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BILAYER FLOATING TABLET – A REVIEW

KM Asha spandana*, SK Senthil kumar, S Parthiban

Department of pharmaceutics, Bharathi College of Pharmacy, Bharathi nagara, Mandya, Karnataka – 571 422, India

ABSTRACT

Over the past 30 years as 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. Incorporation of drug in controlled release gastro-retentive dosage forms which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste and enhance the solubility of drugs that are less soluble in high p^H environment. Several approaches are currently utilized in the prolongation of GRT, including floating drug delivery system, swelling and expanding systems, polymeric bio adhesive systems, high-density systems, modified shape systems and other delayed gastric emptying devices. An attempt has been made in this review article to introduce the society to the current technological development in bilayer floating drug delivery system.

Keywords: Bilayer tablet, Gastro retentive systems, Floating drug delivery system, Bilayer tablet presses.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation as it provides improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulations. The effective oral drug delivery practice depends upon various factors like gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs [1].

Invariably conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repeatedly using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration – time curve [2].

Controlled release drug delivery system (CRDDS) is an attempt to sustain drug blood concentration at relatively constant and effective level in the body by spatial placement or temporal delivery. Thus controlled release drug delivery system offer various advantages viz. Reduce blood level fluctuations, minimize drug accumulation, employ less total drug, improve patient compliance, and minimizes local and systemic side effects.

Gastrointestinal retention

A gastro retentive dosage form will release the drug over an extended period in the stomach and upper GIT thus enhancing the opportunity for absorption [3].

Various approaches have been proposed to control the gastric residence of drug delivery systems in the upper part of the GIT including floating drug delivery systems, high density DDS, mucoadhesive systems, swelling and expanding DDS, modified shape systems and other delayed gastric devices [4].

Stomach overview

The stomach is a J shaped enlargement of the GI tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondria regions of the abdomen. The stomach connects the oesophagus of the duodenum,

Corresponding Author:- **Asha Spandana KM** Email: ashaspandana55@gmail.com

the first part of the small intestine. Anatomically the stomach is divided into 3 regions: fundus, body and antrum (pylorus). Anatomy of stomach is shown in fig.3.

Gastric Emptying

The GIT is always in a state of continuous motility. There are two modes of motility pattern the digestive mode and interdigestive (or fasted) mode involved in the digestion of food. In the fasted state, it is characterized by an interdigestive series of electrical events which cycle both through the stomach and small intestine every 2-3 hrs. This activity is called as interdigestive myoelectric circle or migrating myoelectric complex (MMC) [2,3,20].

Normal gastric residence times usually range between 5 minutes and 2 hours. Migrating myoelectric complex (MMC) is characterized by 4 phases.

Phase – I: period of no contraction (40-60 minutes).

Phase – II: period of intermittent contractions (20-40 minutes).

Phase – III: period of regular contractions at the maximal frequency that travel distally also known as house keeper wave (10 – 20 minutes). Since it serves to sweep undigested materials out of the stomach and down to the small intestine.

Phase – IV: The transitional period of 0-5 min between phase III and phase I.

Advantages of gastro retention system

- The gastro retentive systems are advantageous for drugs meant for local action in the stomach. E.g.: antacids
- Acidic substances like aspirin causes irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- When there is a vigorous intestinal movement and a short time as might occur in certain type of diarrhoea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
- The gastro retentive systems are advantageous for drugs absorbed through the stomach.

E.g. : ferrous salts, antacids [5,6].

Disadvantages of gastro retention systems

- Such system cannot be used in the case of drugs like aspirin and other NSAIDs that induce gastric lesions or for drugs that are unstable in the acidic environment of stomach.
- Many times it is difficult to incorporate a drug in such gastric retention systems. The retention of this system depends on many factors such as gastric motility, p^H and presence of food. It is not easy to design and fabricate a system that can overcome all these difficulties [7].

Introduction to floating bilayer tablet

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Floatation of drug delivery system in the drug can be achieved by incorporating floating chamber filled with vacuum, air or inert gas from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also require to keep the dosage form [4,18,19].

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. 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 controlled rate or by targeted drug delivery in the GI tract using p^H dependent polymers [17].

Bilayer tablets are prepared with one layer of drug for immediate release with second layer design to release drug, later, either as second dose or in extended release manner.

Need of bilayer tablets

- To control the delivery rate of either single or two different active pharmaceutical ingredients.
- For the administration of fixed dose combination of drug, prolong the product life cycle, buccal/mucoadhesive delivery systems, fabricate novel drug delivery system such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- To separate incompatible active pharmaceutical ingredients from each other, to control the release of API from one layer by utilizing the functional property of other layer (such as osmotic property).
- To modify the total surface area available for API layer either by sandwiching with one or two inactive layers inorder to achieve swellable/erodible for modified release [3,8-10].

