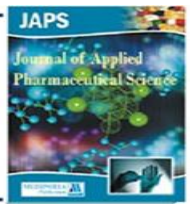
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 04-10-2011
Revised on: 09-10-2011
Accepted on: 12-10-2011

Bilayer tablet technology: An overview

Divya .A, K. Kavitha, M. Rupesh Kumar, Dakshayani S, Jagadeesh Singh SD

Divya .A, K. Kavitha, M. Rupesh Kumar, Dakshayani S, Jagadeesh Singh SD
East Point College of Pharmacy, Bidarhalli, Bangalore, Karnataka-560 049

For Correspondence
Divya.A
Tel: +918792765940
Email:pharmadivya.a@gmail.com

ABSTRACT

Over the past 30 years as the expense and complications involved in marketing new drug entities have increased, 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. 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.

Key words- Bi-layer tablet, push pull technology, tablet press, moisture sorption capacity.

INTRODUCTION

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing 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 primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance (Kumar et al., 2010). 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 (Shiyani et al., 2008). There is various 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.

VARIOUS TECHNIQUES FOR BILAYER TABLET

OROS® push pull technology

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

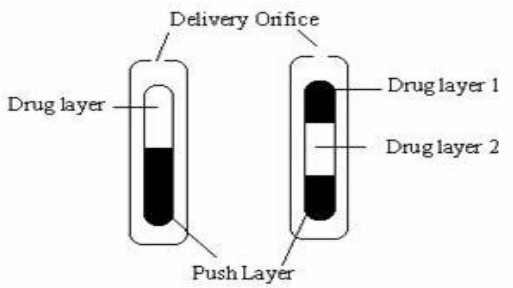


Fig. 1: Bilayer and trilayer OROS Push pull technology.

L-OROS tm technology

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

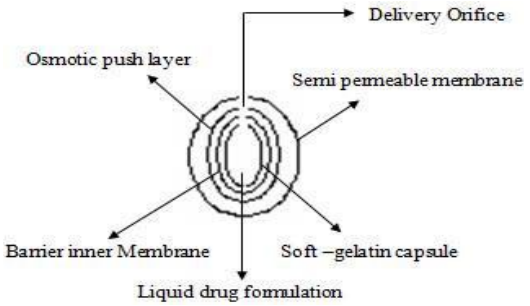


Fig. 2: L – OROS tm technology.

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 (Kale et al.,2011.

DUROS technology

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 miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or Year.

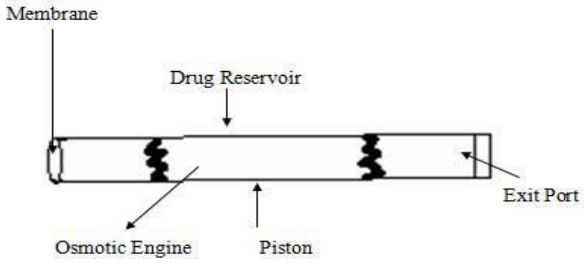


Fig. 3 DUROS Technology

Elan drug technologies' Dual release drug delivery system

(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 tab letting 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:

- Bilayer tabletting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.
- Capability for immediate release and modified release components in one tablet.
- 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 prolongation 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 employed 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 (http://www.port/ technology.com).

BI-LAYER TABLET PRESS

The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, which the main compression station will automatically compress, the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The

bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooths surfaces that permit fast cleaning and changeover (http://www.elan.com/).

The machine concept

Advantages

✓ Flexible Concept
- – Bi-Layer execution with optional single-layer conversion kit
- – Exchangeable turret
- – Turret sizes for product development, scale-up, and mid-range production
- – Full production capability in a scale-up machine
- – Self-contained, fully portable design

✓ Fast and Easy Changeover
- – Internal turret lift device for extreme simplicity in turret removal and installation
- – Clean compression zone with quick-disconnect design

✓ Design Advantages
- – Small-scale bi-layer capability
- – Robust caster base permits full portability
- – Large touch screen flush mounted
- – Unique structural design eliminates vibration and noise
- – Zero clearance feeder for maximum yield and optimal layer separation
- – Retractable second layer feeder for automatic first layer sampling

✓ Full instrumentation
- – Tamping force
- – Pre/Main compression force
- – Ejection force

✓ Touch Screen Control
- – Press force control and single tablet rejection capability
- – Comprehensive data collection and analysis capability
- – Real time display and batch data documentation

✓ Containment Solution
- – WipCon® solution available for potent products.

