AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Overview On: Bilayer Tablet Novel Technology For Oral Drug Delivery System

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ABSTRACT

The expense and complications in new drug entities have increased since last 3 decades, with concomitant recognition of the therapeutic advantages of controlled drug deliver. So focus has been given on development of sustained or controlled release drug delivery system. 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. Bilayer tablet is better than the traditionally used mouthwash, sprays, and gels. For promoting patient convenience and compliance pharmaceutical industries interested in developing a combination of two or more API's in a single dosage form. Bilayer tablet is improves beneficial technology to overcome the shortcoming of the single layered tablet. Bilayer tablet can be a primary option to avoid chemical incompatibilities between APIS by physical separation, and to enable the development of different drug release profile using different technologies. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Several pharmaceutical companies are currently developing bilayer tablet for a variety of reason: patent extension, therapeutic, marketing to name a few. To reduce capital investment quite often existing but modified tablet presses are used to develop such tablets. The present article provides an introduction of bilayer tablet technology, advantages, disadvantages, different approaches, types of bilayer tablet, various techniques, quality and GMP requirements of bilayer tablets.

Keywords: Bilayer tablet, different approaches, types of bilayer tablet press, bilayer tablet techniques, quality and GMP requirements of bilayer tablets.

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Received 14 March 2017, Accepted 15 April 2017

Please cite this article as: Pradhan SS *et al.*, Overview On: Bilayer Tablet Novel Technology For Oral Drug Delivery System. American Journal of PharmTech Research 2017.

INTRODUCTION

Pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. These combined formulations function from a single dosage form, which simplifies the therapy and reduces or eliminates the chances of improper administration. Bilayer formulations carry more than one drug and deliver each of them without any pharmacokinetic or dynamic interactions, with their individual rate of delivery (immediate, timed or sustained) [1]. The major aim of controlled drug delivery is to reduce frequency of dosing. The design of modified release drug product are to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval providing greater patient compliance and convenience [2]. In bilayer tablet one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time [3].

The immediate release layer delivers the initial dose it contains superdisintegrants which promotes drug release rate and attains the onset of action quickly (loading dose) whereas sustained release (maintenance dose) layer released drug in sustained manner for prolonged time period 4. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation and to enable the development of different drug release profiles (immediate release with extended release) [5]. Bi-layer tablets 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 layers is maintenance dose there are various applications of the bi-layer tablets as it consists of monolithic partially coated or multilayered matrices [6,7]. It also avoids repeated administration of drug. Coronary vasodialator, antihypertensive, antihistaminic, analgesic, antipyretics and antiallergenic agent are mainly suitable for bilayer sustained release drug delivery [8.] Generally conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissue with undesirable toxicity and poor efficiency. This factor repetitive dosing and unpredictable absorption led to concept of controlled drug delivery system [6, 9]. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs.

Figure 1: Bilayer Tablet

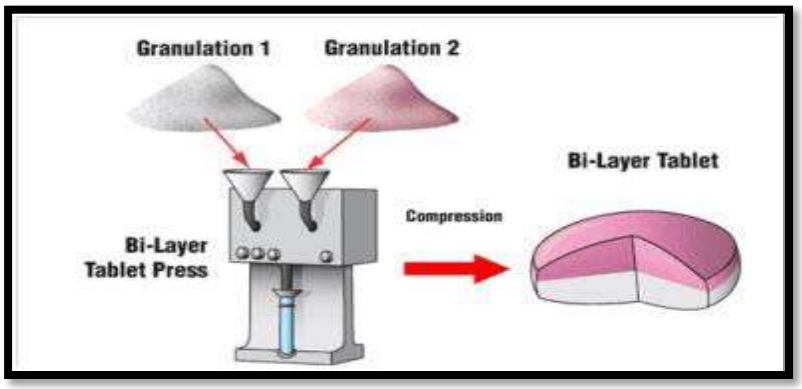

Figure 2: General concept of Bi-layer tablet

Advantages [11, 12, 13, 16]

1. Used for extended or immediate release drugs that can produce the desired level of action.
2. Maximize the efficacy of two different drugs by producing synergetic action as two drugs are simultaneously present in a single dosage form.
3. To forming different layer of drug with separation of incompatible component of drug in single dosage form.
4. They are unit dosage form offers the greatest capability of oral dosage form for the greatest dose precision and least content variability.
5. The formulation cost is less as compared to all of the dosage form.
6. Easy to engulf least disposition for hang up problem.
7. When the two different layers of the tablet contain two different drugs, then the tablet can be easily used in combination therapy.
8. It maintains the chemical and microbial stability.
9. It reduces the dose frequency.
10. In case of drugs having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.

