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[Review article]

Advance Techniques of Bilayer tablet: A Review

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ABSTRACT

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. Bi-layer tablets 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. 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. This article explains why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach to producing bilayer tablet under GMP-condition. Especially when in addition high production output is required.

Key Words: Bilayer tablet, modified tablet press, Individual layer weight control, DUROS technology.

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 frequency of 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 for sustained release tablet in which one layer is loading dose or immediate release and second layer is maintenance dose or sustained release. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API_S by physical separation and to enable the development of different drug release profiles (immediate release with sustained release). Bilayer tablets offer definite advantages over conventional release formulation of the same drug. Several pharmaceutical companies are currently developing bi-layer tablets. The main objective of developing these systems is to increase the safety of a product to extend its duration of action and decrease side effects of drugs. These systems have more flexibility in dosage form design than conventional dosage form.[1-8]

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Multi-layer tablet dosage forms are designed for variety of reasons:[9-13]

- To control the delivery rate of either single or two different active pharmaceutical ingredient (s).
- 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).
- 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.
- To administer fixed dose combinations of different APIs, prolong the drug product life cycle, fabricate novel drug delivery systems.

Advantages of the bi-layer tablet dosage form

- 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, physical 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

General properties of Bi-Layer Tablet Dosage Form

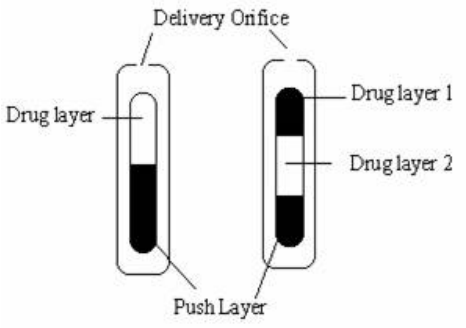
- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing
- Should have the chemical and physical stability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

VARIOUS TECHNIQUES FOR BILAYER TABLET

OROS® push pull technology:[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.

Fig. No.1: Bilayer and Trilayer OROS Push Pull technology

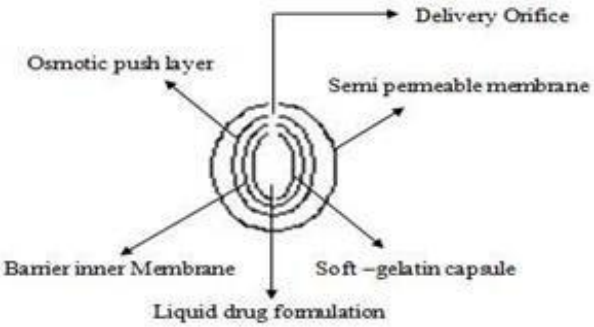


L-OROS tm technology[12]

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 (Fig.2).

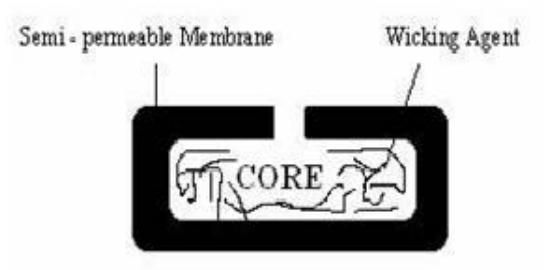
Fig. No. 2: L – OROS tm technology.



EN SO TROL technology:[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 (Kale et al.,2011.

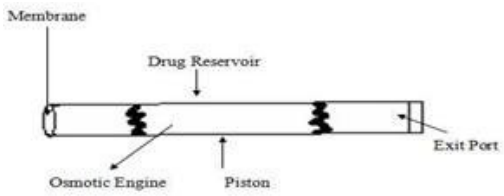
Fig. No. 3: EN SO TROL Technology



DUROS technology:[13]

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. No. 4: 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 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.

Benefits offered by the DUREDAS™ technology include:

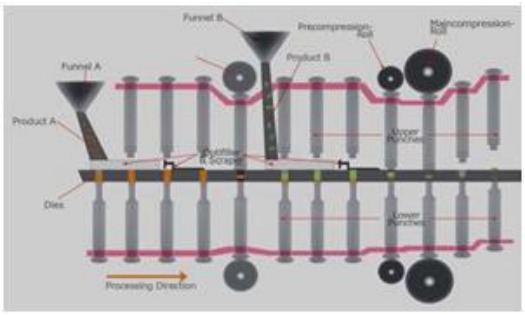
- Bilayer tableting technology.
- Tailored release rate of two drug components.
- Capability of two different CR formulations combined.
- Capability for immediate release and modified release components in one tablet.
- Unit dose, tablet presentation.

