Review Article *ISSN: 2277-8713*
Harika IB, IJPRBS, 2012; Volume 1(5):1-20 *IJPRBS*

ISSN: 2277-8713
IJPRBS
A Path for horizing your innovative work
INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A REVIEW ON EMERGING TRENDS OF BI-LAYERED TABLETS.

I BHAVANI HARIKA*, VNL SIRISHA, P KIRAN KUMAR, B SRUTHI, M NAMRATA, Y KIRAN KUMAR RAO, K PRANAVI, N VAMSI KRISHNA, O.UMA MAHESHWARA RAO, S SINDHURA

Anurag Pharmacy College Affiliated to JNTU-Hyderabad, Kodad, Nalgonda-Dt, Andhra Pradesh, India.

Accepted Date:

30/08/2012

Publish Date:

27/10/2012

Keywords

Bi-layer tablet

Challenges

Current research

Merits and demerits

Tablet presses

Techniques

Sustained release.

Corresponding Author

Ms. I. Bhavani Harika,

Anurag Pharmacy College,

Abstract

The purpose of writing this article is to compile the information regarding the bi-layer tablet technology and the various aspects of the bi-layered tablets which are often considered in the successful development of the dosage form. Bi-layer tablet is a new era in the development of controlled release formulation along with various features to provide a way of successful drug delivery system. It is suitable to prepare the tablets in the form of multi layers which are used for the administration of two drugs which are chemically incompatible. Several pharmaceutical companies are currently developing bi-layered tablets, for a variety of reasons such as patent extension, patient compliance, additive effect, reduction of dosage regimen and to achieve sustained release of drugs with minimal side effects. Apart from the advantages it has many so many disadvantages and problems too. An attempt has been made in this review article to introduce the readers to the various aspects of bi-layered tablet technology and various applications in current research.

INTRODUCTION

Bi-layer tablet is suitable for sequential release of two drugs in combination, separating two in-compatible substances and also for sustained release of drugs in which one layer is immediate dose and second layer is maintenance dose. There are various applications of the bi-layer tablet as it consists of monolithic partially coated or multilayered matrices. In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased, thus promoting patient convenience and compliance. These can be a primary option to avoid chemical incompatibilities between API by physical separation. Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate.

Definition[1]

Dual release tablet is a unit compressed tablet dosage form intended for oral administration. It contains two layers in which one layer is having conventional or immediate release part of single or multiple actives, another layer is sustained or controlled release part of single or multiple actives.

These are termed as bi-layered tablets.[1]

Need of Bi-layer tablets[6-9]

1. For the fixed dose combinations of different API's, prolong the drug product life cycle, buccal/ mucoadhesive drug delivery systems, fabricate novel drug delivery systems such as chewing device and floating tablets for gastro retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredients.
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 separate incompatible active pharmaceutical ingredients 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).

Merits[1]

- They are used as an extension of conventional technology.
- They are used for the separation of the chemically incompatible components.
- Patient compliance is enhanced leading to improved drug regimen efficacy.
- Maintenance of physical and chemical stability.
- Reduction in the dosage regimen.
- Potency is retained and dose accuracy is ensured.
- Potential use of single entity feed granules.

Demerits[1]

- Inaccuracy in individual layer control.
- Cross contamination between the individual layers.
- Insufficient hardness and layer separation.
- Reduction in yield when compared to ordinary tablets.
- Bi-layered tablet presses are expensive and adds complexity during manufacture.

Advantages of Bi-layer tablets over conventional tablets

Blood level of a drug can be held at a consistent therapeutic levels for improved drug delivery, accuracy, safety and reduced side effects. Reduction of adverse effects can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced. These tablets lend themselves to repeat action products, where in one layer provides the initial dose whereas the other provides the maintenance dose. So multi layered tablet system is an alternative approach for the sustained release of drugs over conventional tablets.[5]

Physical parameters of Bi-layered tablets[1]

Size and shape

Size is limited by the capacity of the machine with the total thickness being the same as for a single layer tablet. Many shapes other than round are possible and are limited only by the ingenuity of the die maker. However deep concavities cause distortion of the layers. Therefore standard concave and flat faced bevelled edge make for the best appearance, especially when layers are of different colours. Punches with

bevelled edges or concave faces will make the top and bottom layers. Flat faced tooling will produce the equal thickness of the layers, but unfortunately the edges of the tablets tend to clip readily.

