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Review on Bilayer Tablet: The New Era

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Abstract

Bilayer tablet is new era for the successful development of Controlled Drug Delivery System(CDDS) along with various features to produce a way of successful drug delivery system. Over the past 30 years as the expense and complications involved in marketing new drug entities have enhanced, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. Bi-layer tablets has been developed to achieve controlled delivery of different drugs with pre-defined release profiles. Bi-layer tablet is appropriate for chronological 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. 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 using DUREDAS technology.Use of bi-layer tablets is a very different aspect for anti-hypertensive, diabetic, anti-inflammatory and analgesic drugs where combination therapy is often used. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. This review article provides an introduction to bi-layer tablet technology, challenges in bi-layer tablet manufacturing, various tablet presses used, quality and GMP requirements for their production various techniques used for bi-layer tableting and recent developments in the field of bi-layer technology.

Keywords: Bilayer Floating Drug Delivery System, Bilayer Tablet Presses, L-OROS Technology, DUROS Technology, Manufacturing processes.

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Introduction

Bi-layer tablets have been developed to get CDDS of different drugs with pre-defined release profiles. Usually, conventional dosage form yields wide ranging fluctuation in drug concentration in the systemiccirculation and tissues with consequent undesirable effects and poor efficiency. This dynamic such as repetitive dosing and erratic absorption led to the concept of controlled drug delivery systems. The target in formulation sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The main goal of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. 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. 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[1].

Purposes behind designing bilayer tablet

1. To control the delivery rate of either single or two different active pharmaceutical ingredients.
2. To separate incompatible active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer such as, osmotic property.
3. To modify 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 modified release.
4. To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems such as chewing device, buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery [2].

Ideal features of bilayer tablet

1. It should be free from defects like chips, cracks, discoloration and contamination.

2. It should have sufficient strength during its production, packaging, shipping and dispensing.
3. It should have the chemical and physical stability overtime.
4. It releases the agents in a predictable and reproducible manner.
5. It must have a chemical stability and shelf-life[3].

Challenges in bilayer tablet manufacturing

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. Tablet breaks in to pieces when the two parts of the tablet don't bond totally. The two granulations should adhere properly when compressed into a bilayer tablet. In Practice, there are some manufacturing challenges –

- **Delamination:** Tablet falls apart when the two halves of the tablet do not bond completely.
- **Cross-Contamination:** When the granulation of the first layer intermingles with the granulation of the second layer results cross contamination occurs. Proper dust collection goes a long way toward preventing cross contamination.
- **Production yields:** To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single layer tablets.
- **Cost:** Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation[2,3].

Merits of bilayer tablet

1. It helps in avoiding chemical incompatibilities between API's by physical separation.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odour and taste can be masked by coating technologies.
5. Repetitive dosing is required in conventional dosage forms which can be avoided by bilayer tablet.
6. Offer greatest precision and the least content uniformity.
7. Easy to swallow with least hang up problems [5].
8. Lighter and compact, easiest and cheapest to pack and strip.
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.
12. Prospective use of single entity feed granules.
13. Patient compliance is improved leading to improve drug regimen efficiency.
14. Patient compliance is improved because fewer daily dose are required compared to traditional delivery system.
15. Maintain physical and chemical stability.
16. Product identification is easy.

18. Easiest and cheapest to package and strip[6].

Demerits of bilayer tablets

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. 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.
4. Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
5. Imprecise individual layer weight control.
6. Cross contamination between the layers[3,4].

Different drug delivery system used in bilayer tablet[2,7]

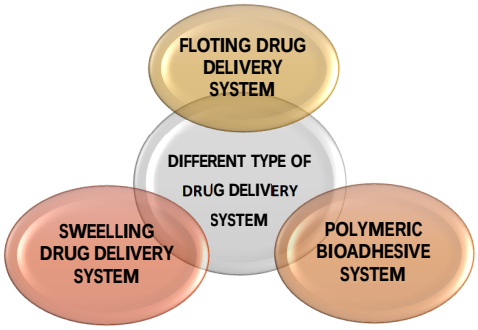


Fig 1: Different approach of drug delivery system

1) Floating Drug Delivery System (FDDS)

FDDS have a bulk density lower than gastric fluid and thus remains buoyant in the stomach for a prolonged period of time. From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs)[8].

