Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Review Article

Received on: 07-07-2015
Accepted on: 17-07-2015
Published on: 15-08-2015

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A Review on Novel Approach of Bilayer Technology

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ABSTRACT

In modern era bi-layer tablet is for successful development of immediate and modified drug delivery system for various diseases and disorders. Bi-layer tablets have been developed to achieve modified release of drug. The primary objective of bi-layer tablet is to avoid chemical incompatibilities between APIs by physical separation and to develop different drug release profiles (immediate release and modified release). In bi-layer tablet the immediate release layer act as the loading dose and modified release layer act as the maintenance dose. To produce a good quality bi-layer tablet, the machinery should be constructed as per GMP. Various machineries are available to overcome common bi-layer problems, such as layer separation, insufficient hardness, inaccurate individual weight control, cross contamination between the layers etc. In this review we focus on the different types of press techniques, how to solve problems of bi-layer tablet.

Key-words: bilayer tablets, technology, novel approaches.

Cite this article as:
B. Mahesh Kumar, P. Vishnu, A. Pratyusha, V. Uma Maheswara Rao, A Review on Novel Approach of Bilayer Technology, Asian Journal of Pharmaceutical Technology & Innovation, 03 (13); 2015. www.asianpharmtech.com*

1.1 Introduction

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. Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. 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. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed.

1.2 Advantages of bi-layer tablets

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 modify 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.

1.3 Disadvantages of bi-layer tablets

1. 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.

1.4 General properties of bi-layer tablet dosage forms

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.

1.5 Various techniques for bilayer tablet

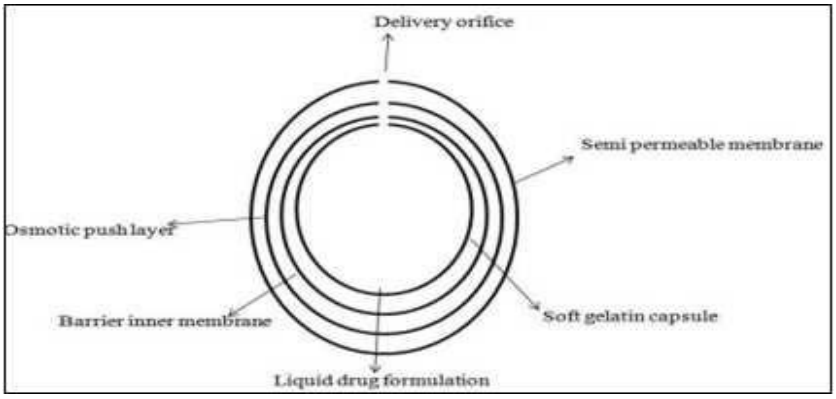
OROS ® push pull technology

This system consist of mainly two or three layer among which the one or more layer are necessary for the drug and other layer are consist of push layer (Fig.5). 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.

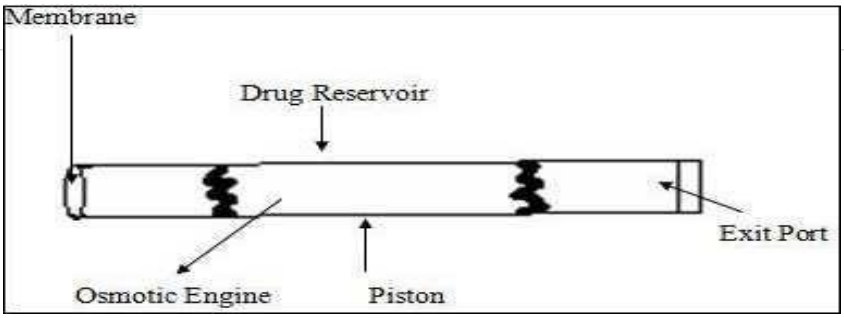
L-OROS ® tm technology

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.6).