Disadvantages [1, 5, 6]

1. Cross contamination occur during formulation.
2. Inadequate hardness, layer separation, reduced yield.
3. Difficult to swallow in case of children and unconscious patients.
4. Few drug show resist compression into dense compact, which having the low density character amorphous nature.

General properties of bilayer tablet [17, 18, 20, 21]

1. Bilayer tablet must provide with prolong drug release pattern.
2. It must have greater physical and chemical stability to maintain it physical attribute overtime.
3. Should have adequate strength to withstand mechanical shock during its production packaging, shipping and dispensing.
4. Product should have particular identity free of defects like, crack, discoloration, chip and contamination.
5. Avoid alteration of medicinal agent; drug should have chemical stability shelf life.

Need of bilayer tablet [2, 13, 21, 23]

1. To control the released API from one layer by utilizing functional property of the other layer (such as osmotic properties) to separate the distinct in compatible API's from each other.
2. For the administration of those drugs having fixed dose in combination of different API, fabricate novel drug delivery system such as chewing device and floating tablet for gastro retentive drug delivery, prolong the drug product life cycle, buccal / mucoadhesive system.
3. To regulate the delivery rate of either single or different API's.
4. To achieve swellable/erodible barrier for modified release, increase in the modification of total surface area of the API layer which is sandwiching between the one or two API layer.

Challenges in bilayer tablet [3, 4, 8, 18]

In this bilayer formulation can be seen as to single layer tablet compressed into one. Following are the manufacturing challenges.

Delamination

The two different granulation layer should adhere when compress. Tablet separation into two or more distinct layer when falls down because doesn't bond completely.

Cross contamination

When the granulation of the first layer intermingle with the granulation of the second layer or vice versa, cross contamination occurs, proper dust collection goes a long way towards preventing cross contamination.

Product yield

During the manufacturing of bilayer tablet have lower yield then single layer tablet to reduce cross contamination, dust collection is required leads to lose.

Cost

The formulation is more expensive then single layer tableting for several reason including, development of two incompatible granulation required more time for its formulation, development, analysis and validation. It requires quality attributes of the bilayer tablet having sufficient mechanical strength to maintain its integrity and individual layer weight control. In bilayer tablet formulation the press run more slowly as a cost of tablet press is more expensive. Therefore, it is critical to obtain and insight into the root causes to enable design of a robust product and process.[5].

Various approaches of bilayer tablet [18, 26, 32]

Floating drug delivery system [31]

The floating drug delivery systems are considerably easy and desirable approaches in the development of gastro retentive dosage form. The system is designed to have a low density and thus float on gastric contents after administration until the system either disintegrates 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. The Bi-layer tablet is designed in such a manner that, one layer gives the immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which floats in the stomach (GI-fluid).

Several approaches to design the FDDS [32]

The following approaches have been given below to design of floating dosage form of single and multiple unit system.

Intragastric-bilayered floating tablet

It is also compressed tablet as contain two layer i.e. immediate layer and sustained release in Figure 3.

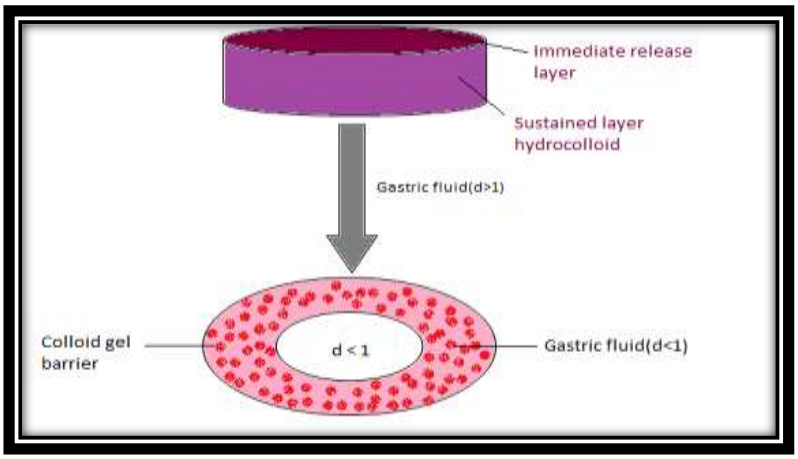

Figure 3: Intra gastric bilayer floating tablet.