For Small-Scale Bi-layer Applications

The KORSCH XM 12 Bi-Layer Tablet Press is a small-scale press which is ideal for product development, scale-up, Clinical trials, and midrange production. The bi-layer execution, single-layer conversion kit, and exchangeable turret Offer unprecedented flexibility. The XM 12 Bilayer tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooths surfaces that permit fast cleaning and changeover. The machine features a 5 kN tamping station, 40 kN precompression station, 80 kN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame.

The result is an extreme reduction in the operating noise level. The XM 12 Bilayer tablet Press features a retractable second speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold, which cleans the die table and completely eliminates any potential for cross-contamination.

Properties

✓ Free format graphic and statistical analysis to allow the export of many data formats.

✓ Reports can be automatically generated in a variety of data formats with and without an electronic signature.

✓ Charts can be dimensioned, comments added, formatted and exported before being processed in the MS Office world.

✓ Finger print recording during production. Overlay Technology allows safe and quick recognition of subsequent waveforms.

✓ Correlation Analysis to establish a "Knowledge Database" that serves to easily compare the properties of known and unknown ingredients. The database enables the user to correlate measuring values from the tableting process and derived and externally recorded quantities (e.g. tablet hardness, density, etc.).

✓ Compaction Analysis allows evaluations e.g. Heckel plot, energy, work of compression, contact time, compressibility.

✓ "Built-in" PAT function, i.e. the database is automatically filled with process data thereby helping to define and complete PAT requirement for Knowledge Space and Design Space.

XM 12 WipCon® Development & Analysis

✓ Minimum space requirements, portable design

✓ Best cleaning / decontamination results for product specific demands

✓ Optimized glove port configuration

✓ All types of make/break connections possible

✓ High containment range for lab scale and medium size batches OEB 5 (1 µg/m³ > OEL >0.1 µg/m³) with RTP transfer system

✓ Medium containment range for small production batches OEB 4 (10 µg/m³ > OEL > 1 µg/m³) with split valve connections

✓ Connection to Wip tablet deduster on same containment level OEB 4 (10 µg/m³ > OEL >1 µg/m³)

✓ Negative pressure control and safe-change filter box attached or separate, depending on space availability (berlin@korsch.de).

Table 1. KORSCH XM 12 Technical Data.

Description	XM 12 12 / 18	XM 12 16 / 22	XM 12 18 / 26	XM 12 28
Tool Execution (EU/IPT)	D	B	BB	BBS
Number of Punch Stations	12 / 18	16 / 22	18 / 26	28

Number of Compression Stations	3	3	3	3
Main Compression Force (kN)	80	80	80	80
Precompression Force (kN)	40	40	40	40
Tamping Force (kN)	5	5	5	5
Tablet Diameter max. (mm)	25	16	13	11
Filling Depths max. (mm)	22	18	18	18
Max. Second Layer Insertion Depth (mm)	11	10–60	11	11
Press Speed Bi-Layer (RPM)	10–60	57.600 / 79.200	10–60	10–60
Output Bi-Layer (Tablets/Hour)	43.200 / 64.800	10–120	64.800 / 93.600	100.800
Press Speed Single Layer (RPM)	10–80	115.200 / 158.400	10–120	10–120
Output Single Layer (Tablets/Hour)	57.600 / 86.400	252	129.600 / 187.200	201.600
Pitch Circle Diameter (mm)	252	8	252	252
Tablet Thickness max. (mm)	8		8	8
Machine Dimensions L x W x H (mm)	1.700 x 900 x 1.950 – Dimensions are identical for all versions			
Net Weight of the Machine (Kg)	2.500	2.500	2.500	2.500
Electrical Load (kVA)	5,5	5,5	5,5	5,5

The new KORSCH XM 12 is in accordance with the valid safety and accident prevention regulations and with the regulations of the workmen´s compensation board of chemistry. The new KORSCH XM 12 has the CE certificate and has been tested according to EMC regulations.

Table: 2 Some examples for combination of drug used as bilayer tablets.

COMBINATION OF DRUGS	REASON
Metformin hydrochloride + Pioglitazone	Reduce frequency of administration and improve patient compliance (Ramesh et al., 2010).
Diltiazem hydrochloride + Lovastatin	Improve patient compliance and better disease management (Kulkarni et al., 2008).
Metformin hydrochloride + Glimepiride	Improve oral therapeutic efficacy with optimal control of plasma drug level (Pattanayak et al., 2011).
Atorvastatin calcium + Nicotinic acid	Develop potential dosage form (Nirmal et al., 2008).
Metoprolol succinate + Amlodipine besylate	Lower doses of drug to reduce patient blood pressure, minimize dose dependent side effects and adverse reactions (Atram et al., 2009).
Salbutamol + Theophylline	Enhance patient compliance and prolong bronchodilation (Nagaraju et al., 2009).
Paracetamol + Diclofenac sodium	Reduce dose frequency and decrease incidence of GI side effects (Gohel et al., 2010).
Tramadol + Acetaminophen	Prolonged release up to 12 h and improve patient compliance (Naeem et al., 2010).
Metoclopramide hydrochloride + Ibuprofen	Effective treatment of migraine and avoid chemical incompatibility between drugs (Shiyani et al., 2008).