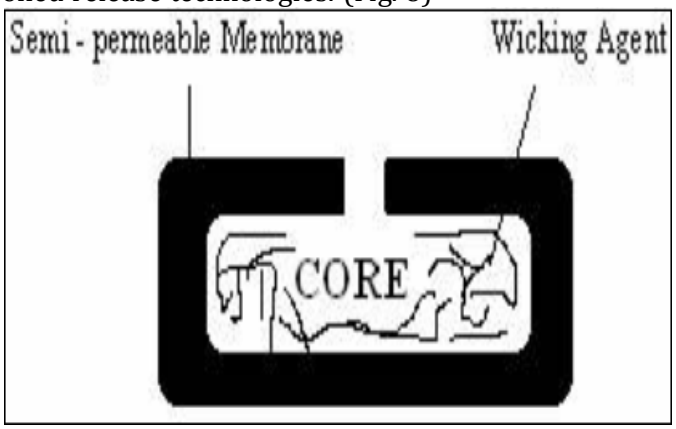
DUROS ® technology

The system consists from an outer cylindrical titanium alloy reservoir (Fig. 7).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. 7)



ENSOTROL® 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. (Fig. 8)



1.6 Bilayered tablets: Quality and GMP requirements

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.

1.7 Types of bi-layer tablet presses

(a) 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.

(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.

(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 an 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.

1.8 Mucoadhesive bilayer tablets

The concept of mucoadhesion was introduced into controlled drug delivery in the early 1980s. Mucoadhesion is the attachment of a natural or synthetic polymer to a biological substrate. It is an important new aspect of controlled drug delivery .It can place a drug or a formulation in a particular region of the body for extended periods of time. This is needed not only for targeting of drugs but also to better control of systemic drug delivery.

Mucoadhesive 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 that include an immediate release (IR) layer and an Extended release (CR) layer. Immediate release layer provide therapeutically effective

plasma drug concentration for a short period of time and extended release (ER) layer maintain uniform drug levels over a sustained period to reduce dose and side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance.

1.9 Mucoadhesion

Definition:

Longer and Robinson defined the term bioadhesion as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface. The general definition of adherence of a polymeric material to biological surfaces (bioadhesive) or to the mucosal tissue (mucoadhesive) still holds [24]. A bioadhesive has been defined as a synthetic or biological material which is capable of adhering to a biological substrate or tissue when the biological substrate is mucus the term was known as mucoadhesive [25].

1.10 Theories of mucoadhesion

There are five theories explain the processes of mucoadhesion which are given as, electronic theory, absorption theory, wetting theory, diffusion theory and fracture theory.

The electronic theory:

This theory is based on the assumption that the bioadhesive material and the glycoprotein mucin network have different electronic structures. When the two materials come in contact with each other electron transfer will occur causing the formation of a double layer of electrical charge at the interface. The bioadhesive force is due to attractive forces across this electrical double layer. The system is charged when the adhesive and the substrate are in contact and discharged when they are separated. However this theory has caused some controversy regarding whether the electrostatic forces are an important cause or the result of the contact between the bioadhesive and the biological tissue.

The absorption theory:

According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished: I) Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds. I I) Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander walls forces and hydrogen and hydrophobic bonds.

The wetting theory:

According to this theory the ability of bioadhesive polymer or mucus to spread and develop intimate contact with their corresponding substrate or bond formation. The contact angle (θ) which should be zero or near zero for proper spreading is related to interfacial tens ions(γ) through young s equations ,

$\lambda tg = \lambda bt + \lambda bg \cos\varphi$.

Where the t, g and b stand for tissue, gastro intestinal contents and bioadhesive polymer s respectively (φ) must equal to zero for spontaneous wetting to occur. Using wetting theory, it is possible to calculate spreading coefficients for various bioadhesive over biological tissues and predict the intensity of the bioadhesive bond. Hence, it provides essential information for development of bio-adhesive drug deliver y system.

Diffusion theory:

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion co efficient, in turn, depends on the value of molecular weight between cross link's and decreases significantly as the cross linking density

increases. This theory suggests that interpenetration and entanglements of bio-adhesive polymer chain and mucus polymer chains produce semi permanent adhesive bonds, and bond strength is believed to increase with the depth of penetration of the polymer chains.

Fracture theory:
This theory analyses the force that is required to separate two surfaces after adhesion. The maximum tensile stress (μ) produced during detachment can be determined by dividing the maximum force of detachment, F by the total m surface area (A) involved in the adhesive interaction.
$\mu=F/A$

The above equation can be used for calculating fracture strengths of adhesive bonds involving hard, bioadhesive material in which the polymer chains may not penetrate the mucus layer.