Advantages of bilayer tablet dosage form

- Bilayer execution with optional single - layer conversion kit.
- Low cost compared to all other dosage form.
- Lighter and compact.

- Greatest chemical and microbial stability over all oral dosage form.
- Suitable for large scale production.
- Flexible concept.
- Objectionable odour and bitter taste can be masked by coating technique.
- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and least content variability.
- Offer greatest precision and least content uniformity.
- Bilayer tablets can be designed in such manner as to modified release as either of the layers can be kept as extended and the other as immediate release.
- Separation of incompatible components.
- Patient compliance is improved leading to improve drug regimen efficiency [3,8-12].

Disadvantages of bilayer tablet dosage form

- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Difficult to swallow in case of children and unconscious patients.
- Adds complexity and bilayer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- Cross contamination between the layers.
- 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 [10-12].

General properties of bilayer tablet dosage form

- It should have physical and chemical stability.
- It should have graceful product identity free of defects like chips, cracks, discoloration and contamination.
- Should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
- Must have a chemical stability shelf life, so as not to fallow alteration of the medicinal agents.
- The bilayer tablet must release drug in a expectable and reproducible manner [13-15].

VARIOUS TECHNIQUES FOR BILAYER TABLET

OROS push pull technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer (Fig.8). 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 [9-11,15,16].

L-OROS tm technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel Product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then osmotic push layer and then a semipermeable membrane, drilled with an exit orifice (Fig 9).

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.

DUROS technology

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 11).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 continuous and consistent form over months or Year.

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 2 separate direct compression steps that combine and immediate release granulate and a controlled-release hydrophilic matrix complex with in 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 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 controlled manner.

Benefits offered by the DUREDAS technology include:

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

A further extension of the DUREDAS technology is the production of controlled-release combination dosage forms. Where by two different drugs are incorporated into the different layers, and the drug release of each is controlled to minimize therapeutic effect of the combination. Again both immediate- release and

controlled- release combination of the two drugs are feasible.

Bilayer tablets: **quality and GMP requirements**

To produce a quality bi-layer 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 [12,14,15].

Compression cycle for bilayer tablet

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 or three layers. More are possible but the design becomes very special. Figure 12. represents compression cycle of bi-layer tablet [4,19].

Types of bi-layer tablet presses

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement [8,9,11].

1. Single sided tablet presses

Various types of bi-layer 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 deaeration, capping and hardness problems. This may be corrected by reducing the turett-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.

Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, precompression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

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

- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
- 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 two layers.
- A clear visual separation between the two layers.
- Maximized yield [3].

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 pre-compression 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.

Fig 1. Plasma level profiles following conventional, sustained and controlled release dosing

