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(Review Article)

A Review on Bi-layer Tablets

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ABSTRACT

The fact that drug delivery systems with altered geometric configurations (particularly tablets) have shown promising results in drug delivery technology and ease of manufacturing is an added advantage to the pharmaceutical industry. It has been elucidated that geometrically altered drug delivery systems, especially bilayered tablets, have provided various advantages to drug delivery technology. The ease of manufacture of these systems adds further benefit in terms of cost. Several pharmaceutical companies are currently developing bi-layer tablets for a variety of reasons: patent extension, therapeutic, marketing , to reduce capital investment, etc. Bi-layer tablets have been developed to achieve controlled delivery of different drugs with pre-defined release profiles. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and 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.The present review summarises various aspects of Bilayer tablets.

Key words: Geometric configurations, Bilayer tablet, Combination drugs, Incompatible

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). Bilayer tablet technology is improved beneficial technology to overcome the shortcoming of the single layered tablet.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. 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[1].

The manufacture of bilayer tablets, produced by sequential compaction of loose powder layers has become an increased interest within the pharmaceutical industry due to tailored release of active ingredients that may be obtained. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets.

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, requiring complicated tablet architectures as well as patient-friendly administration which pose serious challenges to the pharmaceutical scientists/engineers.

General Properties of Bi-Layer Tablet Dosage Forms

- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.

- Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Advantages of Bi-Layer Tablet Dosage Forms

- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Cost is lower compared to all other oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallowing with least tendency for hang-up.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

Disadvantages of Bi-Layer Tablet Dosage Form

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- 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.
- Bitter testing drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.

MANUFACTURE OF MULTILAYER TABLETS

The manufacture of multilayer tablets has been successful for over 50 years[2]. New machine designs developed during the late 60s have made it possible to check the weight of individual layers by sampling without stopping the machine, providing in-process control facilities to ensure correct dosing[3]. However, despite this, a considerable amount of expertise is still required to formulate these tablets and to ensure consistent manufacture to satisfy regulatory requirements [4].One problem that causes great concern is the delamination of layered tablets[5], which has become a more obvious problem with the increase in compression speed on modern high-speed rotary machines. The formulations used for each individual layer should be compressible and compactable on their own i.e. they should show satisfactory reduction in volume and form mechanically strong, coherent solid bodies. Under this assumption the interface between the layers should weld together during compaction and strong adhesion forces should hold the layers together after tablet ejection. However, this is not always the case, and as compressibility and compactability of the individual layers should not be the cause for delamination, other physical mechanisms need to be identified that can explain the problems with delamination that have hampered recent developments of layered tablets[6].

Bilayered tablets have proven to be effective in delivering drugs that require a loading dose followed by a maintenance dose[7]. Commonly, in bilayered systems, one layer contains a quantity of drug for conferring immediate release, while the second layer contains a quantity of drug for extended release. The rapid release layer disintegrates immediately after administration while the matrix layer remains intact during the passage of drug through the gastrointestinal tract. The matrix erodes in a controlled fashion in order to maintain blood levels. Two drugs may also be incorporated into this delivery system for variable release profiles. A bilayered tablet for the delivery of propranolol hydrochloride was developed by Patra and co-workers. These tablets were comprised of an immediate release layer and a sustained release layer. Sodium starch glycolate was employed as the superdisintegrant in the rapid release layers of various formulations, while the polymers Eudragit® RL, Eudragit® RS and EC were utilized in the sustained release layers. Drug release studies illustrated that there was an initial burst release that delivered the loading dose while the rest of the drug was released over 12 hours in a sustained manner [8]. The same concept has been demonstrated in a patent by Kim and co-workers where the system provided release of two drugs in different manners. The controlled release layer delivered metformin while the rapid release layer delivered glimepiride. The controlled release layer was made up of a mixture of hydrophobic and hydrophilic polymers, while the immediate release layer was composed of a disintegrant and glimepiride[9]. This further emphasizes the positive function of these systems in treating chronic conditions such as hypertension and diabetes.Nirmal and co-workers developed a bilayered tablet containing atorvastatin calcium for immediate release and nicotinic acid for extended release for the concurrent treatment of hypercholesterolemia. It has been shown that the combination of these two drugs results in an important reduction of low density lipoprotein cholesterol as well as desirable variations in high density lipoprotein cholesterol[10]. Methocel® K100M was employed as the polymeric matrix for nicotinic acid and the immediate release layer containing atorvastatin calcium was formulated using super disintegrant, croscarmellose sodium. Drug release studies were performed over 12 hours and the results indicated that these tablets were successful in delivering two types of drugs concurrently[10]. This bilayered system design may thus be valuable for future application in the successful treatment of hypertension.