Example: Indomethacin, Furosemide, Cefuroxime axetil, Atenolol, Lovastatin

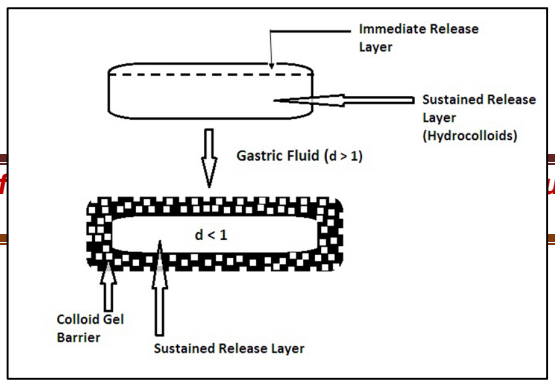
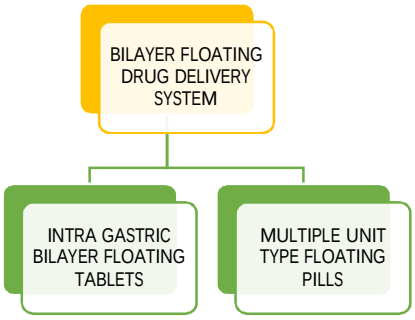


Fig 2: release of bilayer tablet in gastric fluid

The following approaches have been used for the design of floating dosage forms of single and multipleunit systems.

- **Intra gastric bilayer floating tablets:**These are also compressed tablet and contain two layers i.e. Immediate and sustained release.
- **Multiple unit type floating pills:** These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density.



Advantages of Bilayer floating Tablet:

i. Enhanced bioavailability
ii. Sustained drug delivery/reduced frequency of dosing
iii. Targeted therapy for local ailments in the upper GIT
iv. Reduced fluctuations of drug concentration Improved
v. Selectivity in receptor activation
vi. Reduced counter-activity of the body

2) Polymeric Bio-Adhesive Drug Delivery System

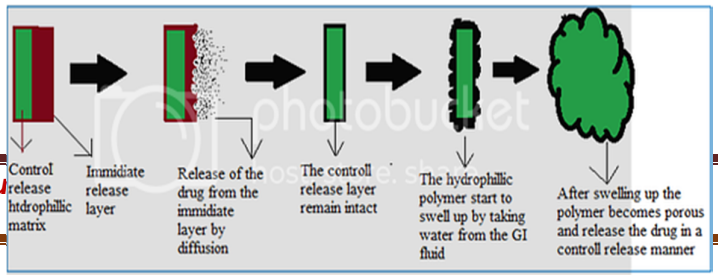
These are designed to swallow fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should support gastric retention until the adhesive forces are weakened. These are prepared as one layer with immediate dosing and other layer with bio adhesive property.

Example: Propranolol HCL, Famotidine.

3) Swelling System

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.

Example: Metoclopramide HCL + Ibuprofen



Types of bilayer tablet press

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.

- **Single Sided Press**

Fig 3: Swelling System of Bilayer Tablet

The simplest intend is a si : feeder separated from each other. Each chamber is gravity or forced fed with different power, producing 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 [9].

Limitations of the single sided press:

i. Very short first layer dwell time due to the small compression roller, possibly resulting in poor desecration, capping and hardness problems.
ii. This may be corrected by reducing the turret rotation speed (to extend the dwell time) but with the effect of lower tablet output.
iii. No weight monitoring / control of the individual layers.
iv. No separate visual separation between the two layers.

- **Double Sided Tablet Press**

In 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 and correct the die fill depth when required[10].

Fig 4: Double sides tablet press machine

- **Bilayer Tablet Press with Displacement Monitoring**

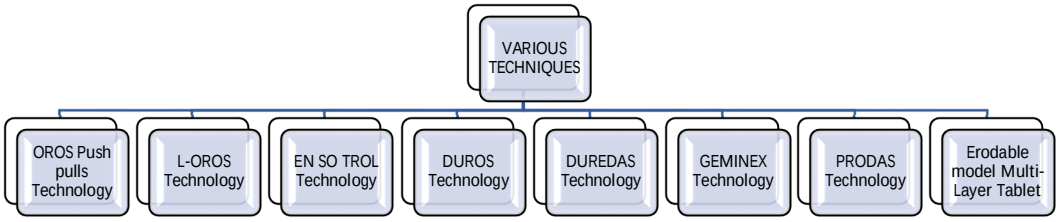
The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

Fig 5: bilayer tablet press machine with displacement

Advantages:

i. Weight control for precise and autonomous weight control of the individual layers.
ii. Low compression force used on the first layer to avoid capping and separation of the two individual layers
iii. Independence from the machine rigidity.
iv. Increased dwell time at precompression of both first and second layer to provide satisfactory hardness at maximum turret speed.
v. Maximum avoidance of cross-contamination between the two layers.
vi. Clear visual division between the two layers and maximized yield.