Multiple unit type floating tablets [18]

It include that sustained release pill as seed as surrounded by double layer. The inner layer consists of effervescent agent like tartaric acid, citric acid .While the outer layer is of swellable membrane layer. When the sustained released pill is immersed in dissolution medium at body temperature, it sinks at once and then swollen pills like balloons, which float as they have lower density in Figure 4

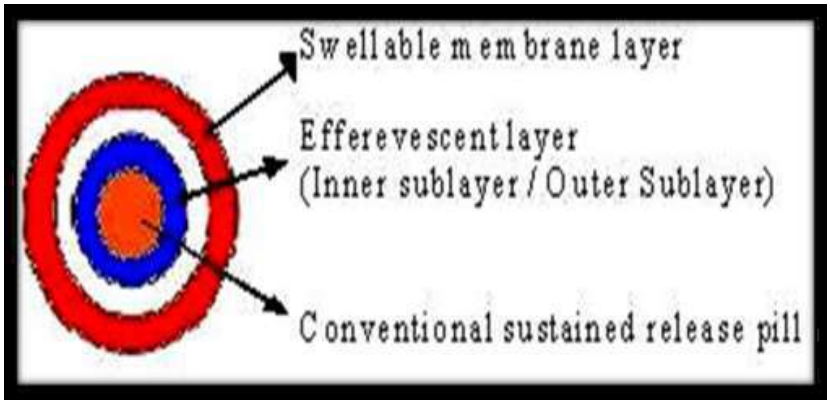

Figure 4: Multiple Units of Oral FDDS

Polymeric bioadhesive system [28]

In this type include the drug delivery system fluid imbibes in the dosage it becomes viscous, tacky material that adhere to the gastric mucosa. The adherence to the mucosa ensures retention of the dosage form due adhesive force. In the gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bioadhesive property.

Disadvantages

The system adhere to mucous not mucosa. The mucosa layer in human would appear to slough off readily, carrying and dosage form with it, Therefore, bio adhesive dosage form would not appear to an offers solution for extended delivery of drug over period of more than a few hours.

Swelling system [28]

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult. On ingestion they rapidly swell or disintegrate 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 stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

Bilayer tablet: quality and GMP requirement [7, 14, 24]

To produce a quality bilayer tablet, in a validation and GMP-may it is important that the selected press is capable of:

1. Providing sufficient tablet hardness.
2. Preventing cross contamination between the two layers.
3. Preventing capping and separation of the two individual layers that constitute the bilayer tablet.
4. Accurate and individual weight control of the layer.
5. Producing a clear visual separation between the two layers.
6. High yield.
7. Types of bilayer tablets [1, 14, 29]

There are two types of bilayer tablets containing subunit that is homogeneous or heterogeneous:

Homogeneous type

In homogeneous bilayer tablet the word homo means same entities. The release profile for bilayer tablets of drug is different from one another. Bilayer tablets allows for designing and modulating the dissolution and release pattern.

Bilayer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose in Figure.5.

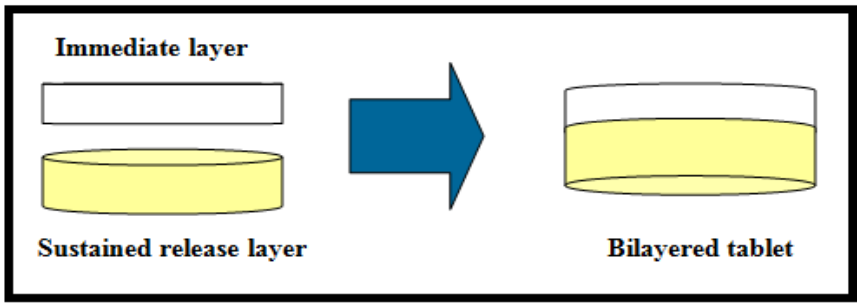

Figure 5: Bilayer tablets (same drug with different release pattern-homogenous).