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[11].

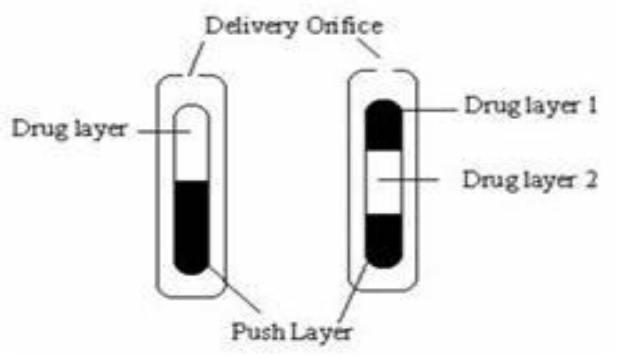

Fig. 1: Bilayer and trilayer OROS Push pull technology

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, then osmotic push layer followed by a semi permeable membrane, drilled with an exit orifice (Fig.2)[11].

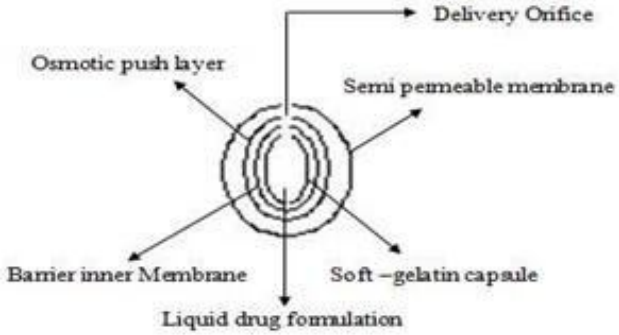

Fig 2: L – OROS tm technology

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 (Fig.3)[11].

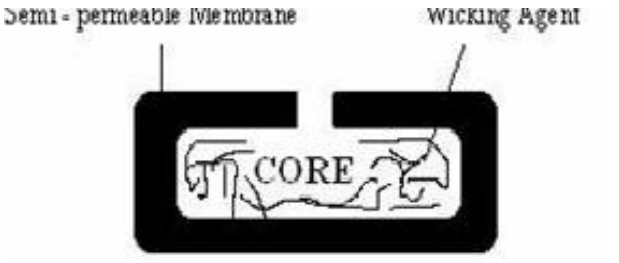

Fig 3: EN SO TROL Technology

DUROS Technology

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(Fig.4)[12].

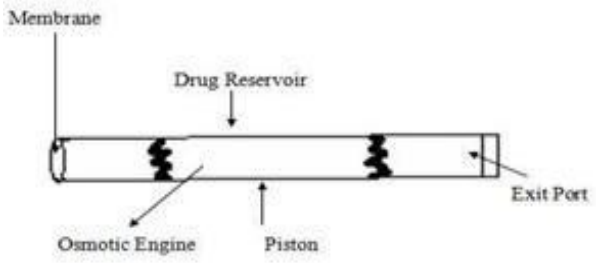

Fig 4.: The DUROS technology

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 tabletting process can provide an immediaterelease 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.

