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Bilayer Tablet via Microsphere: A Review

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ABSTRACT

The aim of the present work is to develop bilayer tablets containing sustained release microspheres as one layer and immediate release as another layer. The proposed dosage form is intended to decrease the dosing frequency and the combined administration of an anti-diabetic agent. 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. One such approach is using microspheres as carriers for drugs also known as micro particles. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release, but also for targeting of anti-diabetic drugs. Bilayer tablet via microsphere is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Especially when in addition high production output is required. An attempt has been made in this review article to introduce the society to the current technological developments in bilayer and floating drug delivery system.

KEYWORDS

Bilayer tablet, Anti diabetic, Microsphere, Floating drug delivery system.

INTRODUCTION

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced[1]. Diabetes is one of the major causes of death and disability in the world. World Health Organization estimate for the number of people with diabetes worldwide, in 2000, is 171 million, which is likely to be at least 366 million by 2030[2]. Non-insulin dependent (Type 2) diabetes mellitus is a heterogeneous disorder characterized by an underlying insufficiency of insulin.

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This insufficiency results from defective insulin utilization and can be corrected by administration of one or more of the currently available oral hypoglycemic agents[3].Combination therapy have various advantages over mono therapy such as problem of dose-dependent side effects is minimized, a low dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet[4].

Sidney Walter Fox (24 March 1912 - 10 August 1998) was a Los Angeles-born biochemist responsible for discoveries on the origins of life. Fox explored the synthesis of amino acids from inorganic molecules, the synthesis of proteinous amino acids and amino

acid polymers called "proteinoids" from inorganic molecules and thermal energy, and created what he thought is the world's first "protocells" out of proteinoids and water. He called these protocells "microspheres" and they have now been named "protobionts." Fox believed in spontaneous generation of life and suggested that his experiments possessed conditions that are similar to those of primordial Earth. In his experiments, he demonstrated that it is possible to create protein-like structures from inorganic molecules and thermal energy. Dr. Fox went on to create microspheres that he said closely resembled bacterial cells and concluded that they could be similar to the earliest forms of life[5].

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm (1 mm)). Microspheres are sometimes referred to as micro particles.

Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on what material they are constructed of and what size they are.

Polyethylene, polystyrene and expandable microspheres are the most common types of polymer microspheres.

Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immunio precipitation. Proteins and ligands adsorb onto polystyrene readily and permanently, which makes polystyrene microspheres suitable for medical research and biological laboratory experiments.

Polyethylene microspheres are commonly used as permanent or temporary filler. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of colored and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital displays.

Expandable microspheres are polymer microspheres that are used as a blowing agent in e.g. puff ink, automotive underbody coatings and injection molding of thermoplastics. They can also be used as light weight filler in e.g. cultured marble, waterborne paints and crack fillers/joint compound. Expandable polymer microspheres can expand to more than 50 times their original size when heat is applied to them. The exterior wall of each sphere is a thermoplastic shell that encapsulates a low boiling point hydrocarbon. When heated, this outside shell softens and expands as the hydrocarbon exerts a pressure on the internal shell wall.

Glass microspheres are primarily used as a filler and volumizer for weight reduction, retro-reflector for highway safety, additive for cosmetics and adhesives, with limited applications in medical technology.

Ceramic microspheres are used primarily as grinding media.

Microspheres vary widely in quality, sphericity, uniformity, particle size and particle size distribution. The appropriate microsphere needs to be chosen for each unique application[5,6].

Methods of Preparation of Microspheres[7]

1. Solvent removed technique

- Emulsion – solvent evaporation technique.

i) Oil in water (o/w) emulsion solvent evaporation

ii) Water in oil (w/o) emulation solvent evaporation

iii) Water in oil in water (W/O/W) emulsion solvent evaporation

- Emulsion solvent extraction.
- Emulsion solvent diffusion.

2. Coacervation and phase separation technique

- By temperature change.
- By incompatible polymer addition.
- By non-solvent addition
- By salt addition
- By polymer polymer interaction
- By solvent evaporation

3. Cross – linking technique

- Chemical cross linking.
- Thermal cross linking.