Layer thickness

This can be varied with a reasonable proportion within the limitations of the tablet press. Thickness depends on the fineness of the granulation.[1]

TABLET PRESSES[3]

Ideal properties of bi-layer tablet press[3]

- It should give high yield and accurate individual layer weight control of the two layers.
- It should produce clear visual separation between the two layers.
- It should prevent cross contamination between the two layers.
- It should prevent capping and separation of two individual layers that constitute bi-layer tablet.

Types of bi-layer tablet press[1]

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layered tablet press with displacement monitoring.

Single sided tablet press

It contains both the chambers of the doublet feeder separated from each other. Each chamber is gravity or force fed with different powders, thus producing the individual layers of the tablets. When the die passes under the feeder, it is at first loaded with first layer powder followed by second layer powder.

Limitations[10-11]

- No weight monitoring of the individual layers.
- No distinct visual separation between the two layers.
- Very short dwell time for first layer due to the small compression roller, possibly resultingin poor deaeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration. Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially

when compressing a difficult formulation. To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, precompression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

Double sided presses[1]

These 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 the main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

Bi-layer tablet press with displacement[1,3]

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 pre-compression force.

The advantages of this are

- Weight control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the individual layers.
- Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.

Various techniques for bi-layer tablet

OROS® Push Pull Technology[6, 12]

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. 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.

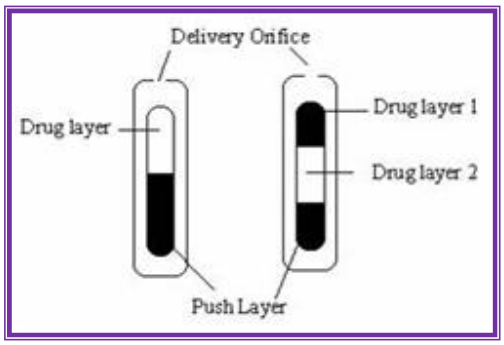

Figure 1 Bi-layer and tri-layer OROS Push pull technology

L-OROS tm Technology[6, 12]

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.

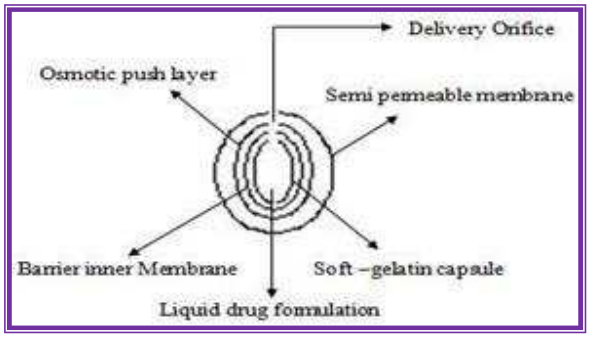

Figure 2 L – OROS tm technology

EN SO TROL Technology[6, 12]

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.

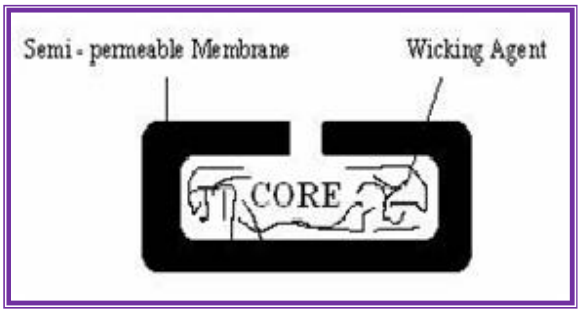

Figure 3 EN SO TROL Technology

DUROS Technology[6,12]

The system consists from an outer cylindrical titanium alloy reservoir. 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.

