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THE FORMULATION AND EVALUATION OF BILYAER TABLET

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ABSTRACT

In this research a bi-layer tablets used to deliver the two different drugs having different release profile. These tablets are used to deliver the loading dose and maintenance dose of the same or different drug. These kind of tablets are mainly used in combination for modified release.

Bi-layer tablets are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.

Bilayer tablet is the novel technology for the development of controlled release formulation. Developing a combination of two or more active pharmaceutical ingredients in a single dosage form is known as a bilayer tablet. Bilayer tablet is more suitable for gradual release of two active ingredients in combination. Bi layered tablet technology helps in separating the two incompatible substances in which one layer is immediate release as loading dose and second layer is controlled/sustained release as maintenance dose. Two incompatible drugs can also be formulated into a bilayer tablet by adding an inert intermediate layer.

INTRODUCTION

A tablet is a pharmaceutical oral dosage form (OSD). Tablets may be defined as the solid unit dosage form of medicament or medicaments with suitable excipients and prepared either by molding or by compression. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. Compression of powdered, crystalline, or granular active materials (API) form the tablets, alone or in combination with certain excipients as required, such as binders, disintegrants, sustained release polymers, lubricants, diluents, flavours and colorants.

- Bi-layer tablets are used to deliver the two different drugs having different release profile.
- Bi-layer tablets are used to deliver the loading dose and maintenance dose of the same or different drug.
- Bi-layer tablets are mainly used in combination for modified release.

- Bi-layer tablets are used for bi-layer floating tablets in which one layer is floating layer another one is immediate release layer of the drug.

Advantages of the bilayer tablets

- Bi-Layer execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odor and bitter taste can be masked by coating technique.
- Flexible Concept.
- 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.
- Easy to swallowing with least tendency for hang-up.
- Suitable for large-scale production.

Disadvantages of bi-layer tablets

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

Types of bi-layer tablet presses

- Single sided tablet press.
- Double sided tablet press.
- Bi-layer tablet press with displacement
- Multilayer compression basics.

MATERIALS AND METHODS

For Glimepiride: 2 mg of Glimepiride to be prepare by Dry granulation method by using polymer in a different ratio. Drug and polymer will mix homogenously then lubricant and filler will added. All ingredients will mix and weigh accurately and compress in tablet punching machine in low compression force.

For Metformin HCL: The tablet contains 250 mg of Metformin will prepare by wet Granulation method by using polymer in a different ratio. All ingredient should passed through sieve mesh no:

40 separately. Drug and polymer shall be mix homogenously then Lubricant and filler shall added. All ingredients shall mix and weigh accurately and compress in a tablet-punching machine.

S. No.	Material Required
1	Metformin hydrochloride
2	Glimepiride
3	Acetone
4	Ethanol
5	Methanol

Evaluation Parameters:

Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules determined by the funnel method. Accurately weighed powder blend take in the funnel. Height of the funnel adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend allowed to flow through the funnel freely on to the surface. Diameter of the powder cone measure and angle of repose calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose; h = height in cm; r = radius in cm

The angle of repose used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of powder, previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = weight of powder / Bulk volume.

$$D_b = M / V_0$$

M = mass of the powder; V_0 = bulk volume of the powder.

Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder Weigh accurately 25 g of powder, which previously passed through 22# sieve and transferred in 100 ml graduated

cylinder of tap density tester which operate for fixed number of taps until the powder bed volume has reached a minimum, thus calculated by formula. Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_t)$$

M = mass of the powder; V_t = tapped volume of the powder.

Weight variation: According to IP 1996, 20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The individual weight was then compared with the average value to find the deviation in weight.

Sr. No	Average weight of tablet	% Deviation
1	80mg or less	10
2	More than 80mg but less than 250mg	7.5
3	250 More	5

Hardness

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed, a pointer rides along a gauge in the barrel to indicate the force.

Friability

Pre-weighed tablets (20) were placed in Roche Friabilator and were subjected to 100 revolutions at 25rpm for 4 minutes at a height of 6 inches. The tablets were dedusted and reweighed. A loss of less than 1% in weight is generally considered acceptable. It is calculated by the formula.

$$\text{Friability \%} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness

The thickness of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm. (n=3)

FT-IR studies

Infrared spectrum was taken for the metformin hydrochloride and glimepiride tablet. FT-IR studies was carried by KBr disk method using computer mediated Fourier transformed infrared spectroscopy (FTIR) .