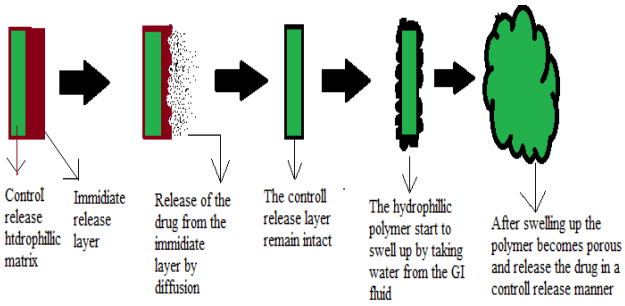

Fig 5: DUREDAS technology consists of control release and immediate release layer.

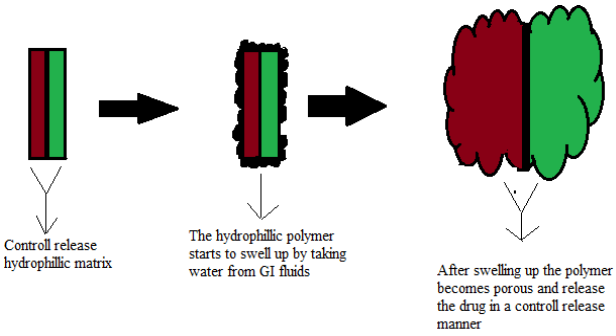

Fig 6: DUREDAS technology consist of two control release layers.

Benefits offered by DUREDAS™ Technology

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

The DUREDAS™ system can easily be manipulated to allow incorporation of two controlled release formulations in the bilayer. 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 bilayer 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.

RoTab Bilayer [13]

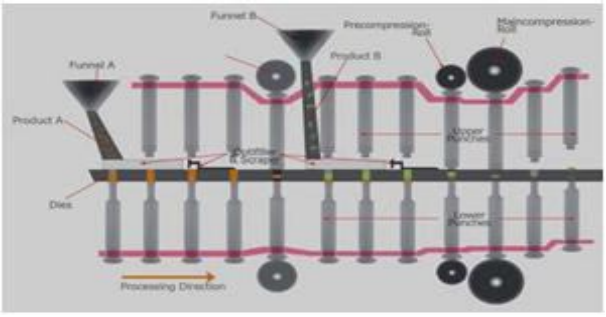

Fig 7: RoTab Bilayer

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.

Basic Technique

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

RandD Modified Technique

Basic package for galenical RandD on the RoTab Bilayer. Contains evaluation and graphical visualization of instrumented measuring points, as compression 1st layer pre main compression and ejection force on a 15" touchscreen display. Punch tightness control can be selected as an additional alarm function. Upgrade to RandD Plus is possible at any time.

RandD Plus

Contains all functions of Basic and RandD plus the possibility to evaluate and visualize the following special instrumentations on the 15" touch-screen display Punch tightness control, tablet scraper force and display of force displacement. With RandD Plus the RoTab Bilayer sets new standards in tabletting technology.

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, 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 [15].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[14].

SMALL-SCALE BI-LAYER

a) 5 KN First Layer Tamping Force.
b) 40 KN Precompression Force.
c) 80 KN Main Compression Force.
d) Single-Layer Conversion Capability.

BI-LAYER APPLICATION[16]

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.

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

ADVANTAGES[17,18]

a)Flexible Concept.
b) Bi-Layer execution with optional single-layerconversion kit.
c) Exchangeable turret.
d) Turret sizes for product development, scale-up, andmid-range production.
e) Full production capability in a scale-up machine.
f) Self-contained, fully portable design.
g) Fast and Easy Changeover.
h) Internal turret lift device for extreme simplicity inturret removal and installation.
i) Clean compression zone with quick-disconnect design.