4. Polymerization Technique

- Normal polymerization.
- Vinyl polymerization.
- Interfacial polymerization.

5. Spray drying and spray congealing
6. Freeze drying technique
7. Precipitation technique
8. Multi orifice centrifugal process
9. Pan coating
10. Air suspension coating
11. Melt dispersion technique

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. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity[8].

Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). 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. This oral presentation details the major challenges associated with bilayer compression and rational strategy to deliver the desired bilayer tablet performance[9].

Bilayer technique will be used to prepare oral extended release dosage form. Bilayer tablets are those with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner prepared either by wet granulation/ direct compression/ melt granulation methods etc[10].

Advantages of Bi-layer Tablets[11, 12]

1. Bi-layer execution with optional single layer conversion kit.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odor and taste can be masked by coating technologies.
5. Flexible concept.
6. Offer greatest precision and the least content uniformity.
7. Easy to swallow with least hang up problems.
8. Fit for large scale production.
9. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to

maximize the efficacy of combination of two drugs.

10. Bi-layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release.
11. Expansion of a conventional technology.
12. Pro/spective use of single entity feed granules.
13. Separation of incompatible components.
14. Patient compliance is improved leading to improve drug regimen efficiency.

Disadvantages of Bi-layer Tablets[12, 13]

1. Adds complexity and bi-layer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Imprecise individual layer weight control.
4. Cross contamination between the layers.
5. Difficult to swallow in case of children and unconscious patients.
6. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.
7. Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability.

General properties of bi-layer tablet dosage forms[13]

1. It should have graceful product identity free of defects like chips, cracks, discoloration, and contamination.
2. Should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.
3. Should have physical and chemical stability.
4. The bi-layer tablet must release drug in an expectable and reproducible manner.
5. Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.

Various Techniques for Bilayer Tablets

Oros ® Push Pull Technology[12, 14, 15, 16]

This system consist of mainly two or three layer among which the one or more layer are necessary for 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 comprise 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.

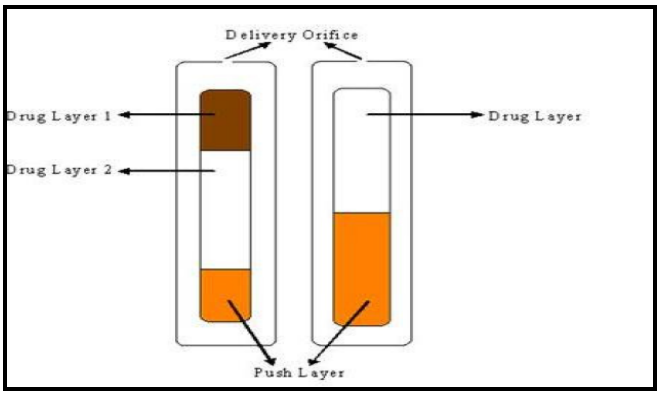

Figure 1: Bilayer and trilayer OROS Push pull Technology

L-OROS Technology[6, 9, 14, 15]

This system used for the solubility concern 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 then a semi permeable membrane, drilled with an exit orifice (Fig. 2).

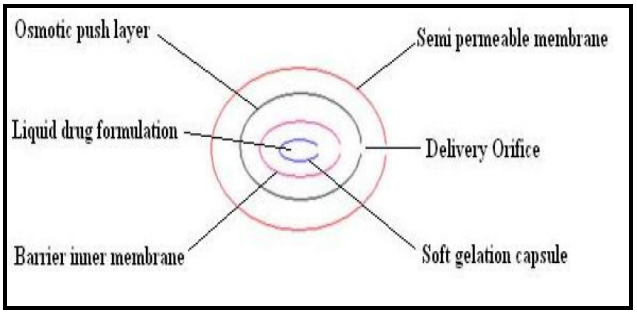

Figure 2: L-oros tm technology.

***DUROS Technology*[6, 9, 16, 17]**

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 minuscule drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form.

