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BILAYER TABLET AND DUREDAS TECHNOLOGY – A REVIEW

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ABSTRACT

The expense and complications in new drug entities have increased since last 3 decades, with concomitant recognition of the therapeutic advantages of controlled drug delivery. So focus has been given on development of sustained or controlled release drug delivery systems. Bilayer tablet is new novel of tablet for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. For promoting patient convenience and compliance pharmaceutical industries interested in developing a combination of two or more API's in a single dosage form. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. 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 using DUREDAS technology (immediate release with extended release/ both layer 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. 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 a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required.

KEY WORDS

Bilayer tablet, DUREDAS, Immediate release, sustained release

INTRODUCTION

The bilayer tablet is a concept utilized by Skye Pharma PLC in their Geomatrix tablet, which is composed of different layers. The system allows the incorporation of more than one drug into the dosage form. Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers.[1] However, these drug delivery devices are mechanically complicated to design/manufacture and harder to predict their long term mechanical properties due to the poor mechanical and compression characteristics of the constituent materials in the compacted adjacent layers, elastic mismatch of the layers, insufficient hardness, inaccurate individual mass control, cross contamination between the layers, reduced yield, and their tendency to delaminate at the interface between the adjacent compacted layers during and after the various stages of production downstream of the compaction process. Therefore, the major problem, that has to be overcome, is to understand in detail the

sources of these problems in micro- and macro-scales and to develop remedies to solve them during solid dosage delivery design. [2]

ADVANTAGES OF BILAYER TABLET OVER THE OTHER CONVENTIONAL TABLET [3][4][5]

- This formulation can be used to separate two incompatible substances.
- When the two different layers of the tablet contain two different drugs, then the tablet can be easily used in combination therapy.
- It makes possible Extended-release preparations with the immediate-release quantity in one and the slow-release portion in the second layer.
- In case of drags having a low half-life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Analytical work may be simplified by separating of the layer prior to assay.
- Two-layer tablet require less material than compression coated tablets, weight less, and may be thinner.
- The weight of each layer can be accurately controlled, in the contrast to putting one drug of a combination product in a sugar coating.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance.
- For chronic condition requiring repeated dosing.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.

LIMITATIONS OF BILAYER TABLET [3][4][5]

- One of the major challenges in bilayer formulation is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
- The adjacent layers of a bilayer tablet are bonded together by mechanical means, so the factors influences the stress state is very important. The mechanical properties of each layer and the tablet, and compression parameters along with specialized techniques and compression condition plays a very important role for the same.
- Administration of sustained release bilayer tablet does not permit the prompt termination of therapy.
- The physician has a less flexibility on adjusting the dose regimens.

DUREDAS TECHNOLOGY

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer-tabletting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The immediate release layer, release the drug immediately after going into the GIT (stomach or intestine) in a diffusion and dissolution manner and the controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.[3] 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 the drug release of each is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible. The DUREDAS™ technology was initially employed in the development of a number of over the counter controlled release analgesics.[6]

BI-LAYER TABLETS: QUALITY AND GMP-REQUIREMENTS [7][8]

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 obvious but 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.

MANUFACTURING ASPECT OF BI-LAYER TABLET [8][9][10][11][12][13][14]

The manufacturing process of bi-layer tablets requires special rotary presses where the first layer is fed into the die and partially pressed, but not ejected from the die. Then the second layer is fed followed by compaction and ejection.

The development and production process of a tablet is well known and easy. But in fact it is a matter of a very complex process. The simple compression of a bulk material, either powder or granulate, to a robust tablet is dependent on a great number of influences, mainly force transfer, particle deformation and the formation of adhesive forces. The mechanism of compaction not only depends on the powder properties; but is also affected by particle size, shape, moisture content and experimental conditions, e.g. applied pressure, velocity of compaction, consolidation time, dwell time, relaxation time. In addition, the properties of the resulting compact can be influenced by the presence of a lubricant and binder as well as pressure. As tablet excipients as well as drugs have very different properties, it is quite difficult to make general statements about their compression behavior. Wu et al. developed a simple predictive model for the tensile strength of binary tablets based upon Ryshkewitch–Duckworth equation and showed that the model can accurately predict the tensile strength of binary tablets made of some commercial excipients. The relative interfacial strength of bilayer compacts of the commonly utilized excipient microcrystalline cellulose (MCC) was shown to be a function of both the ultimate applied initial layer and final layer compaction stress: the magnitude of which governs the degree of deformation endured by the particle assembly. Under a relatively large compressive load the intimate contact area between the particles increases which result in increment of the strength of tablet. Knowledge of the morphology and surface properties of pharmaceutical particles commonly utilized in tableting applications, in a free or a consolidated state, can assist with the characterization of a materials mechanical response to an applied load. For example the hollow microfibrillar structure of microcrystalline cellulose (MCC) is considered to be responsible for MCC having a high fraction of elastic recovery relative to other commonly used pharmaceutical excipients.