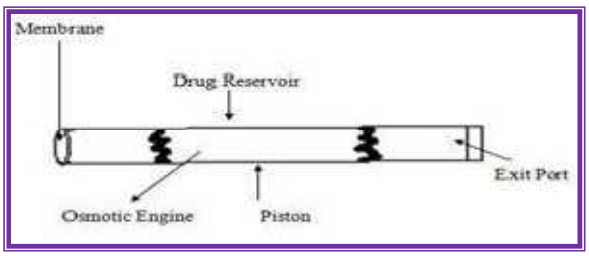

Figure 4 The DUROS technology

Elan drug technologies' dual release drug delivery system[6, 12]

(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 tabletting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers

Benefits offered by the duredas™ technologyinclude[6, 12]

- Bi-layer tabletting technology.
- Tailored release rate of two drug comp onents.
- Capability of two different CR formulati ons 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. 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 where by 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.

Ro Tab BI-LAYER [12]

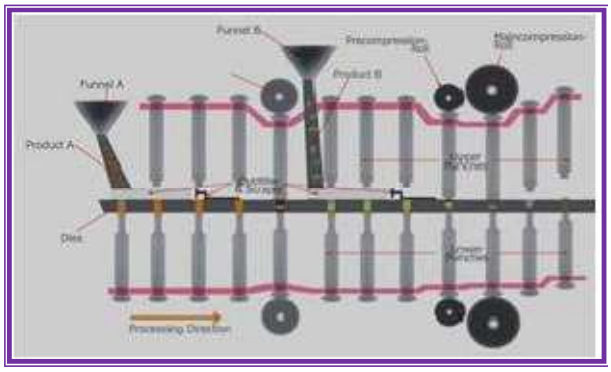

Figure 5 Ro Tab Bi-layer

Software

This software is modular designed and can be upgraded with additional functions at any time. An advanced industrial PC-system with 15" touch-screen guarantees precise results and fast graphical evaluations. The wide range of instrumentations allows a nearly perfect simulation of production machines in laboratory scale.[12]

Basic Technique

Software package for prevailing use of RoTab Bi-layer in production mode. Operation with 15" touch-screen display, by automatical dosing regulation by compression force and adjustment o die table and Opt filler speed. Optional independent hardness regulation available.[12]

R&D Modified Technique

Basic package for galenical R&D on the RoTab Bi-layer. Contains evaluation and graphical visualization of instrumented measuring points, as compression 1st layer pre main compression and ejection force on a 15" touch screen display. Punch tightness control can be selected as an additional alarm function. Upgrade to R&D Plus is possible at any time. [12]

Bi-Layer Tablet Press[12]

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, 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 crosscontamination. WipCon® solution available for potent 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 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and changeover.7 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.

Bi-Layer Application[12]

The XM 12 features an exchangeable turret capability to permit a single machine to run all press tool sizes to provide maximum flexibility and versatility. An internal lift arm eliminates the cost and space requirement of a large external turret removal device.

- Single layer conversion kit adds yet another dimension of flexibility.
- Single Layer Conversion.
- 30 Minute Conversion Time.
- High Speed Single-Layer Capability (120 RPM)

Advantages[12]

- Flexible Concept.
- Bi-Layer execution with optional single-layer conversion kit.
- Exchangeable turret.
- Turret sizes for product development, scale-up, andmid-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 inturret removal and installation.
- Clean compression zone with quick-disconnect design.

Challenges in the formulation of bi-layered tablets[3]

- One of the major challenges is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which often results in interfacial crack driven by residual stresses.
- The compacted layers should not be too soft or too hard, they will not bond securely with each other which

can lead to compromised mechanical integrity.

- The other challenges include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force and cross contamination.

Applications of Bi-layered tablets [1]

- Bi-layer tablets are mainly used in the combination therapy.
- These are used to deliver the loading dose and sustained dose of the same or different drugs.
- These are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug. These are used to deliver the two different drugs having different release profiles.

Various aspects used in the bi-layered tablet[11]

Floating drug delivery system:

These are 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 buyoyancy 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 way 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.

Disadvantages

- It may not have the controlled loss of density alternatively required for it to eventually exit from the stomach.
- These are not applicable to higher dose levels of highly water soluble drugs where large amounts of polymer is needed to retard the drug release.
- The performance of floating formulation may be posture dependent.

Polymeric Bioadhesive system

These are designed to imbibe fluid following administration such that the outer layer becomes viscous, tacky material that adheres to the gastric mucosa/ mucus layer. This should encourage 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 success seen in animal models is not translated to human models due to differences in mucous amounts. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bioadhesive dosage form would not appear to offer a solution for extended drug delivery.