Different techniques for bilayer tablets[11]:



- **OROS Push-Pull Technology:**

This system consists of mainly two or three layers among which the one or more layer is essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So, this drug layer comprises of drug which is in poorly

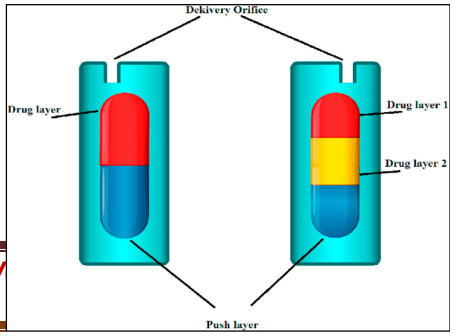


Fig 6: OROS Push-Pull Technology

soluble form. There is further addition of suspending agent and osmotic agent. A semi-permeable membrane surrounds the tablet core[12].

- **L-OROS Technology:**

A liquid formulation is particularly well suited for delivering insoluble drug and macromolecules. 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 semi-permeable membrane, drilled with an exit orifice.

The L-OROS system was designed to provide continuous delivery of liquid drug formulation and improve bioavailability of drugs.

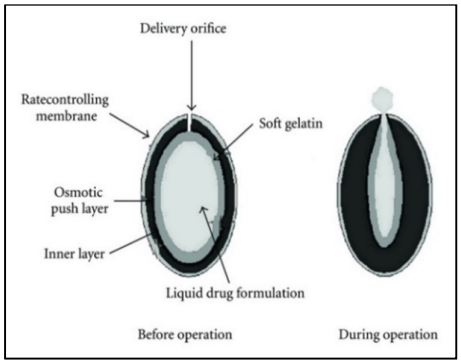


Fig 7: Schematic diagram of L-OROS

- **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.

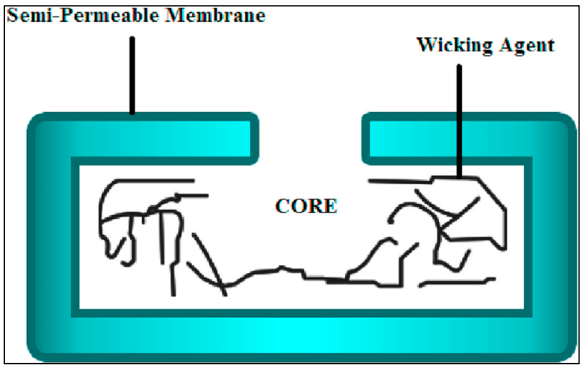


Fig 8: schematic diagram of EN SO TROL Technology

- **DUROS Technology:**

The DUROS implant system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. In this system water enters into one end of the cylinder through a semipermeable membrane, the drug is delivered from a port at the other end of the cylinder at a controlled rate appropriate to the specific therapeutic agent. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and release minute quantity of concentrated form in continues and consistent from over months or year.

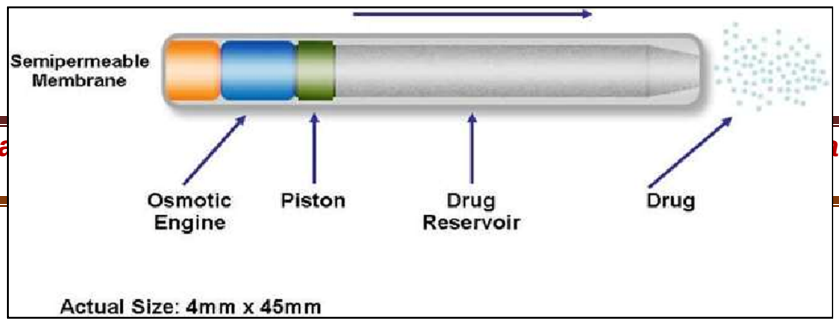


Fig 9: DUROS Technology

- **DUREDAS Technology:**

DUREDAS technology is a bi-layer tablet which can provide immediate or sustained-release of two drugs or different release rates of the same drug in one dosage form. The tableting 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[13].