Heterogeneous type

In heterogeneous bilayer tablet the word hetero means different entities. Bilayer tablet appropriate for sequential release of two drugs in combination, separate two incompatible substances in Figure 6.

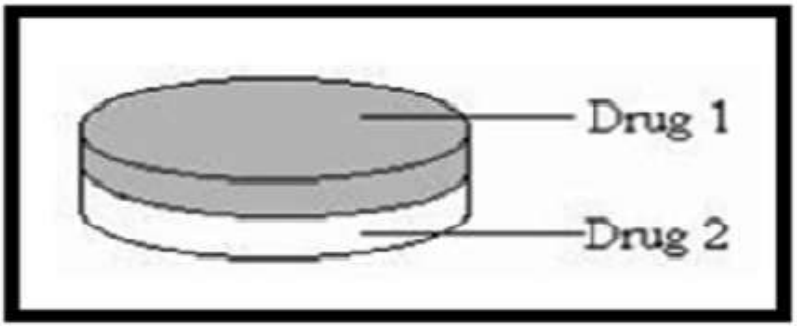

Figure 6: Bilayer tablets (with two different drugs-heterogeneous)

Types of bilayer tablet press [22, 26, 30, 31]

1. Single sided tablet press
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring
4. Multilayer compression basis

Single sided tablet press [31]

The single sided tablet press is a simple type of tablet press. In these single sided tablet press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or force fed with different power. Manufacturing the two individual layers of tablets when die passes under the feeder it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitation of Single sided tablet press [23]

1. There is no weight monitoring for the control of the individual layer.
2. There is no distinct visual separation between the two layers.
3. Very difficult first layer tablet sampling, sample transport to a test unit for in line quality control and weight re-calibration.
4. Dwell time due to the small compression roller, possibly resulting de aeration, hardness and capping problem. It can be correct by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

Dwell time [22]

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

Compression force

Various bilayer formulations need a first layer compression force of less than 100 daN in order to maintain the ability to bond with the second above than 100daN. The bonding ability between the both layers may not be sufficient resulting in separation of the two layers and low hardness of tablet becomes fragile.

Double sided tablet press [28]

To overcome the drawback of single sided press with double sided automatic tablet press. Double sided tablets presses offer an individual fill station, pre compression and main compression for each layer. The bilayer tablet will go through four compression stages before being ejected from the press. In the double sided tablet presses provided 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 single used out of tolerance and correct the die fill depth when required.

Advantages

1. Displacement weight monitoring for accurate and independent weight control of the individual layer.
2. To prevent the cross contamination between two layers, then provide maximized yield.
3. Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. It shows clear visual separation between the two layers.

Limitations of double sided tablet press

1. The low compression force required, when compressing the first layer unfortunately reduce the accuracy of the weight monitoring/control of the first layer in case of tablet press with compression force measurement.
2. Separation of the two individual layers is due to sufficient bonding between the two layers during final compression of bilayer tablet.
3. Most of the double sided tablet press with automated production control used compression force.

Bilayer tablet press with displacement [29]

In this case accuracy increases with reduce compression force. The displacement tablet weight control principle is based on fundamentally different from the principle of compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depend on applied precompression force. At higher production speed the risk of capping and separation increases but can be reduced by sufficient dwell time at all force compression stage.

Advantages

1. Low compression force is required on the first layer to avoid capping and separation of the two individual layer
2. Independence from the machine stiffness.
3. It provides accurate and independent weight monitoring of individual layer.
4. Maximum prevention of cross contamination between the layers.

Multilayer compression basics

The multilayer tablets concepts have been utilized to develop sustained release formulation such tablets have fast releasing layer and may contain bi-layer or tri-layer to sustain drug release from the tablet. In pharmacokinetic advantages of last releasing granules leads to sudden rise in concentration however the blood level is maintained at a steady state as the drug is released from the sustained granule. Now a day presses can be designed especially for multilayer compression or a standard double press can be converted for the multilayer.