QUALITY AND GMP-REQUIREMENTS[19,20]

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

- Preventing capping, separation of the two individual layers that constitute the bi-layer tablet.
- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Accurate and individual weight control of the two layers these requirements seem obviousbut are not as easily accomplished as this article aims to demonstrate.
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) 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 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, pre -compression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.

LITERATURE REVIEW OF BILAYER TABLETS

Chinam Niranjan Patra et al., 2007 employed water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustained action of propranolol hydrochloride. Bilayer tablets showed an initial burst effect to provide the loading dose of the drug, followed by sustained release for 12 h, indicating a promising potential of the propranolol hydrochloride bilayer tablet as an alternative to the conventional dosage form.

Girish S.Sonar et al., 2007 reported that tablets of rosiglitazone maleate were buoyant for up to 8 h in the human stomach. The floating ability of the tablets was studied by gamma scintigraphy.

Bhavesh Shiyani et al., 2008 repoted that metoclopramide hydrochloride gets degraded when prolonged contact with acidic NSAID i.e., ibuprofen .so Bi-layer tablet technology was suitable for preventing direct contact of these two drugs and thus to maximize the efficacy of combination of two drugs for treatment of migraine.

Atram SC et al., 2009 optimized bilayer tablet for antihypertension patients using Metoprolol succinate and Amlodipine besylate . In this study a 3^2 factorial design was employed in formulating bilayer tablet with individual release layer .The main effect and interaction terms were quantitatively evaluated using this mathematical model. The ANNOVA showed the predetermined effect of both the dependant and independent variable in both the cases.

Remya P.N et al., 2010 developed a robust formulation of Bi-layer tablets of Ibuprofen and Methocarbamol, an alternative to the currently available conventional tablets using Povidone k-30 as binder by wet granulation method.

Yamsani Madhusudan Rao et al., 2010 reported that release of the drug from the matrix tablets containing hydrophilic polymers generally involves factors of diffusion. In this study Hydroxyl propyl methyl cellulose (HPMC K 4M) and Sodium Carboxy Methyl cellulose (SCMC) were used as the matrix forming polymers.

Dr. S. D. Barhate et al., 2010 investigated that the Response Surface Methodology involving multiple response optimization was found to be a suitable tool to design and optimize controlled release pharmaceutical formulations.

MC Gohel et.al., 2010 reported that the combination of conventional paracetamol with MR diclofenac sodium can provide analgesic and anti-pyretic effect. This combination formulation is also beneficial for the patients who are on multiple drug therapy requiring both anti-pyretic and analgesic activity.

P.Dinesh Kumar et al., 2010 has prepared a bilayer gastro retentive tablets of ranitidine using direct compression technology. In this study they optimized the type and concentration of polymer to give maximum retentive effect with good drug release profile. HPMC-K-100, HPMC-K-4M, HPMC-E-15, CARBOPOL-934 were used. Based on the performance with respect to buoyancy, lag time, floating time and the release characteristics the best formulation was selected and was taken up for animal studies as approved by Institutional Animal Ethical Committee.

Shiva Kumar Yellanki et al., 2010 describes the development of an intragastric drug-delivery system for Amoxicillin trihydrate for treatment of Helicobacter pylori. In this study Calcium carbonate was incorporated as a gas-generating agent. The tablets were evaluated and effect of polymers,diluents on drug release profile, floating properties were investigated. It is evident that the polymer with lower viscosity HPMC K4M was found to be beneficial than higher viscosity(Carbopol 971P) in improving the release properties facilitating local action due to prolonged residence time in stomach.

Ashish A Pahade et al., 2010 developed bilayer sustained release tablet of Isosorbide mononitrate, an anti-anginal organic nitrate vasodilator. The tablets were prepared by wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, and polyox were used, the influence of hydrophilic and hydrophobic polymer and granulation technique was studied. The *in vitro* drug release characteristics were studied in distilled water for a period of 24hr.