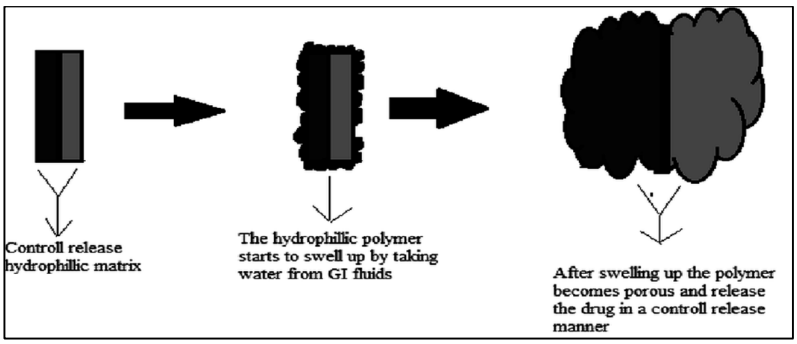


Fig 10: Schematic diagram of DUREDAS

- **GEMINEX Technology:**

GEMINEX is a dual release technology, which provides the independent release of one or more active ingredients in a single bilayer tablet. The active ingredients release can be determined at different rates which may involve two different controlled release profiles, or a controlled release and an immediate release profile simultaneously. Bi-layer tablet is the basis of this technology which utilizes TIMERx matrix in the controlled release layer or layers.

- **PRODAS Technology:**

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

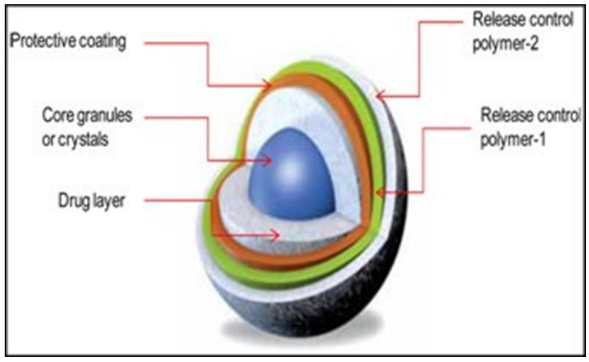


Fig 11: PRODAS technology

Manufacturing processes of bilayer tablet

Bi-layer tablets are prepared with one layer of drug for immediate-release with the second layer designed to release drug later, either as a second dose or in an extended-release form. The bi-layer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included[12].

1. Compactation

To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bi-layer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and / or lamination. The compaction of a material involves both the compressibility and consolidation.

2. Compression

Compression is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts[13].

- Steps Occur in Bilayer Tablet Compression:

I. Initial layer die filling and compaction.
II. Initial layer compaction showing the predominant stress transmission profile.
III. Density profile of initial layer before die filling of the final layer.
IV. Final layer die filling and compaction.
V. Final layer compaction showing the predominant stress transmission profile.
VI. Density profile of bi-layer tablet before ejection.
VII. Ejection of a bi-layer tablet.

3. Consolidation

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

Necessity of quality and GMP

To produce a quality bi-layer tablet, in a validated and GMP way, it is important that the selected press is capable of:

1. Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
2. Preventing cross-contamination between the two layers.
3. Producing a clear visual separation between the two layers.
4. Providing sufficient tablet hardness and high yield.
5. Accurate and individual weight control of the two layers these requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.

Evaluation of bilayer tablet

Tablet Thickness and Size:

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using venire calliper.

Tablet Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2.

Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Friability:

Friability is the measure of tablet strength. Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator[14].

% Friability = 1 - (Loss in weight / Initial weight) x 100

Uniformity of weight:

Uniformity of weight is an essential parameter of tablets. Here, twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards.

Weight Variation:

Weight variation test would be a satisfactory method for determining drug content uniformity of drug distribution.

Stability Study:

The bi-layer tablets would be packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets would be withdrawn after a period of 15 days and analysed 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.

Dissolution Studies:

The release of drug from the tablet into solution per unit time under standardize condition is called dissolution test. Bi-layer tablets would be subjected to in-vitro drug release studies in

simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Dissolution medium can be chosen according to site of dissolution[15].

Drug Content:

The assay of the drug content would be carried by weighing 10 tablets and calculated the average weight. Then the tablets would be triturated to get a fine powder.