Content Uniformity test of bi-layer tablets

Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 20mg of metformin hydrochloride and glimepiride was weighed and dissolved in 100ml of pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, the absorbance was measured at wavelength 276 nm using double beam UV-Visible spectrophotometer (IP, 2007). Content uniformity was calculated using formula % Purity = 10 C Absorbance of unknown (Au)Absorbance of Standard (As) Where, C – Concentration

Swelling study

The swelling properties and the erosion characteristics of tablets were evaluated by determination of the percentage of hydration and matrix erosion or dissolution (DS). The percent values were calculated according to the following equations:

$$\% \text{ hydration} = \frac{(W2-W1)}{W2} \times 100 \qquad DS = \frac{(W1-W3)}{W1} \times 100$$

Each tablet was weighed (W1) and immersed in a acidic buffer at pH 1.2 for predetermined times (0, 6, and 12 h). After immersion, excess surface water was removed from the tablets using filter paper and weighed (W2). The swollen tablets were dried at 60 °C for 24 h in an oven and kept in a desicator for 48 h prior to reweighing (W3). This experiment was performed in triplicate.

***In-Vitro* Disintegration Time**

Disintegration test was done in tablet disintegration apparatus. The tablet is placed in a basket in a buffer medium. Time is noted when the tablet is completely dissolved in the basket. This time was taken as disintegration time.

***In-Vitro* Dissolution study**

Drugs release studies were carried out in a dissolution test apparatus using a specified volume of 900 ml of dissolution media maintained at 37°C ± 0.5°C. The tablet was directly placed in the medium and immediately operates the apparatus at specified rate within the time interval specified (1hr, 2hr, 4hr, 8hr & 12hr) withdraw a specimen from zone midway between the surface of the dissolution medium and the top of the rotating paddle not less than 10mm from the vessel wall and same volume of fresh medium is replaced each time. The samples are filtered and from the filtrate 1 ml was taken and diluted to 10 ml. These samples were analyzed, and further calculation was carried out to get drug release.

Drug release kinetics

Model dependent methods are based on different mathematical functions, which describe the release profile. Once a suitable function has been selected, the release profiles are evaluated depending on the derived model parameters. The data obtained from *ex vivo* permeation studies were plotted in different models of data treatment as follows;

- Zero Order model
- First Order model
- Higuchi‟s Model
- Korsmeyer-Peppas model

- ***Zero order kinetics***

It can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc. In its simplest form, zero order release can be represented as:

$$Q_0 - Q_t = K_0 t$$

Where, Q_t is the amount of drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero-order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug permeation studies were plotted as cumulative amount of drug released *versus* time.

- ***First order kinetics***

It can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\text{Log } C = \log C_0 n K_t / 2.303$$

Where, C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of nK/2.303.

- ***Higuchi's Model***

This model expected to pronounce drug release from a matrix system. Primarily regarded for planar systems, it was then extended to different geometrics and porous systems. This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible), (iii) drug particles are much smaller than system thickness, (iv) matrix swelling and dissolution are negligible, (v) drug diffusivity is constant, and (vi) perfect sink conditions are always attained in the release environment.

Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion. Simplified Higuchi equation is following;

$$Qt = KH\ (t)\ 0.5$$

Where, Q_t is the amount of drug released in time t and KH is the release rate constant for the Higuchi model. When the data is plotted as cumulative drug released versus square root of time, it yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to „KH".

- ***Korsmeyer-Peppas Model***

Korsmeyer derived a simple relationship, which described drug release from a polymeric system (105). The release rates from controlled release polymeric matrices can be described by the equation proposed by Korsmeyer *et al.*

$$Q = Kt_n$$

Where, Q is the percentage of drug released at "time t" K is a kinetic constant incorporating structural and geometric characteristics of the tablets and „n" is the diffusional exponent indicative of the release mechanism.

For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89. The Korsmeyer-Peppas model was plotted between log cumulative % drug releases versus log time.