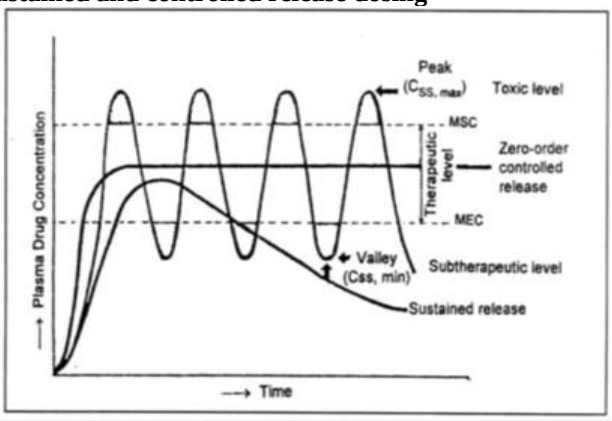


Fig 2. Different approaches of gastric retention

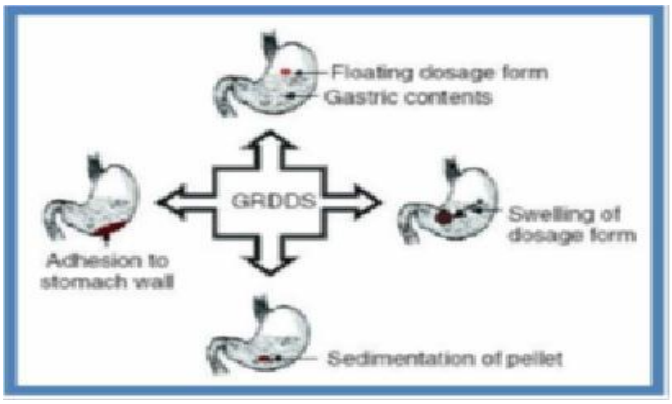


Fig 3. Anatomy of stomach

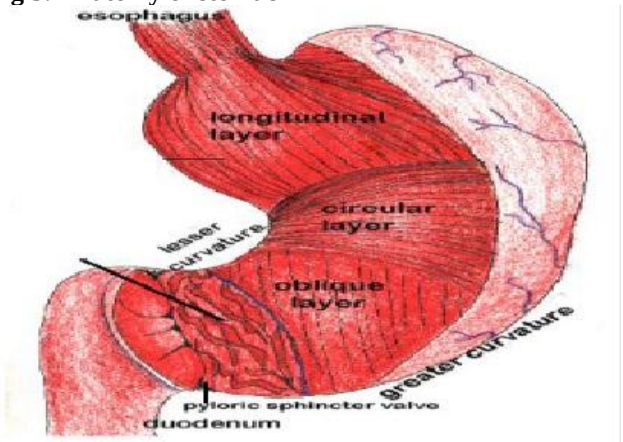


Fig 4. Typical motility patterns in fasting state

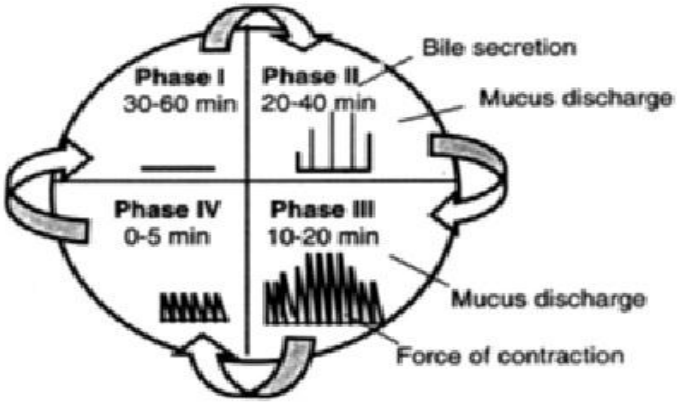


Fig 5. Conventional bilayer tablet structure

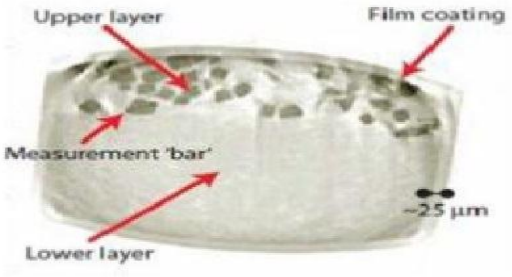


Fig 6. bilayer floating tablet

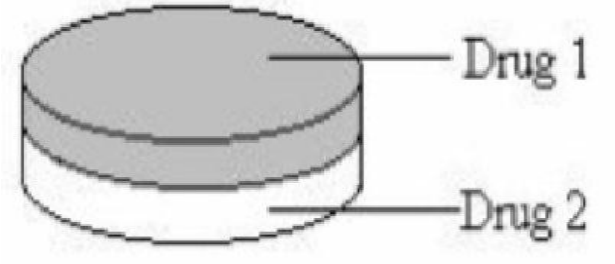


Fig 6. bilayer floating tablet

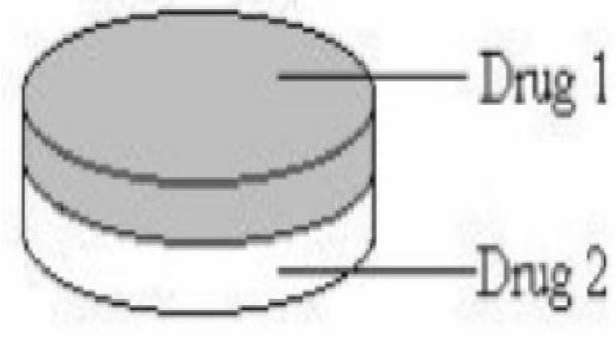


Fig 7. Release pattern of bilayer floating tablet

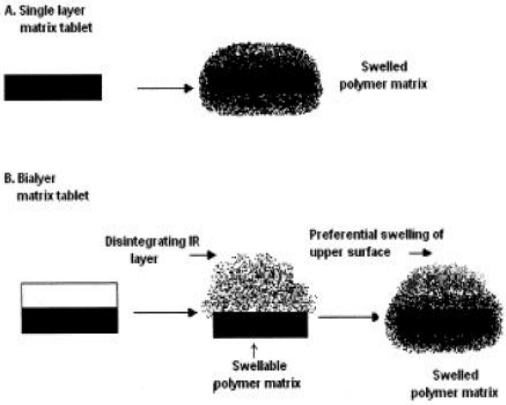


Fig 8. Bilayer and trilayer push pull technology

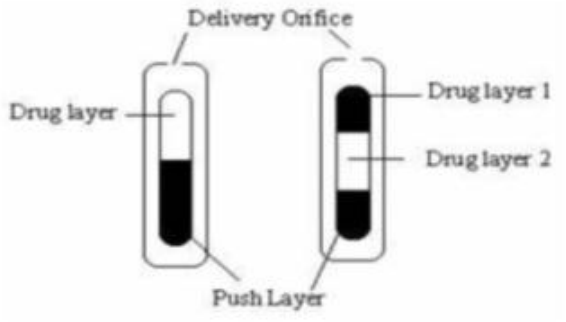


Fig 9. L – OROS tm technology