Method of preparation of bilayer tablet [12, 13, 27]

1. Bilayer tablets are prepared using two different active ingredients with different released i.e. one layer of drug for immediate released with second layer designed to extended released form.
2. The bilayer tablets with two incompatible drugs can also be prepared by compressing of separate layer of each drug to minimize area of contact between two layers.
3. To produce adequate tablet formulation, certain requirement such as sufficient mechanical strength and desired drug released profile must be meeting.
4. For formulator it is the challenges to achieve formulation of bilayer tablet, where the compression technique involved, because of poor flow and compatibility characteristics of the drug which result lead to capping and /or lamination.

Compaction

To formulate quality attributes for tablet formulation, certain requirements such as sufficient hardness and desired drug release profile should be meet. The compaction of a material involves both the compressibility and consolidation.

Compression

It is the reduction in bulk volume eliminating void and bringing particles into closer contacts.

Consolidation

It is the property of the material in which there is increased mechanical strength due to interparticulate interaction. The compression force on layer one was found to be major factor influencing tablet delamination.

Bilayer compression basics (Figure 7) [1, 29]:

1. Initial layer die filling and compaction
2. Initial layer compaction showing the predominant stress transmission profile
3. Density profile of initial layer before die filling of the final profile
4. Final layer die filling and compaction
5. Final layer compaction showing the predominant stress transmission profile
6. Density profile of bilayer tablet before ejection
7. Ejection of a bilayer tablet

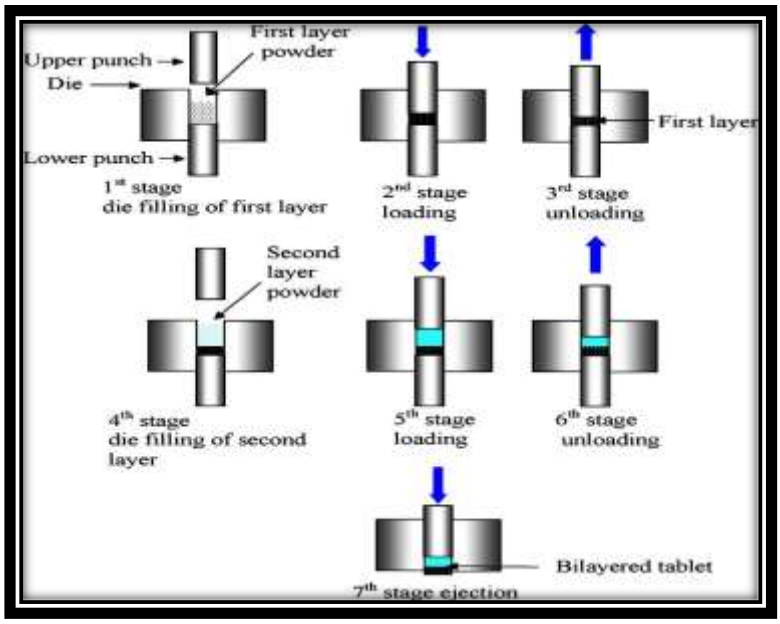

Figure 7: Schematic diagram showing the manufacture of bilayer tablets.

Dashed arrows show the postulated radiant expansion due to energy dissipation. Black areas correspond to regions of localized high density. Arrows show the direction of the direction of the applied stress in Figure 8:

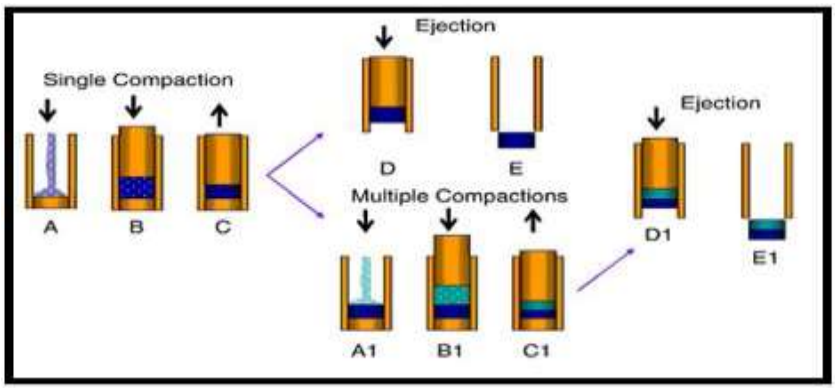

Figure 8: Schematic diagram showing the manufacture of single and bilayered tablets utilizing uniaxial compaction.