Buoyancy Determination:

The time taken for dosage form to emerge on surface of medium is called floating lag time, duration of time by which the dosage form constantly emerges on surface of medium is called total floating time (TFT). One tablet from each formulation batch would be placed in dissolution apparatus containing 900 ml dissolution medium using desired RPM. The temperature of medium would be maintained at 37±2°C. The time would be taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remains on surface of medium would be noted[16].

Swelling Study:

The individual tablets would be weighed accurately and kept in 50 ml of water[17]. Tablets would be taken out carefully after 60 min, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling would be calculated by using formula:

Swelling study = Wet weight - Dry weight / Dry weight x 100

Conclusion

Bi-layer 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. There is various application of the bi-layer tablet it consists of monolithic partially coated or multi-layered Matrices. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. 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. The objective of the dosage form is to ensure that the drugs available to the patient are not only safe and effective, but are also properly manufactured and packaged to meet the established quality and target product profile over its shelf-life. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the layer tablet quality.

So, layered tablets may be considered as improved beneficial technology to overcome the shortcoming of other tablets.

References

1. Divya A., Kavitha K , Kumar MR, Dakshayani S, Singh J. SD. Bilayer Tablet Technology: An overview. Journal of Applied Pharmaceutical Science.43-47 (2011).
2. Gopinath C, Bindu VH, Nischala M. An Overview on Bilayer Tablet Technology. Journal of Global Trends in Pharmaceutical Sciences 2013.
3. Ghosh R., Md. Anwarul Haque, Paul T. R., Al-Amin, M. Ahmed Bhuiyan, Dewan I., BILAYER TABLET TECHNOLOGY: AN OVERVIEW. World Journal of Pharmaceutical Research 2014.
4. Aggarwal S, Syan N, Mathur P. Bi-Layer Tablet Technology - Opening New Ways in Drug Delivery Systems: An Overview. International Journal of Research in Pharmaceutical and Biomedical Sciences 2013.
5. JSK Anusha, M. Karthik, A Review on Bilayer Tablets. Journal of Pharmacy and Pharmaceutical Science 2016.
6. Sowmya C., Reddy C.S., Tabasum S.G., Varma V., AN OVERVIEW ON BI-LAYER TABLETS. International Journal of Pharmacy and Technology 2012.
7. Deshpande R.D., Gowda D.V., Mahammed N., Maramwar D.N., BILAYER TABLETS-AN EMERGING TREND: A REVIEW. International Journal of Pharmaceutical Science and Research. 2011.
8. Chauhan M., Suthar S., A. Shah, Polara M. , Patel M., Patel J., Bilayer Tablet: Immediate Release and Sustained Release: An Overview. Research J. Pharm. And Technology2012.
9. Rao S. V., Priyanka B., Padmalatha. Bilayer Tablet Technology: A Novel Approach. GSC Biological and Pharmaceutical Sciences 2019.
10. Ashok PH, Kumar TA. A Novel Approach of Bilayer Tablet Technology: A Review. International Research Journal of Pharmacy 2012.
11. Bhavani HI, Sirisha VNL, Kumar PK, Sruthi B, Namrata M, Rao YKK et al. A Review on Emerging Trends of Bi-Layered Tablets. International Journal of Pharmaceutical Research and Bio-Science 2012.
12. Mishra A, Bhatt GK, Kothiyal P. Review: Bilayer Tablet and Evaluation. International Journal of Drug Research and Technology 2013.
13. Patel M.G., Nanjan S., Challenges in the Formulation of Bilayered Tablets: A Review, International Journal of Pharma Research and Development 2010.
14. Singh PK and Kumar S. Bilayer and floating bio adhesive tablets: Innovative approach to gastro retention. Journal of Drug Delivery & Therapeutics 2011.
15. Ramesh DS, Guruvaiah, Harani A. Formulation and evaluation of bilayer sustained release matrix tablets of Metformin HCl and Pioglitazone. Amer-Euras J Sci Res 2010.
16. Biswal B., Design Development and Evaluation of Trimetazidine Dihydrochloride Floating Bilayer M.R Tablets, International Research Journal of Pharmacy 2011.
17.Girish S. Sonar, Devendra K. Jain, Dhananjay M. More, Preparation and invitro evaluation of bilayer and floating-bio adhesive tablets of rosiglitazone maleate, Asian Journal of Pharmaceutical Sciences, pp 161-16, 2007.

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