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AN OVERVIEW ON BI-LAYER TABLETS

C. Sowmya*, C. Suryaprakash Reddy, S.G.Tabasum, V. Varma

* Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Saigram, Krishnam Reddy Palli Cross, Anantapur- 515721, Andhra Pradesh, India.

Email: drsowmyariper@gmail.com

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Abstract

Bi-layer tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bi-layer tablets has been developed to achieve controlled delivery of different drugs with pre defined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layer tablets, for a variety of reasons patent extension, therapeutic, marketing to name a few. To decrease capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains about different techniques of bi-layer tablet and why development and production of quality bi-layer tablets need to be carried out on purpose built tablet presses to conquer common bi-layer problems, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc. There are various applications of the bi-layer tablet consists of monolithic partially coated or multilayered matrices.

Key words: Bi-layer tablet, GMP requirement for bi-layer tablets, Insufficient hardness, Layer separation, OROS Push pull technology, Various tablet presses.

Introduction

Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor efficiency. This dynamic such as repetitive dosing and irratic

absorption led to the concept of controlled drug delivery systems. 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[1].Several pharmaceutical companies are presently developing bi-layered tablets for a variety of reasons: patent extension, therapeutic, marketing to a name a few[2]. 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[3,4].

Formulation of layers are done by using more than one rate controlling polymer, thus enabling different types of drug delivery of one or more drugs, where the dug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract . There is a variety of application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity. There are number of issues concern to the production of bi-layered tablets. The mechanical strength of bi-layered tablets has been observed not to be a controlling factor in drug release. The determination of this property could be useful in understanding the adhesion between various layers and an improved description of the systems[5]. Other challenges during development of layer tablets include the order of layer sequence, layer weight ratio, elastic mis match of the adjacent layers, first layer tamping force and cross contamination between layers. If these factors not well controlled in one way or other will effect the bi-layer compression perse (insufficient or uncontrolled process) and the quality attributes like mechanical strength and individual layer weight control. Therefore care must be taken to enable design of a vigorous product and process[6,7,8].

Since the adjacent compacted layers of a bi-layer tablet are bonded together by mechanical means, understanding what influences the stress state, the mechanical properties of each layer and the resultant bi-layer tablet, and compression parameters along with specialized techniques to forecast failure as a function of layer properties and compression conditions are primary requirements for successful development of bilayer tablets[6].

Need of developing bi-layer tablets[9,10,1,12] :

For the supervision 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.

1. Controlling the delivery rate of either single or two different API'S.
2. 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.
3. 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).

Advantages of bi-layer tablets[9,13]:

1. Bi-layer execution with optional single layer conversion kit.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odor and taste can be masked by coating technologies.
5. Flexible concept.
6. Offer greatest precision and the least content uniformity.
7. Easy to swallow with least hang up problems.
8. Fit for large scale production.
9. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
10. Bi-layer tablets can be designed in such a manner as to modified release as either of the layers can be kept as extended and the other as immediate release.
11. Expansion of a conventional technology.
12. Prospective use of single entity feed granules.
13. Separation of incompatible components.
14. Patient compliance is improved leading to improve drug regimen efficiency.

15. Patient compliance is improved because fewer daily dose are required compared to traditional delivery system.
16. Maintain physical and chemical stability.
17. Product identification is easy.
18. Easiest and cheapest to package and strip.

Disadvantages of bi-layer tablets[9,13]:

1. Adds complexity and bi-layer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. imprecise individual layer weight control.
4. Cross contamination between the layers.
5. Difficult to swallow in case of children and unconscious patients.
6. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.
7. Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability.

General properties of bi-layer tablet dosage forms[13]:

1. It should have graceful product identity free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.
3. Should have physical and chemical stability
4. The bi-layer tablet must release drug in a expectable and reproducible manner.
5. Must have a chemical stability shelf life , so as not to follow alteration of the medicinal agents.

Various techniques for bilayer tablet

Oros ® push pull technology[6,9,14,15]:

This system consist of mainly two or three layer among which the one or more layer are necessary for the drug and other layer are consist of push layer(Fig. 1). The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprise of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core.