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.

Characterization of Bi-layer Tablet[12-14]

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.

$\tan \emptyset = h/r$

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 x (1-ÞB/ÞT)

Evaluation of sustain release bi-layer tablet [12, 14, 15]

Tablet Thickness and Size [14, 15]

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

Tablet Hardness [14, 15]

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: [14, 15]

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.

% loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

Uniformity of Weight[14, 15]

Twenty tablets were selected at random and the average weight was calculated. Weight variation was calculated

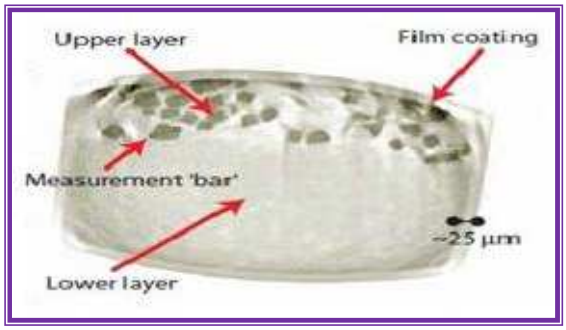

Figure 6 Conventional bi-layer tablet structure

Table 1.

Some examples of polymers used and evaluation methods for bi-layered tablets [5]

Sr. No	Drugs/Dosage form	Polymers	Evaluation Method
1.	A bi-layered SR tablet or caplet composition of heparin and insulin, consisting of two layers, One layer contains the active agent, the delivery agent and a release controlling Polymer. The second layer contains a swellable Polymer. [(5)]	Release-controlling polymer (e.g., polyethylene oxide, Having a molecular weight of about 200,000). Swellable polymer (e.g. polyethylene oxide having a molecular weight of 700,0000 and carbopol.	Swellable studies, dissolution studies,Gastric retention studies.
2.	Bi-layer oval matrix tablet of valsartan. [(5)]	Layer-1: active agent, avicel, Methocel, Sodium chloride, Magnesium Stearate Layer-2: same as above and contains coluring agent such as yellow iron oxide	Dissolution studies done in USP type-II apparatus at 50 rpm.
3.	A bi-layer tablet formulation of acyclovir, Gancyclovir, Ritonavir,minocycline,	Water soluble polymers such as polyethylene oxide, HPC, HPMC, HEC,	In vivo study was done on dogs in the fed state and the concentration

	Cimetidine,ranitidine,captopril, Methyldopa,Selegiline, Fexofenadine,Metformin,Bupropion, orlistat and metformin. [5]	sodium CMC, Methyl cellulose poly acrylic acid	in the sample is measured by HPLC
4.	A CR multilayered tablet of theophylline with, two barrier and one drug layer.All layers are formed from swellable, erodible polymers[5].	Swellable erodible polymer comprises of polyethylene oxide,HPMC K 4M Second layer consists of active agent polyethylene oxide, Lactose anhydrous, Third layer of lactose anhydrous polyethylene oxide, Sodium bicarbonate and magnesium stearate.	Dissolution study in 0.1N Hcl solution at 50 rpm.the amount of theophylline released at each point was measured by photo diode array spectrophotometer. For each tablet, a buyoyancy lag time was determined. The matrix erosion and dissolution was measured.
5.	Floating bi-layer tablet of fluoroquinolone antibiotic such as ciprofloxacin. [5]	Matrix forming gelling agent is HPMC which has a viscosity from 4000cps to 100000cps.combination of matrix forming gelling agent of methocels K4M and methocels K 100M, ratio in the range of 1:0.25 to about 1:5	Dissolution study in 0.1 N HCl using USP apparatus 1 at 100 rpm is done.

Research work done on bi-layered tablets: [4]

The multilayered concept has been long utilized to develop sustained release formulations. The pharmacokinetic advantage relies on the fact that drug release from one of the layer i.e., immediate release layer leads to a sudden rise in blood concentration.

Table 2.