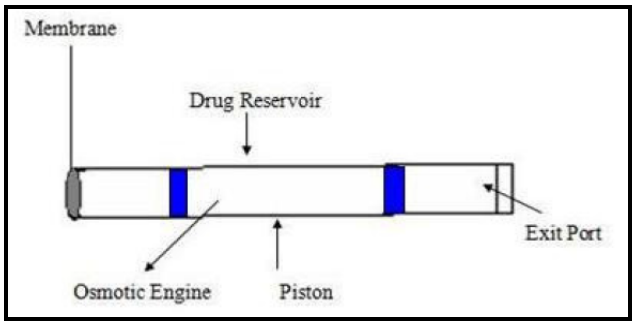

Figure 3: DUROS technology.

***Elan Drug Technologies' Dual Release Drug Delivery System*[14]**

(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 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

1. Bilayer tabletting technology.
2. Modified release rate of two drug components.
3. Ability of two different CR formulations combined.
4. Ability 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 bi-layer. Two different release rates can be achieved from each side. In this way greater persistence 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 is initially engaged 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.

***EN SO TROL technology*[14, 15]**

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. 4).

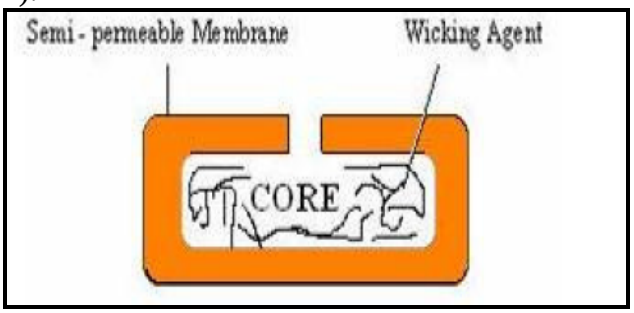

Figure 4: EN SO TROL technology.

Bilayered Tablets: Quality and GMP Requirements[12, 20]

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bilayer tablet 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.
- Precise and individual weight control of the two layers.

Types of Bi-Layer Tablet Presses

- Single sided tablet press.
- Double sided tablet press.
- Bi-layer tablet press with displacement.

A. Single Sided Tablet Press[12, 14]

The simplest design is the single sided press with both chambers of the double feeder separation from each other. Each chamber is gravity or forced fed with different powder, thus producing the two individual layers of the tablets. When the die passes under the feeder, it is first loaded with the first-layer powder followed by the second layer powder. Then the intact tablet is compressed in one or two steps.

Limitation of Single Sided Press[12]

- No weight monitoring / control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly ensuing in poor deaeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the result 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.

B. Double Sided Tablet Press or "Compression Force" Controlled Tablet Presses

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 four compression stages before being ejected from the press. Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance tablet and correct the die fill depth when mandatory.

Advantages[12]

1. Displacement weight monitoring for accurate and independent weight control of the individual layer.
2. Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
3. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
4. Maximum prevention of cross contamination between two layers.
5. A clear visual separation between the two layers.
6. Maximized yield.

Limitations[21]

Separation of the two individual layers is due to insufficient bonding between the two layers during final compression of 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. Bonding is too restricted if first layer is compressed at a 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 of the double sided tablet presses with automated production control use compression force to monitor and control tablet weight. Compression force control system is always based on measurement of compression force at main compression but not at pre-compression.

C. Bilayer Tablet Press with Displacement

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 operation point,but depends on the applied pre-compression force. In fact the lower the pre-compression force, the more the monitoring control system and this ideal for good interlayer bonding of the bi-layer tablet. The upper pre-compression roller is attached to an air-piston which can move up and down in air cylinder. The air pressure in the cylinder is set as a product parameter at initial product set-up and is kept at a constant value by the machine's control system. This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller are pushed downwards against affixed stop. The lower pre-compression roller is mounted on a yoke and its vertical position can be adjusted through the control system by means of a servomotor. The position of the lower pre-compression determines the precompression height. At every pre-compression the upper punch hits the upper roller and is initially pushed downwards into the die. As the lower punch is pushed upwards by the lower roller the power is being compressed, while the exerted compression force increases. At a certain point the reaction force exerted by the power on the upper punch equals the force exerted by the air pressure on the piston. The punch has to continue its way under the roller because the torrent is spinning.