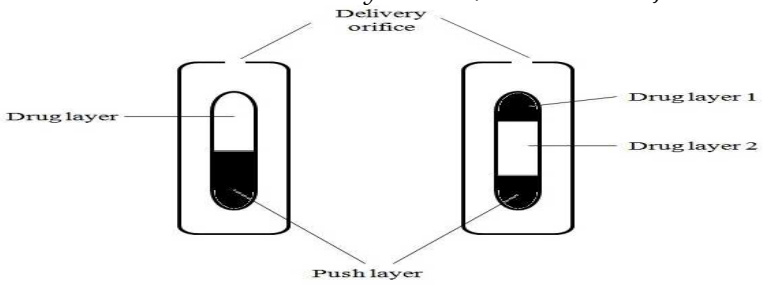

Fig 1 : bilayer and trilayer OROS Push pull technology

L-oros tm technology[6,9,14,15]:

This system used for the solubility concern Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and than a semi permeable membrane, drilled with an exit orifice (Fig. 2).

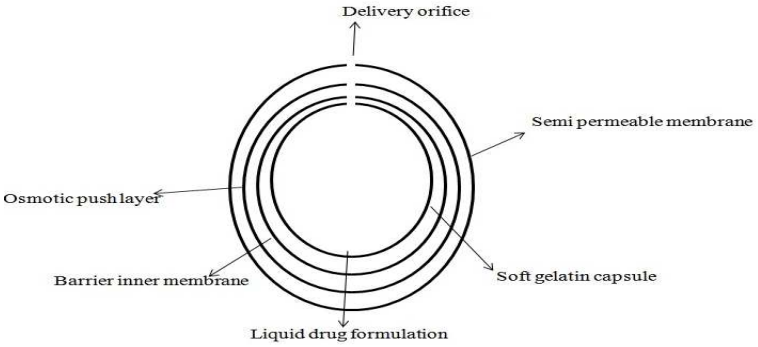

Fig 2: L-OROS tm technology

DUROS technology[6,9,16,17]:

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 3).This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the minuscule drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form.

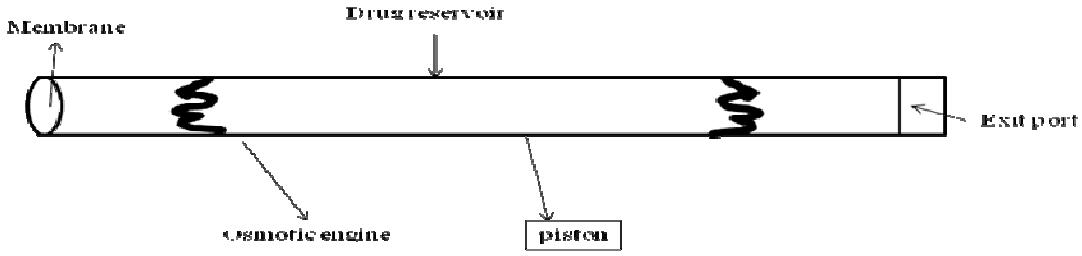

Fig 3 : The DUROS technology

Elan drug technologies' Dual release drug delivery system[6]:

(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 tabletting 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:

1) Bilayer tabletting technology.

2) Modified release rate of two drug components.

3) Ability of two different CR formulations combined.

4) Ability for immediate release and modified release components in one tablet.

5) 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 persistence 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 engaged 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.

EN SO TROL technology[6,14]:

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 (Fig. 4).

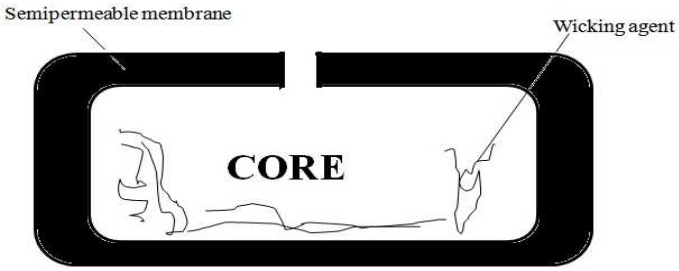

Fig 4: EN SO TROL technology

Bilayered tablets: Quality and GMP requirements[5,9]

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

- Single sided tablet press.
- Double sided tablet press.
- Bi-layer tablet press with displacement.