1.11 Factors Affecting Mucoadhesion
Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. A variety of factors affect the mucoadhesive properties of polymers. There are some polymer related factors namely molecular weight which indicates that there is certain molecular weight at which bioadhesion is maximum. The interpenetration of polymer molecules is favorable for low molecular weight polymers whereas entanglement is favoured for high molecular weight polymers. After molecular weight second is the concentration of polymer, Bremecker (1983) maintains that there is an optimum concentration of polymer corresponding to best bioadhesion. In highly concentrated systems the adhesive strength drops significantly. In fact in concentrated solutions the coiled molecule becomes solvent poor and chains available for interpenetration are not numerous. The third factor was the flexibility of polymer chains which is important for interpenetration and enlargement. As cross- linking density increases, the effective length of chain which can penetrate into mucus layer decreases even further and mucoadhesive strength is reduced. Fourth factor was the hydrogen bonding capacity is an important factor in mucoadhesion of a polymer. For mucoadhesion to occur desired polymers must have functional groups that are able to form hydrogen bonds. It was also confirmed that flexibility of the polymer is important to improve its hydrogen bonding potential.

Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid) as well as all their copolymers are polymers with good hydrogen bonding capacity. Then cross linking density was another factor in this the average pore size, the number average molecular weight of the cross- linked polymers and the density of cross-linking are three important and interrelated structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin. However, hydration was the last factor which is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and electrostatic interaction between the polymer and the mucous network.

Finally charge on the polymers also has some impact such as the non- ionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties especially in a neutral or slightly alkaline medium [55]. After studying the polymer related factors thereare some environment related factors which includes the mucoadhesion of a polymer not only depends on its molecular properties but also on the environmental factors adjacent to the polymer. Saliva as a dissolution medium affects the behaviour of the polymer. The pH of the microenvironment surrounding the mucoadhesive polymer can alter the ionization state and therefore the adhesion properties of a polymer.

1.11 Mucoadhesive Polymers

Mucoadhesive polymers are water-soluble and water insoluble polymers which are swellable networks joined by cross- linking agents. These polymers posses optimal polarity to make sure that they permit the mutual adsorption and interpenetration of polymer and mucus to take place. Two classes of polymers are currently used for mucoadhesion which include hydrophilic polymer and hydrogels. It has been found recently that hydrophilic polymers that adhere to the mucin epithelial surface can be conveniently divided into three broad categories.

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, noncovalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site on title self surface.

Thepromising mucoadhesive polymers include sodium alginate, hydroxypropyl methylcellulose, hydroxyethyl cellulose and cationic hydrogels such as chitosan etc. In recent years hydrophilic matrices have attracted considerable attention as sustained drug release devices. Various types of polymers can be used in the hydrophilic matrix and the hydration of these polymers results in the for mation of an outer gel layer that controls drugs release. HPMC the nonionic cellulose ether is commonly used in the formulation of hydrophilic matrix systems. On the other hand acrylic acid derivatives Carbopol have also attracted interest in their use in controlled drug delivery.

Characteristics of ideal mucoadhesive polymers

There are various characteristics of an ideal mucoadhesive polymer which are explained as, the polymer and its degradation products should be non-toxic, non- irritant and free from leachable impurities, it should have good spreadability, wetting, swelling and solubility and biodegradability properties, the pH should be biocompatible and should possess good visco elastic properties.

Classification

In general, adhesive polymers can be classified by various ways as synthetic vs. natural, water- soluble vs. water insoluble and charged vs. uncharged polymers. However, Examples of the recent polymers classified in these categories are listed in below Table:

Table 1: Classification of mucoadhesive polymers:

Criteria	Categories	Examples
Source	Semi- natural/natural	Agarose, Chitosan.
	Synthetic	Hyaluronic acid, Guargum,Na-alginate, Sodium CMC, HEC,HPMC, Carbopol.
	Water- soluble	CP, HEC, HPC, HPMC, Sodium CMC etc.
	Water- insoluble	Chitosan (soluble in dilute aqueous acids).
	Cationic	Aminodextran, Chitosan, Trimethylated.
	Anionic	Chitosan- EDTA, CP.
	Non- ionic	Hydroxyethyl starch, HPC, PVA,PVP
	Covalent	Cyanoacrylate.
	Hydrogen bond	Acrylates, CP, PVA.
	Electrostatic interaction	Chitosan.

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