Some examples for combination of drugs used as bi-layered tablets [4]

Sr. No.	Combination of drugs	Reason
1.	Metformin hydrochloride + Pioglitazone	Reduce frequency of administration and improve patient compliance (Ramesh et al., 2010).
2.	Diltiazem hydrochloride + Lovastatin	Improve patient compliance and better disease management (Kulkarni et al., 2008).
3.	Metformin hydrochloride + Glimepiride	Improve oral therapeutic efficacy with optimal control of plasma drug level (Pattanayak et al., 2011).
4.	Atorvastatin calcium + Nicotinic acid	Develop potential dosage form (Nirmal et al., 2008).
5.	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).
6.	Salbutamol+ Theophylline	Enhance patient compliance and prolong bronchodilation (Nagaraju et al., 2009).

7.	Paracetamol + Diclofenac sodium	Reduce dose frequency and decrease incidence of GI side effects (Gohel et al., 2010).
8.	Tramadol+ Acetaminophen	Prolonged release up to 12 h and improve patient compliance (Naeem et al., 2010).
9.	Metoclopramide hydrochloride + Ibuprofen	Effective treatment of migraine and avoid chemical incompatibility between drugs (Shiyani et al., 2008).

Miscellaneous Research on Bi-layered Tablets

Muniyandy Saravanan, et al., (2002) reported that the study was to formulate

Metformin/Gliclazide extended release tablets with Eudragit NE30D by wet granulation technique. Two batches were prepared in order to study influence of drug polymer ratio on the tablet formation and *in vitro* drug release. The percentage of polymer, with respect to Metformin/Gliclazide, required to produce tablets with acceptable qualities was 9 to 13.45. The percentage of polymer below this range released the drug immediately and above this range produced granules not suitable for tablet formation. The quantity of Metformin/Gliclazide present in the tablets and the release medium were estimated by a validated HPLC method. [16]

Yamsani Madhusudan Rao et al., (2010) reported that the study was to develop bi-layered tablets containing Glimepiride for immediate release using sodium starch glycolate as super disintegrant and Metformin hydrochloride (HCl) for sustained release by using Hydroxyl propyl methyl cellulose (HPMC K 4M) and Sodium Carboxy Methyl cellulose (SCMC) as the matrix forming polymer showed the in vitro release studies as zero order release and diffusion was the dominant mechanism of drug release. The polymer (HPMC K4M, SCMC) and binder PVPK-30 had significant effect on the release of Metformin HCl matrix tablets (F5). Thus formulated bi-layer tablets provided immediate release of

Glimepiride and Metformin HCl as sustained release over a period of 8 hours. [17]

NG Raghavendra Rao et al., (2010) reported that the study was to develop controlled zero-order release glipizide bi-layered matrix tablets using different grades of hydroxy propyl methyl cellulose (HPMC) as novel release modifier along with xanthan gum (XG), guar gum (GG), and karaya gum (KG) as release retardants. Bi-layered matrix tablets of glipizide were prepared by wet granulation method. The release rate were modulated by varying concentration of different types of rate controlling material as well as in a combination of two different rate controlling material. After evaluation of physical properties of tablets, the *in vitro* release study was performed in phosphate buffer pH 7.4 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. It was observed that bi-layer matrix tablets contained polymer blend of HPMC/Ethyl cellulose were successfully sustained the release of drug up to 12 hrs. All above polymers can be successfully used to achieve desired zero order drug release.[18]

HK Ibrahim., (2010) reported that the study was to combine two Antidiabetic agents with different mechanisms of action, namely, metformin HCl and rosiglitazone maleate, in a tablet to improve glycemic control in patients with type II diabetes. The preformulation study started with development and validation of an HPLC method for the determination of both drugs in the mixture. The results of visual inspection, TLC, DSC, and FT-IR verified the absence of any physical or chemical interaction between both compounds. Four compatible excipients were selected for the formulation of the tablets by wet granulation according to a 22 factorial design. They released 100% of the drug during the first 45 min, displaying higher dissolution efficiency than commercially available Rosiplus tablets. The tablet formulation that passed the physical and chemical stability study for 24 months at ambient conditions was tested *in vivo* on healthy volunteers in a cross-over design.[19]