MA Naeem et al., 2010 found that Microencapsulation based on phase separation by temperature change was employed to formulate and separate microparticles of tramadol HCl (TmH) and acetaminophen (AAP) microparticles which were further compressed as bilayer tablets.

R.Natarajan et al., 2011developed a stable formulation of Antihypertensive drugs of the Telmisartan and Hydrochlorothiazide immediate release Bilayer tablets. In this study formulations with higher proportion of sodium starch glycolate showed satisfactory physical parameters, and better in-vitro release when compared with the release profile of innovator product.

Kiran muscle et al., 2011 investigated that microcrystalline cellulose is a compressible hydrophilic excipient and also works as auxillary disintegrant, hence MCC granules were added extragranularly. The disintegrating time of paracetamol can be tailored by optimizing quantinty of PEG

6000, povidone and MCC. Use of HPMC provided sustained release of diclofenac.

Vinay Mishra et al., 2011 reported that Candesartan cilexetil and captopril loaded bilayered tablet having the potential for the abatement of kimmelstiel wilson syndrome due to its unique release patterns as candesartan cilexitel releases very fast on the other hand captopril is released slowly from the bilayered tablet fulfilling the entire physical requirement.

Subas C. Dinda et al., 2011 reported that developing suitable bilayer tablets using valsartan as an immediate release layer and metformin HCl as a sustained release could be a potential fixed dose combination form for the simultaneous treatment of hypertension and diabetes

S. Mohideen et al., 2011 reported that Bilayer tablet prepared by wet granulation method using optimized formula was found to be best suited method for fixed dose combination of sustained release Metformin Hydrochloride and immediate release Atorvastatin calcium

Tiwari et al., 2011 suggested that selection of proper amount of superdisintegrant sodium starch glycolate and HPMC K 100 can be useful tool for providing the loading dose of the drug aceclofenac sodium , followed by sustained release of drug for 24 hrs.

G.Vinoth Kumar et al., 2011 employed Wet granulation process for the formulation of both layers to develop a robust formulation of Bi-layer tablets of Cefixime trihydrate and Dicloxacillin sodium using povidone k-30 as binder.

R.T.Jadhav et al., 2011 has done Formulation and evaluation of bilayered tablet of Piracetam and Vinpocetine . Wet granulation process was used for the formulation of both layers and the final film coated tablets were evaluated. Among the formulation, tablets of batch V2 of vinpocetine and batch P3 of piracetam was taken as optimized formula due to its higher rate of dissolution

S. Jayaprakash et al., 2011 repoted that that diffusion is the predominant mechanism of drug release and follows first order kinetics in case of Bilayer tablets of Amlodipine besilate (IR) Metoprolol succinate (SR).

Jain Jitendra et al., 2011 developed a bilayer-floating tablet (BFT) for Indomethacin using direct compression technology .The present research was carried out using PEG-6000 as disintegrant and ac-di-sol for fast release layer. The modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. Which is evident from an initial burst of loading dose of drug, followed by sustained release for 24 hrs. Solid dispersion can be prepared by mixed solvency concept, which can increase the dissolution rate of drug to ensure quick absorbtion**.**

Swamy P.V et al., 2011 used ethyl cellulose as an impermeable backing layer to release the drug in a unidirectional way towards the mucosa, thus avoiding loss of drug due to wash out by saliva during the preparation of buccal bilayer tablets

Preeti Karwa et al., 2011 reported that using HPMC K100M as the release retarding polymer solved the sleep complaints and prolonged the total sleep duration . In this study biphasic release was designed to mimic initial dosing while the controlled release of drug maintains a plasma concentration for a longer duration of time.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. The manufacture of bi-layer tablets, produced by the sequential compaction of loose powder layers has recently become of increased interest within the pharmaceutical industry due to the tailored release profiles of active ingredients that may be obtained. Bilayered tablets have proven to be effective in delivering drugs that require a loading dose followed by a maintenance dose

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