(a) Single sided tablet press[6,9]:

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[9]:

- 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 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.

(b) 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[9]:

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

Limitations[10]:

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.

(c) 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 pre-compression 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[6,10]:

- 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 turett speed.
- Maximum prevention of cross contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

Various aspects used in the bi-layer tablet[5]:

Floating Drug Delivery Systems (FDDS)[18]:

From the formulation and technological point of view, the floating drug delivery systems are significantly easy and consistent 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 bi-layered floating tablets:

These are also compressed tablet contain two layers i.e.,

i) Immediate release layer ii) Sustained release layer.

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(Fig. 5). 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.

Table-1: Previous studies done on bilayer tablets.

DRUG	PURPOSE OF THE STUDY	AUTHOR NAME
Amoxicillin trihydrate	Hydrodynamically balanced bi-layer tablet- The local action by gastric retention- to treat bacterial infections like H.Pylori infections.	Shiva Kumar yellanki et al.,[19]
Propranolol HCL	Mucoadhesive bi-layer tablets- To treat hypertension, Angina pectoris and other cardiovascular diseases	Vishnu M.Patel et al.,[20]
Diltiazem HCL and lovastatin	Design of floating bi-layer tablets	Ajit S.Kulkarni et al.,[21]
Rosiglitazone maleate	Preparation and in vitro evaluation of bi-layer and floating bio adhesive tablets- To treat	Girish S . Sonar et al.,[22]

	diabetes	
Tramadol and Acetaminophen	Development and evaluation of microencapsulated controlled release bi-layer tablets containing – Analgesic action	M.A.Naeem et al.,[23]
Famotidine	Development and evaluation of novel trans bucco adhesive bi-layer tablets – To treat ulcers	M. Alagusundaram et al.,[24]
Metformin HCL and Pioglitazone HCL	Formulation and evaluation of sustained release bi-layer tablets – To treat diabetes	N.N.Rajendran et al.,[25]
Propranolol HCL	Formulation development and in vitro characterization of bi-layer floating bioadhesive tablets – To treat hyper tension, Angina pectoris	Akash yadav et al.,[26]
Trimetazidine Dihydro chloride	Design development and evaluation - floating bi-layer tablets	Biswajit Biswal et al.,[27]
Atenolol	Effect of psylium -floating bi-layer tablets –To treat hypertension	Jeetendra singh Negi et al.,[28]
Metaclopromide HCL and Diclofenac sodium	Formulation and evaluation of bi-layered tablets of Metaclopromide HCL and Diclofenac sodium	Surendra G.Gattarhet al.,[29]

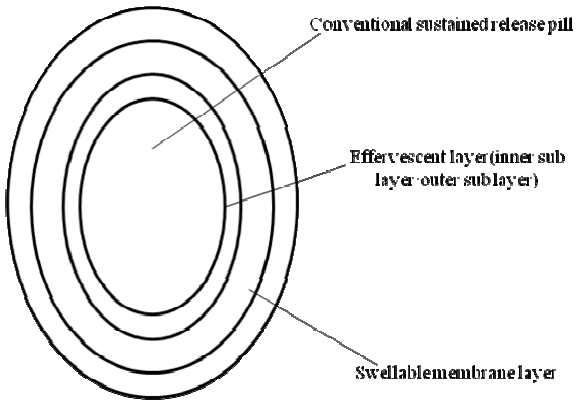

Fig 5 : Multiple units of oral FDDS

Conclusion

Bi-layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered Matrices. 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. 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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Corresponding Author:

C. Sowmya*,

Email: *drsowmyariper@gmail.com*