The DUREDAS™ system can be easily 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.

RoTab Bilayer[14]:

Fig.5: 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 automatically dosing regulation by compression force and adjustment of die table and Optifiller speed. Optional independent hardness regulation available.

R&D MODIFIED TECHNIQUE

Basic package for galenical R&D 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 touch-screen display. Punch tightness control can be selected as an additional alarm function. Upgrade to R&D Plus is possible at any time.

R&D PLUS

Contains all functions of Basic and R&D plus the possibility to evaluate and visualize the following special instrumentations on the touch-screen display Punch tightness control, tablet scraper force and display of force displacement. With R&D Plus the RoTab Bilayer sets new standards in tableting 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 cross contamination. 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.

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.

Instrumentation

Tamping force
Precompression force
Main compression
Ejection force

BI-LAYER APPLICATION

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)

Instrumentation
Precompression force
Main compression force
Ejection force

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.

Bi-layer tablets: quality and GMP-requirements is as follows: [17, 18]
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 and 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.

Bilayer Tablets: Limitations of the Single Sided Press:[19-22]
Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression). The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer-separation occurs when the tablet is produced. This is the simplest way of producing a bilayer tablet. The limitations of such single-sided press are:

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.

The fact that it is not possible to monitor and control the weight of the individual layers raises the question whether we can consider this production GMP? Individual layer-weight control on a single-sided press requires some form of measurement of the first layer and of the total tablet. The first control loop indirectly monitors weight and controls the fill depth of the first layer. The second loop indirectly monitors the total tablet weight, but adjust only second-layer fill depth. In general, compression force is used to monitor tablet- or layer-weight. But to do so it is necessary to apply a compression force to the first layer before adding the second layer-powder. To apply a compression force to the first layer prior to adding the second layer, it is necessary to use two separate powder feeders with a compression station in-between. This can be achieved on a single-sided press by installing an additional feeder between the pre- and main-compression station. Very often the precompression roller must be reduced to a much smaller size in order to create the space required for the second feeder. Additional limitations of such single sided press are

- Very short first layer-dwell time (*) due to the small compression roller, possibly resulting in poor de-aeration, causes 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.

(*) dwell time is defined as the time during which compression force is above 90% of its peak value.

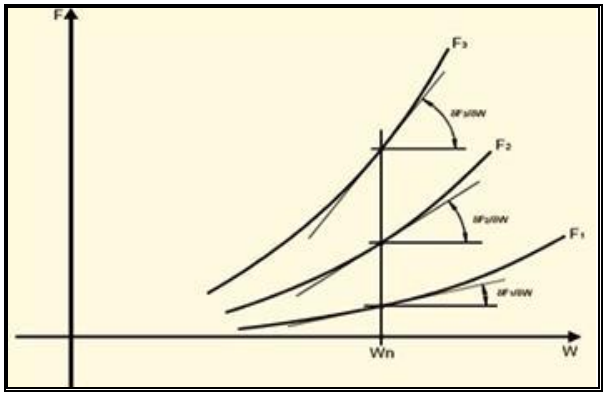
Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation. To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, precompression and main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

Bi-layer tablets

Limitations of "compression force" - controlled tablet presses [9]:

Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed at a too-high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with "compression force measurement". 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 that layer. There exist a typical exponential relationship between the measured peak compression force [F] and layer or tablet weight [W] as indicated in

Fig. No. 6: Forces versus weight sensitivity at different compression force level



This measured peak compression force [F] (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablets and correct the die fill depth when required. The above graph indicates that the sensitivity δF/δW decreases with decreasing compression force (i.e., when the distance between the compression rollers is made greater). This decreasing sensitivity is inherent to an exponential relationship and therefore inherent to the compression force-controlled system. The rate at which the sensitivity decreases depends on the formulation or powder characteristics.