1. Die filling
2. Compression
3. Decompression
4. Lower punch removal and reapplication of load to the upper punch
5. Tablet fully ejected

Various techniques for bilayer tablet [1, 16, 27, 32, 33]

OROS push pull technology [16]:

In this technology includes two or three layer, among which the one or more layer is essential of the drug and other layers are consisting of push layer (Fig.9). This drug layer comprises of drug which is in poorly soluble few along with addition of suspending agent and osmotic agent. The drug layer mainly consists of drug along with two or more different layer. Tablet core is surrounded with the semi-permeable membrane.

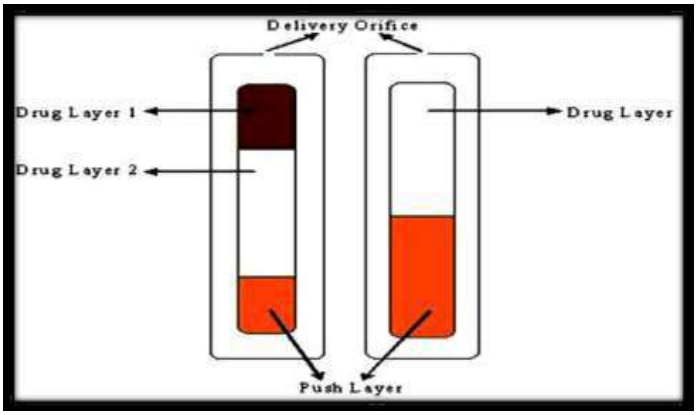

Figure 9: Belayed and trilayer OROS Push pull technology

L-OROSTM technology [3]:

This technology developed for solubility issues Alza developed the L-OROS system where a lipid soft gel product containing drug in dissolved state is initially manufactured and then coated with a

barrier membrane, then a semi permeable membrane than osmotic push layer, drilled with an exit orifice (Figure 10).

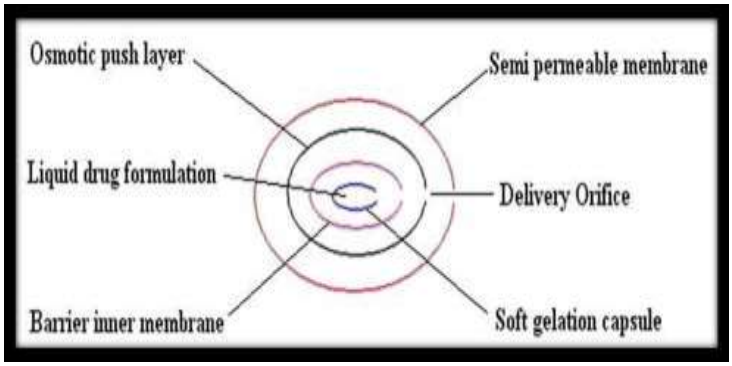

Figure 10: L-OROSTM technology

EN SO TROL technology [9]:

This technology is utilized for solubility enhancement of an order of magnitude or to create optimized dosage form either laboratory or it is used for integrated approach to drug delivery focusing on identification of an incorporation of the identified enhancer into controlled released technologies (Figure 11)

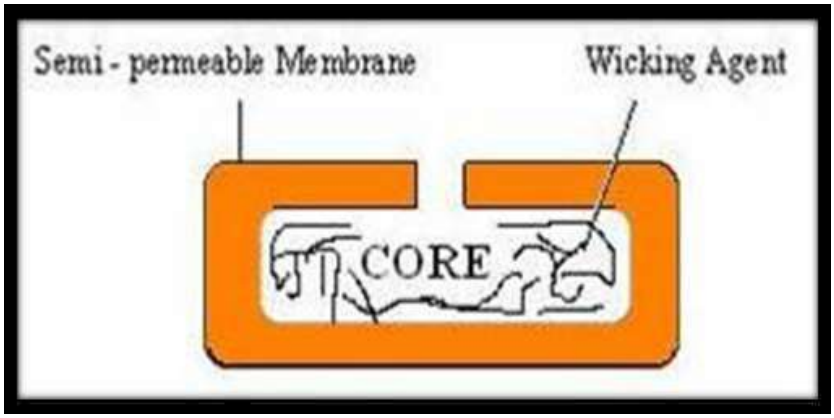

Figure 11: EN SO TROL technology

DUREDAS™ Technology [32] :

Duredas or dual released drug absorption system (Élan Corporation) utilizes bilayer tablet technology, which has been specifically developed to provide to different released rates or dual released of a drug from a single dosage form (Fig.12).