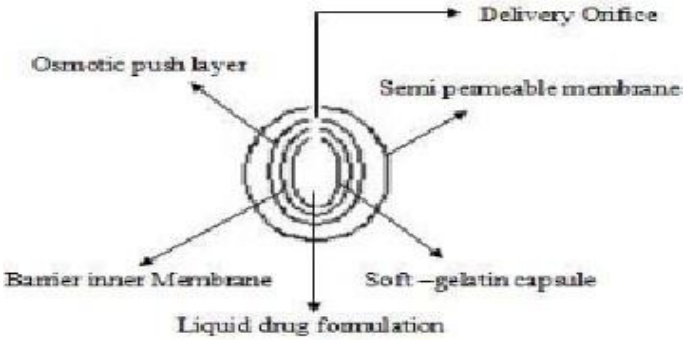


Fig 10. EN SO TROL technology

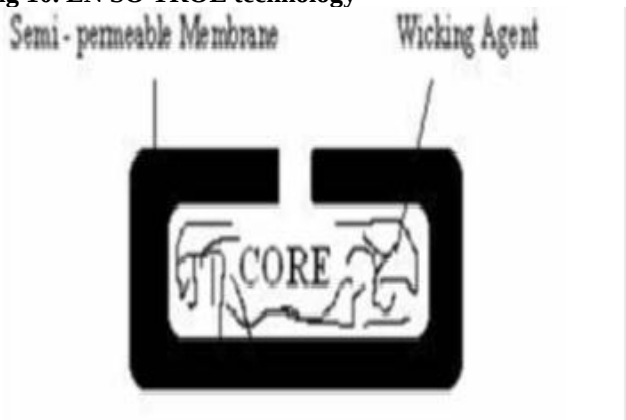


Fig 11. DUROS Technology

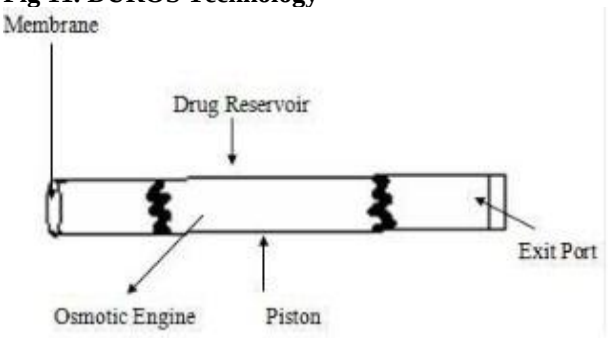


Fig 12. Compression cycle of bilayer floating tablet

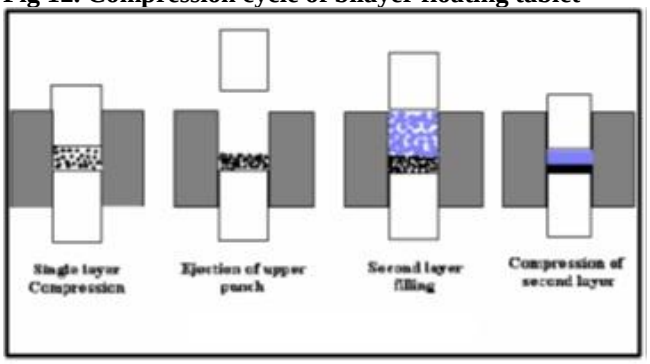
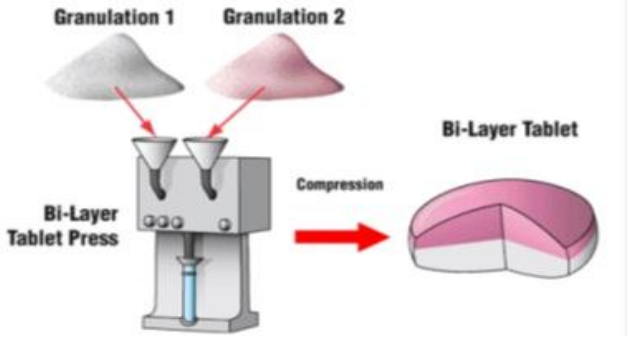


Fig 13. Bilayer tablet press



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. Many different types of presses are being used to produce bilayer tablets, ranging from simple single-sided press to highly sophisticated machines such as the courtoy-R292F. The preparation of tablets in the form of bilayers 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.

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