This is the very reason why a compression force control system is always based on measurement of compression force at main-compression and not at pre-compression since a higher compression force is required to obtain sufficient sensitivity, thus allowing a more accurate control. A weight control system based on compression force monitoring is not the best solution for first layer weight control in a bi-layer tableting process. A compression force-controlled system requires a minimal compression force of several hundreds of daN. However, many bi-layer formulations require a first layer compression force of less than 100 daN in order to retain the ability to bond with the second layer.

Above 100 daN, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bi-layer tablet and separation of the two layers. This basic problem, inherent to the principle of compression force monitoring is overcome by using a different weight monitoring system based upon 'displacement'.

"Displacement measurement" as the alternative to "compression force measurement" has the advantage that accuracy increases with reduced compression force. At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at all four compression stages. Weight monitoring based upon 'displacement' also provides increased dwell-time in addition to good bonding between the two layers, with improved and accurate weight monitoring/control of the first layer. A double-sided tablet press with "displacement measurement" is thus the preferred press to produce bi-layer tablets.

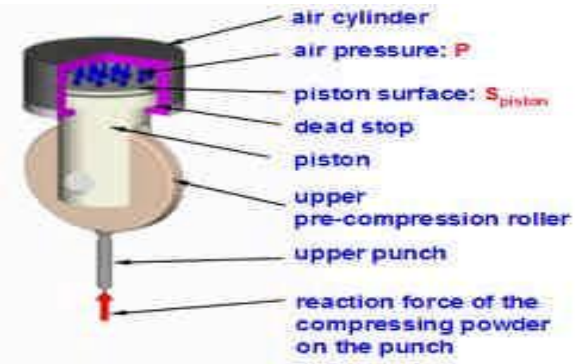
The Courtoy R292F

"Bilayer" tablet press with 'Displacement monitoring':

This double-sided tablet press has been specifically designed and developed for the production of quality bi-layer tablets and provides:

- 'Displacement' weight monitoring/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 two individual layers.
- Increased dwell time at precompression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers.
- A clear visual separation between the two layers.
- Maximized yield.

Fig.7: Pneumatic compensator



Additional important features

The Courtoy-R292F

The R292F can be used for both single-layer double output production and bi-layer single-output tableting. The press is equipped with 'air compensation' on both pre-compression stations for 'displacement'- based tablet weight control as described above. However, the R292F has several extra features specifically designed for the production of bi-layer tablets.

- The R292F has a pneumatically driven ejection cam, allowing the sampling of first-layer tablets for in-line process control and automatic weight recalibration. The required time to sample is extremely short to minimize powder loss. The time delay between sampling and re-calibration is also very short to minimize the length of the control loop.
- One powder is always re-circulated around the die table using a standard feeder with recuperation of re-circulated powder, while the other feeder is a closed type feeder. This closed type feeder is provided with a suitable wear plate to maximize its life expectancy.
- The R292F is equipped with several blow and suction nozzles, located at carefully determined points around the die table. The combined action of blowing and extracting air allows for very specific powder removal, which is vital to the elimination of cross-contamination. At the same time, powder loss is reduced to a minimum.

EVALUATION OF BILAYER TABLET

TABLET THICKNESS AND SIZE:[27-28]

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.

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

UNIFORMITY OF WEIGHT

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

DISINTEGRATION STUDY

Tablet disintegration study was performed for immediate layer of the bilayer tablet as per IP1996. Disintegration time was determined using USP

tablet disintegration tester (ED-2L, Electrolab Pvt. Ltd. Mumbai) in distilled water.

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Bi-layer tablet is suitable for sequential release of two drugs or different release rates of the same drug in one dosage form. Separate two incompatible substances and 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. Low pre-compression forces are necessary to secure interlayer bonding. But at low forces, the compression force control system is not sufficiently sensitive and therefore lacks in accuracy. The use of higher compression forces may rapidly result in separation and hardness problems when compressing bilayer tablet. 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 such as the Courtoy-R292F. 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 and the special attention to reduced interlayer cross contamination risk, provide sufficient hardness make the Courtoy-R292 an excellent bilayer tablet press.