Husen S *et al.* (2015) prepared bilayer tablet of Metoclopramide hydrochloride (MTH) and Aceclofenac (ASF) for separate layers to avoid the degradation of the drug to maximize the efficacy of both drugs in combination for the effective treatment of migraine. ASF was formulated as conventional release layer using PVP K-30 and MCC as binder and disintegrants respectively. MTH was formulated as immediate release layer by using various disintegrants like Sodium starch glycolate (SSG), Cross carmellose sodium (CCS) and

Pre-gelatinized starch (PGS). SSG and CCS in a concentration of 7.5% and 4.5% respectively gave a disintegration time of 9 sec, and 98.67% release at 15 min.

Karim S *et al*. (2015) prepared a sustained release formulation of glimepiride to investigate the effect of polymers on the release profile of glimepiride. Glimepiride sustained release tablets were prepared by direct compression method using different ratios of various release retarding polymers such as carbopol, ethyl cellulose, methocel K4 MCR, methocel K15 MCR, methocel K100 MCR and xanthum gum. These formulations were also compared with glimepiride immediate release tablets. The percent releases of all the formulations were 73.11%- 98.76% after 8 hours. On the other hand, 100% drug was released within 1 hour from the immediate release tablet of glimepiride.

Karpe MS *et al.* (2015) prepared a bilayer tablet of Metformin HCl (MET) and Glimepiride (GLP) to offer immediate release of GLP and gastroretentive layer of MET. Bilayer tablets was formulated using super disintegrant Sodium starch glycolate and gastroretentive layer formulated with polymers like HPMC K4M and HPMC K100M to modulate the biphasic drug release. Wet granulation method was employed to formulate bilayer tablets. The *in vitro* release profile shows desired biphasic release behaviour after storage at accelerated for 6 months.

Suribabu B *et al*. (2014) prepared a bilayer floating tablet for ciprofloxacin HCL using direct compression method. Bilayer floating tablets contains of two layers, immediate release layer and controlled release layer. Immediate release layer contains sodium starch glycolate as a super disintegrating agent and controlled layer contains HPMC K grade polymers as controlled release polymers. Sodium bicarbonate is used as a gas generating agent. The formulation F8 tablets showed controlled and complete drug released over a period of 12 hrs.

Junga SH *et al.* (2014) evaluated the comparative bioavailability and tolerability of the test and reference formulations in healthy male adult volunteers. This single-dose, randomized, double-blind, two-way crossover trial was conducted. The subjects were randomized to receive an FDC tablet containing the glimepiride/metformin (2/500 mg) test or reference formulation. After a 1-week washout period, the other formulation was administered and the P_K parameters were measured. The test and reference formulations had similar P_K parameters. The test formulation of glimepiride/metformin (2/500 mg) FDC tablets met the regulatory criteria for bioequivalence.

Wagh KS *et al.* (2014) designed and evaluated bilayered tablets of metformin hydrochloride as sustained release (SR) and glimepiride as immediate release form for the treatment of diabetes mellitus. Immediate release layer of glimepiride prepared using different super disintegrants. The use of a hydrophobic carrier along with a hydrophilic polymer effectively controls the initial rapid release of a highly water-soluble drug

like metformin HCl. SR granules were prepared by hot melt extrusion technique. Results confirmed the complete and rapid release of immediate release layer while sustaining effect for sustained layer observed for 10 hrs.

Sarangi MK *et al.* (2014) prepared bilayer tablet of Paracetamol and Tizanidine. Paracetamol with the dose 600mg/tablet was considered under the matrix layer and Tizanidine with the dose 2mg/tablet was considered under immediate release layer. The polymers like HPMC (Hydroxy propyl methyl cellulose) K100 & K4 grades, guar gum is used for development of matrix layer. The formulation of sustained release layer was optimized, showing a release rate more than 90%.

Roy SK *et al.* (2014) prepared sustained release bilayer tablets of anti-hypertensive drugs propranolol hydrochloride. The tablets were prepared by direct compression method by using superdisintegrants Sodium Starch Glycolate (SSG) for immediate release layer and mucoadhesive materials such as Hydroxy Propyl Methyl Cellulose (HPMC-K4M) and Carbopol 934 P for sustained release layer which could release the drug up to 12 hours in predetermined rate. The formulation ME5 containing HPMC-K4M and Carbopol 934 P in the ratio of 3:1 gave an initial burst effect and followed by sustained release of drug without disintegration up to 12 hours.