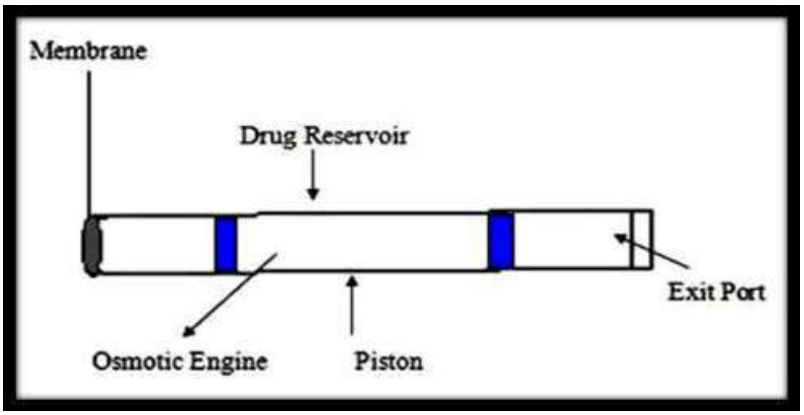

Figure 12: DUREDAS™ Technology

In this technology tablet are prepared by two separate direct compressions that combine immediate release and control release hydrophilic matrix within one tablet. The control released matrix remain intact and slowly absorbed fluid from GI tract which causes matrix to expand and transform the hydrophilic polymer into a porous, viscous gel and serve as a barrier between the drug and surrounded fluid. As the gel continues to expand fluid penetrate further into a dosage form, dissolving the drug and allowing the resulting a solution to diffuse out in control manner.

Benefits offer by the DUREDAS technology includes [32]

1. Bilayer tabletting technology.
2. Capability of two different CR formulations combined.
3. Capability for immediate released and modified released component in a one tablet.
4. Tailored released rate of two components.
5. Unit dose and tablet presentation.

Geomatrix technology [23]

Geomatrix is a multilayer tablet with a matrix core tablet containing the active ingredient and one or more active modulating layer applied to the core during the tabletting process. The function of these barriers is to delay the interaction of code with the dissolution medium. The main objective is that zero-order release provide a constant rate of drug release over a definite period of time, binary release is used to provide controlled release of two different drugs in a single tablet, quite slow release provide a quick burst of drug release followed by a constant rate of release over a defined period of time, slow quick release provide an initial constant rate of release followed by a quick burst of drug release at a predetermine time, positioned release delivers the drug to a predetermine position in the digestive system before it beings to release the active drug components, accelerate release provides a constantly accelerating rate of drug release, delayed release provides a

predetermine time lag before it begins releasing drug molecules, multiple pulse provides an initial quick burst of drug release followed by a predetermine period of no release.

Geminex technology [23]

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. Pen west is actively applying its Geminex technology to the following therapeutic areas: cardiovascular disorders, diabetes, cancer, and disorders of the central nervous system.

PRODAS or programmable oral drug absorption system (Elancorporation) [1]

It is a multiparticulate system having encapsulation of controlled release minitab in the size range of 1.2-4mm in diameter. This system is a combination of multiparticulates and hydrophilic matrix tablet technology which provides benefits of both these drug delivery system in a one dosage form PRODAS technology also unable targeted drug delivery of a drug to specific site of absorption through the GI tract.