CHARACTERIZATION OF BILAYER TABLET

Particle size distribution

The particle size distribution was measured using sieving method

Photo-microscope Study

Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope

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 and r are the height and radius of the powder cone.

Moisture Sorption Capacity

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g 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.

Density

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulas.

LBD ¼ weight of the powder=volume of the packing ð2Þ

TBD ¼ weight of the powder=tapped volume of the packing ð3Þ

Compressibility

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

$$C = 100 \times (1 - ÞB/ÞT)$$

(Indian Pharmacopoeia, 1996; United States Pharmacopoeia, 2000:1944).

Hausnser'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 (Atram et al., 2009).

EVALUATION OF SUSTAIN RELEASE BILAYER TABLET

Tablet Thickness and Size

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

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/cm2.

Friability

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = [(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) / \text{Initial wt. of tablets}] \times 100$$

Uniformity of weight

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards (Singh and Kim., 2000).

Dissolution Studies

Bilayer tablets were subjected to in vitro 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. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis (Atram et al., 2009).

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered 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. Bilayer 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 such as the Courtoy-R292F. Whenever high quality bilayer 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 (Kale et al., 2011).

REFERENCES

Atram SC, Udavant YK, Salunke RJ, Neb GB, Shahi SR, Gulecha BS, Padalkar AN. Formulation and evaluation of bilayer tablet containing Metoprolol succinate and Amlodipine besylate as a model drug for anti hypertensive therapy. J Pharm Res 2009;2(8):1335-47.

berlin@korsch.de

Gauniya A, Bhadana V. A review on latest advancement in patented controlled/sustained release drug delivery system. Pharm Rev 2007;5(6).

Gohel MC, Parikh RK, Nagori SA, Jethwa BA. Fabrication and evaluation of bilayer tablet containing conventional Paracetamol and modified release Diclofenac sodium. Ind J Pharm sci 2010; 72(2):191-96.

http://www.elan.com/

http://www.port/ technology.com

Kale SS, Saste VS, Prajkta L, Ughade, Dheeraj T, Bhaviskar. Bilayer tablet:Review. Int J Pharm Sci Rev and Res 2011;9(1):25-30.

Kumar KK, Mahesh M, Sasikanth K. Design, development and characterization of sustained release of Metformin hydrochloride and Gliclazide bilayered tablets by wet granulation method. Int J Biopharm 2010;1(2):67-71.

Kulkarni AS, Manish S. Design and floating bilayer tablets of Diltiazen HCl and Lovastatin. PDA J Pharm Sci Technol 2008;62(5):344-52.

Naeem MA, Mahmood A, Khan SA, Shahiq Z. Development and evaluation of controlled release bilayer tablets containing microencapsulated Tramadol and Acetaminophen. Trop J Pharm Res 2010;9(4):347-54.

Nagaraju R, Kaza R. Formulation and evaluation of bilayer sustained release tablet of Salbutamol and Theophylline. Int J Pharm Sci Nanotechnol 2009;2(3):638-46.

Nirmal J, Sasivam S, Peddanna C, Muralidharan S, Kumar SG, Nagarajan M. Formulation and evaluation of bilayer tablets of Atorvastatin calcium and Nicotinic acid. Chem Pharm Bull (Tokyo) 2008;56(10):1455-8.

Pattanayak DP, Dinda SC. Bilayer tablet formulation of Metformin HCl and Glimepiride:A novel approach to improve therapeutic efficacy. Int J Drug Discovery Herb Res 2011;1(1):1-4.

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;5(3):176-82.

Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm Sci Tech 2008;9(3):818-27.

Singh BN, Kim KH. Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention, J Control Rel 2000,63,p.235-59.

The Indian Pharmacopoeia, Vol. 2, 4th Ed. The Controller of Publication, Govt. of India, Delhi, 1996, p.A82-A85.

The United States Pharmacopoeia, United states Pharmacopoeial convention, Inc., Rockville, MD, 2000:1944.