DP Pattanayak et al., (2011) reported that the study was to formulate a fixed dose combined drug formulation of valsartan (VAL) as an immediate release layer and metformin HCl (MHCl) as a sustained

release form using bi-layer tablet technology, which enables biphasic drug release for once daily dosing to get a better therapeutic efficacy. The immediate release layer was prepared using super disintegrant crospovidone and extended release layer using hydroxypropylmethylcellulose (HPMC K100M), sodium carboxy methyl cellulose and povidone K90. The *in-vitro* release studies indicate that bi-layer tablets effectively control the drug release. The amount of VAL and MHCl released at different time intervals were estimated by HPLC method indicates that VAL and MHCl could be a potential fixed dose combination form for the simultaneous treatment of hypertension and diabetes and can be developed into suitable bi-layer tablets.[20]

Chirag K. Parmar et al., (2011) reported that the study was to develop bi-layer tablet to improve therapeutic efficacy with optimum drug plasma level which contains two antibiotics. This formulation comprises of Cefuroxime axetil as immediate releasing layer using superdisintegrant Crosscarmellose and Potassium clavulanate as extended release layer using different concentrations of HPMC K4M.Both layer compositions were prepared separately by dry granulation. Bi-layer tablet after compression were film coated and final bi-layered tablets were evaluated for various physical parameters, in vitro dissolution profile. In vitro dissolution kinetics followed the Higuchi model via diffusion mechanism after initial immediate release.[21]

CONCLUSION

Bi-layer 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. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one Layer is immediate release as initial dose and second layer is maintenance dose. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. 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. Despite of the advantages and applications, there are critical challenges too for the formulation of a successful bi-layered tablet.

REFERENCES

1. Gilbert SB, Neil RA: Tablets, in Leon Lachman, Herberta Liebermann, Joseph LK, the theory and practice of industrial pharmacy, Edition-3. Page no. (a) 293-294, (b) 330-331, (c) 430-431.

2. William CG and Robert GB: In: Herbert A. Liebermann, Leon Lachman, Joseph B. Schwartz pharmaceutical dosage form: tablets edition-2 Macel Dekkar. Inc., Newyork 1989, 1,274.

3. Patel Mehul, Ganesh Nanjan Sockan, Kavitha and Tamizh Mani: IJPRD. 2:30-38.

4. Divya A, K Kavitha, M Rupesh Kumar and Dakshayani S: JAPS. 2011: 43-47.

5. Mohamed HG and Furquan NK, IJHR, 2009; 2(1): 23-24.

6. Panchal Hiten Ashok and Tiwari Ajay kumar: IRJP. 2012:44-49.

7. Shiyani B, Gattani S and Surana: SAAPS Pharm Sci Tech 2008; 9(3): 818-827.

8. Pranjal kumar singh and Sanjoo kumar: Journal of drug delivery and therapeutics, 2011; 1(1): 32-356.

9. Kulkarni A and Bhatia M: Development and evaluation of bi-layer floating tablets of atenolol and lovastatin for biphasic release profile. Iran. J. Pharm. Res. 2009; 8: 15–25.

10. Rohan D. Deshpande, DV Gowda, Nawaz Mahammed and Deepak N. Maramwar: IJPSR, 2011; 2(10): 2534-2544.

11. ME Aulton, Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 1974.

12. Shaikh TK, Gadhave MV, Jadhav SL and Gaikwad DD: IJUPLS. 2012: 450-460

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

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

15. Singh BN and Kim KH, Journal of Control Rel. 2000; 63: 235-59.

16. Enose Appavoo Arno, Prithiviraj Anand, Kesavan Bhaskar, Somasundaram Ramachandran, Muniyandy Saravanan, and Radhakrishnan Vinod Chem. Pharm. Bull. November 2002 :1495-1498.

17. Reddy Sunil, Panakanti Pavan Kumar, Kandagatla Rajanarayana and Yamsani Madhusudan Rao: IJPSN. 2010; 3: 851-859.

18. NG Raghavendra Rao**,** Ashok Yadav and Upendra Kulkarni: IJCPR. 2010; 2:34-42

19. Howida K. Ibrahim, Ahmed MA, Mahmoud MG, Drug Discoveries & Therapeutics. 2010; 4(2):100-108

20. Durga Pattanayak, Subas SD and Ulna LN: Int j pharm sci tech. 2011; 6(1):44-63.

21. Chirag KP and Priti PP, IJPRD, 2011; 3(7): 16 – 23.