weight monitoring/control of the first layer. A double sided tablet press with "displacement measurement" is thus the preferred press to produce bi-layer tablets.

"Bilayer" tablet press with 'displacement monitoring' using Courtoy R292F

This double-sided tablet press has been specifically designed and developed for the production of quality bi-layer tablets and provides:

- ✓ 'Displacement' 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
- ✓ Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed
- ✓ Maximum prevention of cross-contamination between the two layers
- ✓ A clear visual separation between the two layers
- ✓ Maximum yield

VARIOUS ASPECTS OF BILAYER TABLET

1) Floating or buoyant drug delivery systems (FDDS)

These are designed to have a low density and thus should float on gastric contents after administration until the system either disintegrates (and presumably the resultant particles empty from the stomach) or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.

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 bi layered floating tablets

These are also compressed tablet as shown in figure and contain two layers i.e. I**)** Immediate release layer and II) Sustained release layer.

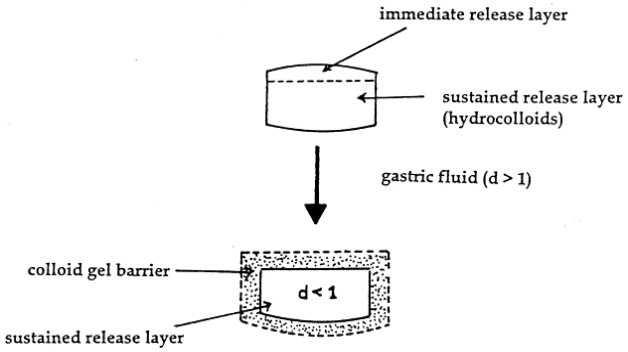

Figure 11: Intra gastric bilayer floating tablet

Multiple unit type floating pill

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.

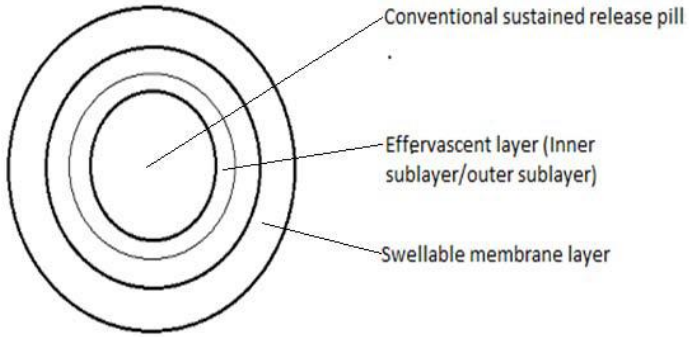

Figure 12: Multiple unit type of floating pill

2) Bioadhesive systems

These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened for example by continuing hydration of the outer layer of the device or by the persistent application of shear.

3) Swelling and expanding systems

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (for example, less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet). On ingestion they rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave the stomach.

EVALUATION PARAMETERS

Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was to be measure using venire caliper. The thickness and diameter was measured in mm.

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 to be measure by using Monsanto hardness tester. The hardness was measured in kg/cm^2.

Friability

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP), Roche friabilator was to be used for testing the friability using the following procedure. 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. P. 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 are to be 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.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is 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 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. Bilayer 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 such as the Courtoy-R292F. Whenever high quality bilayer tablets need to be produced at high speed, the use of an 'air compensator' in combination with displacement control appears to be the best solution. Accurate individual layer weight monitoring/control at high speed and in combination with reduced layer separation risk , the increased dwell time provided by the 'pneumatic compensator' and the special attention to reduced interlayer cross-contamination risk make the Courtoy- R292F an excellent bilayer tablet press.

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