Table 1: Marketed drug products with their mechanism based classification:

Sr.no.	Technology	Brand name	Drug	Manufacturer
1.	Diffusion controlled release	Welbutrin XL	Bupropion	GlaxoSmithKline
2.	Matrix system tablet	Ambien CR	ZolpidemTartarate	Sanofi-Aventis
3.	Method using ion Exchange	TussionexPennkinetic ER suspension	Hydrocodone Polistirex&Chlor-pheneraminePolistirex	UCB Inc.
4.	Methods using osmotic pressure : a)Elementary Osmotic Pump	Efidac 24®	Chlorpheniramine Maleate	Novartis
	b)Push-Pull Osmotic Systems	Glucotrol XL®	Glipizide	Pfizer Inc.
5.	pH independent formulation	Inderal® LA	Propranolol HCl	Wyeth Inc.
6.	Altered density formulation	Modapar	Levodopa &Bense-razide	Roche Products,USA

Table 2: Some important materials used for preparing Bilayer sustained release tablets.

Matrix characteristics	Release retarding material
Insoluble, inert	Polyethylene, Polyvinyl Chloride Methyl acrylate-methacrylate copolymer, Ethyl Cellulose.
Insoluble, erodible	Carnauba wax, Steryl alcohol, Stearic acid, Polyethylene glycol Polyethylene glycol monostearate Triglycerides.
Hydrophilic	Methyl cellulose, Hydroxyethyl cellulose HydroxypropylmethycelluloseSodium, carboxymethylcelluloseCarboxypolymethylene Sodium alginate, Galactomannose.

Characterization of bilayer tablet [3, 9, 38, 39, 40]

Particle size distribution: By using sieving method to determine particle size distribution.

Angle of repose: The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\text{Tan } Ø = h/r$$

Where, h=height, r=Radius of the powder cone.

Hausner's Ratio: It is calculated by the formula,

$$H = \rho_T / \rho_B$$

Where, ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped density of the powder.

Density: The loose bulk density (lbd) and tapped bulk density (tbd) were determined and calculated using the following formulas.

LBD1/4 weight of the powder = volume of the packaging ð2þ

TBD1/4 weight of the powder = tapped volume of the packaging ð3þ

Compressibility: The compressibility index of the disintegrate was determined by Carr's compressibility index.

$$C = 100x\ (1 - þb/þt)$$

Moisture sorption capacity: All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1g of disintegrate uniformly distributed in petri-dish and kept in stability chamber at 37+_1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

Evaluation of sustained release bilayer tablet [19, 38, 39, 40]

Tablet Thickness and size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier Calliper.

Tablet Hardness

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm2**.**

Friability

Friability is the measure of tablet strength. Electrolab EF2 fribilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and place in the tumbling apparatus that revolves at 25 RPM dropping the tablet through a distance of 3 inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in the tablet weight was determined.

% Loss = (initial wt. of tablets – Final wt. of tablets)/ initial wt. of tablets X 100

Uniformity of weight

20 tablets were selected at random and the average weight was calculated. Weight variation was calculated and was compared with IP Standards.

Dissolution studies

Bilayered tablets were subjected to invitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 RPM, 37± 0.5 °C, and pH 1.2 buffer (900 ml) (i.e. 0.1N HCl) for 2 Hrs, since the average gastric emptying time is about 2 Hrs. the dissolution medium was replaced with pH 6.8 Phosphate buffer (900 ml) and experiment continued for hrs. at different time intervals, 5 ml of the sample were withdrawn and replace with 5 ml of drug free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis.

Table 3: Acceptance criteria for Weigh Variation Test as Per USP

Average weight of tablet(mg)	Percentage Deviation
130/less	10
>130mg or < 324mg	7.5
324mg or more	5

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Stability study (temperature dependent)

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (visual defects, Hardness, friability and dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

Table 4: Stability condition as per ICH guideline

Study	Storage condition	Minimum time period
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate term	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated term	40°C ± 2°C/75% RH ± 5% RH	6 months

CONCLUSION:

Bilayer tablet is improved beneficial technology to overcome the shortcoming of single layered tablet. Bilayer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. To develop a dynamic bi-layer tablet a complete mechanistic understanding must be developed through the application of scientific and quality risk management tools: Pharmaceutical development and quality risk management. Bi-layer tablet quality and GMP-requirements can vary widely. This explains why many different types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines. Whenever high quality bi-layer tablets need to be produced at high speed, the use of an ‘air compensator’ in combination with displacement control appears to be the best solution.

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