Advantages[14, 21]

- 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.
- Provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross contamination between the two layers.
- Clear visual separation between the two layers and maximized yield.

Various Aspects Used in the Bi-Layer Tablet[20]

Floating Drug Delivery Systems (FDDS)[22]

From the formulation and technological point of view, the floating drug delivery systems are significantly easy and consistent approach in the development of Gastro retentive dosage forms (GRDFs).

Approaches to Design Floating Drug Delivery System

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

Intra Gastric Bi-Layered Floating Tablets

These are also compressed tablet contain two layers i.e.,

i) Immediate release layer ii) Sustained release layer.

Multiple Unit Type Floating Pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swell able membrane layer (Fig. 5). When the system is immersed in dissolution medium at body temp, it sinks at

once and then forms swollen pills like balloons, which float as they have lower density.

Evaluation of Bilayer Tablets[23, 24]

Thickness of Tablets

Thickness and diameter is measured using a calibrated dial caliper. Three tablets of the formulation are picked randomly and thickness is measured individually.

Hardness of Tablets

Hardness is measured using Monsanto hardness tester. For each batch three tablets are tested.

Friability

Twenty tablets are weighed and placed in the Roche friabilator and apparatus is rotated at 25 rpm for 4 minutes. After revolutions the tablets are deducted and weighed again. The percentage friability will measured using the formula,

% F = {1-(Wt. /W)} x 100

Where, % F = Friability in percentage

W = Initial weight of tablet

Wt. = Weight of tablets after revolution

Weight Variation

Twenty tablets are randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets is calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in and none deviate by more than twice the percentage.

Drug Content

The assay of the drug content is carried by weighing ten tablets and calculated the average weight. Then the tablets are triturated to get a fine powder. From the resulting weighed accurately about 155 mg of the powder (equivalent to 100 mg) of metformin hcl is taken, shake with 70 ml of water for 15 minutes, dilute to 100 ml with water and filter. Dilute 10 ml of the filtrate to 100 ml with water. Further dilute 10 ml to 100 ml with water and measure the absorbance at the maximum at about 233 nm.

Buoyancy Determination

The time taken for dosage form to emerge on surface of medium is called floating lag time, duration of time by which the dosage form constantly emerges on surface of medium is called Total floating time (TFT).One tablet from each formulation batch is placed in USP type II dissolution apparatus containing 900 ml 0.1 N HCl dissolution medium using paddle at a rotational speed of 75 rpm. The temperature of medium is maintained at 37° ± 2°c. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium will be noted.

Swelling Study

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

Swelling study = wet weight – dry weight/ dry weight X 100

In-Vitro Drug Release Study

Dissolution of the tablet of each batch is carried out using USP type II apparatus using paddle. 900 ml of dissolution media is filled in a dissolution vessel and the temperature of the medium are set at 37° ± 2°c. one tablet is placed in each dissolution vessel and the rotational speed of paddle is set at 50 rpm.The 10 ml of sample is withdrawn at predetermined time interval for 12 hours and same volume of fresh medium is replaced. The samples are analyzed for drug content against dissolution media as a blank at 233 nm using double beam UV visible spectrophotometer.

CONCLUSION

Bi-layer tablet quality and GMPrequirements can vary widely. In the present study, bilayer tablets of metformin with pioglitazone are

prepared with modified direct compression techniques with substantial result in drug release study. Thus the formulations may prove to be potential candidate for multiple unit delivery, may result in new therapeutic possibilities with substantial benefit to the patient. These bilayer tablets mainly prepared for reduction of lag time and may also increase the bioavailability of the drugs by utilizing the drug to full extent avoiding unnecessary high plasma level. 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.

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