REFERENCES

[1] Chien YW, Fundamentals of controlled-release of drug administration in: J. Swarbrick (Ed.), Novel Drug Delivery System Marcel Dekker, New York, 1982, pp. 465–574.
[2] Buri P, Puisicux F., Doelker E., Benoit JP, Formes Pharma centiques Nouvelles, Ed. Technique et Documentation, Lavoisier, Paris, 1985.
[3] Wilding IR, Coupe AJ, Davis SS, The role of gamma scintigraphy in oral drug delivery, Adv. Drug Deliv. Rev. 1991; 7: 87– 117.
[4] Lee L. Diffusion-controlled matrix systems, in: A. Kydonieus (Ed.), Treatise on Controlled Drug Delivery, Marcel Dekker, New York, 1992, pp. 155– 198.
[5] Peppas NA. Hydrogels in Medicine and Pharmacy, vols. I, II and III, CRC Press, Boca Raton, FL, 1988.
[6] Martindale. The Extra Pharmacopoeia, 31st Ed. The Pharmaceutical Press, London1996, pp. 936–937.
[7] Martin A, Bustamante P and Chun A, Micromeritics, in Physical Pharmacy-Physical Chemical Principles in the Pharmaceutical Sciences, 4th ed., Lippincott Williams and Wilkins, Baltimore 2002, pp. 446–448.
[8] Bogan, R.K. Treatment options for insomnia—pharmacodynamics of zolpidem extended-release to benefit next-day performance. Postgrad. Med. 2008; 120: 161–171.
[9] Aulton ME,. Pharmaceutics – the science of dosage from design, second edition, Churchill Livingstone 2002, 200-206,412,423-439, 575.
[10] Bogda MJ. Tablet compression: Machine theory, design and process troubleshooting.
[11] Encyclopaedia of Pharmaceutical Technology. J. Swarbrick, J. Boylan (eds.). Marcel and Dekker Inc 2 nd edition (2002), 2669-2688
[12] Remington's- The science & practice of pharmacy, 21st edition 2005,vol. 1, 894-896
[13] www.durect.com
[14] http://www.port/ technology.com
[15] www. Flamel. technologies.com
[16] http://www.elan.com/
[17] www.lifeclinic.com
[18] Lachman L, Kanig. J., Theory and Practice of industrial pharmacy, Third edition. Verghase publishing house Mumbai, 1987, 297,66-95,430-453.
[19] Robinson JR, Lee, VH, Controlled Drug Delivery: Fundamentals and Applications 2nd Ed., Marcel Dekker, New York,1987, p.4-36.

[20] Shaikh TK*, Gadhave MV, Jadhav SL, Gaikwad DD,.different techniques of bilayer tablet: A review, International Journal of Universal Pharmacy and Life Science.2012,2.(2).450-460.
[21] Banker S, Gilbert J, Rhodes T. Christopher, Modern Pharmaceutics, Marcel Dekker, Inc.,New York, p.575.
[22] Schaumann W, Pharmacokinetics of isosorbide dinitrate and isosorbide-5-mononitrate,
[23] Int. J. Clin. Pharmacology There Toxicology. 27, 1989, p.445–453.
[24] Abshagen U, Spo ¨rl-Radun S, First data on the effects and pharmacokinetics of isosorbide-5 mononitrate in normal man, Eur. J. Clin.Pharmacol. 19, 1981 p.423– 429.
[25] Hutt V, Bonn R, Fritschi E, Jaeger H, Evaluation of the pharmacokinetics and absolute bioavailability of three isosorbide- 5-mononitrate preparation in healthy volunteers, Arzneim.-Forsch./Drug Res. 19, 1995, p.142–145.
[26] Reiniger G, Blasini R, Bru ¨gmann U, Rudolph W, Toleranzentwicklung hinsichtlich der anti ischamischen Wirkung von Isosorbid dinitratbei regelmassiger, mehrfach taglicher Verabreichung, Herz 9, 1984, p.146– 152.
[27] Herrmann H, Kuhl A, Maier-Lenz H, Influence of the time of dosage of isosorbide mononitrate on objective and subjective angina pectoris parameters,Arzeim.- Forsch./Drug Res. 38, 1988, p.694–698.
[28] Raparla D V and Murthy TE. Formulation and evaluation of oral controlled release Glimepiride matrix tablets. Adv. Phamacol. Toxical. 8, 2007, p.59-62.
[29] The Indian Pharmacopoeia, Vol. 2, 4th Ed. The Controller of Publication, Govt. of India, Delhi, 1996, p.A82-A85.
[30] The United States Pharmacopoeia, United states Pharmacopoeial convention, Inc., Rockville, MD, 2000:1944.

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