BI-LAYER TABLET PRESS

1. Single sided press [9]

Till date various types of bi-layer presses have been designed. Single-sided press with both chambers of the double feeder separated from each other is the simplest one. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet.

The powder of the first layer followed by the second layer was loaded as die passes under the feeder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression).

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.

Limitations of single-sided press: [4][5][9]

- No weight monitoring/control of the individual layers
- Mixing slightly at the interface hence no distinct visual separation between the two layers
- 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 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.

2. Doubled sided press: [9]

The limitations of single-sided press can be overcome by a double-sided tablet 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.

- Start the feeding granules corresponds to the end of compression of the first layer. At this stage, we obtain a density distribution that is specific to a flat-faced tablet compressed such that the lower punch is stationary. In the present example, in order to get frictional effects, the friction coefficient was set, which is a relatively high value, specific to clean (un lubricated) die wall conditions.
- After compression of the first layer, the powder for the second layer is delivered into the die. The initial density of the second layer is uniform.
- At this stage, densification occurs in the second layer and the density distribution in the first layer has not yet changed.

The mismatch of the die wall gradually disappears towards the end of the bilayer compaction. At the final stage it is also interesting to note that the interface between the two layers becomes distorted.

3. Compression force-controlled tablet presses [5][9][17]

Separation of the two individual layers is due to 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. 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. But; this will not happen in case of protein & peptide formulation which are more sensitive to compression force decreasing pharmacological activity of protein- peptide during compression. 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.

4. Displacement controlled tablet press:[2][5][9]

The 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.

Advantages:

- '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

'Displacement' control and first- layer compression: The main problem of a compression force-controlled press for first-layer compression, is its sensitivity dF/dW decreasing with decreasing force, resulting in the need to exert a compression force often above what is allowed to have good interlayer bonding. This problem does not occur in case of a 'displacement'-controlled system. The sensitivity of such a system is

dd /dW = 1 / (r x S)

First of all, this 'displacement'-sensitivity is independent from the operating point [i.e. it does not depend on the actual values of W (layer weight) and d (displacement)]. Moreover, the sensitivity increases with decreasing density of the pre-compressed slug. This means that the sensitivity increases with decreasing pre-compression force. This is one of the most important advantages of a Bilayer press using 'air compensation' on pre-compression and based on 'displacement' control: the first layer pre-compression force can be set to a known, constant and importantly a very low compression force (as low as 50 daN). At this low force, the interlayer bonding is optimal, while the control system's sensitivity is maximal. Moreover, displacement tolerance is calculated automatically based on the first-layer weight tolerance, making the system very easy to set up. The displacement signal of first-layer pre-compression is used to adjust the first layer fill depth in case the displacement is outside the correction tolerance limits. In case the displacement is outside the rejection tolerance limits, the final bi-layer tablet will be rejected at the moment of ejection from the die. After first-layer pre-compression (and weight control), the first-layer powder slug has a height varying in linear relationship to its weight. In order to achieve the required overfill depth for the second layer powder, it is necessary to push down the first layer slug in the die to this specific depth. The required level is set at the first-layer main compression station: the

upper punch penetration in the die determines the overfill depth for the second layer. The position of the lower main-compression roller determines the exerted compression force. This force should also be kept very low, in order not to affect interlayer bonding. Typically, the compression force in this first-layer main compression station is only a few daN more than that of the first-layer precompression. Its sole purpose is to bring all first-layer slugs to the same thickness and the same depth in the die. The slug is then ready to receive the second layer. After feeding the second layer into the die, the final tablet is precompressed and compressed to form the final bi-layer tablet. As the first-layer weight is already checked, the indirect measurement system of the second compression cycle is meant to control only the weight of the second layer. The exerted compression force once more appears to be of the utmost importance. As weight variations need to be monitored for the second layer only, the indirect measurement should be carried out under a pre-compression force which is LOWER than the force under which the indirect measurement of first layer was carried out. If this is not the case, the first layer will be further compressed together with the second layer and its weight will influence the measured signal. In this case, the measured signal will reflect the weight variation of the sum of both layers instead of that of the second layer only. The correct way to solve this problem is once again to use an air compensator and to measure 'displacement' under constant force.

The 'displacement' measured in this case, reflects weight variations of the second layer only and is used to adjust the fill depth of the second layer and/or reject the final tablet if the rejection limits are exceeded. An example of a real life situation will make this clear:

- Pre-compression force Side A: 80 daN, i.e. low in order to avoid separation of the individual layers
- Main-compression force Side A: 100 daN: i.e. only a few daN more, just to compress all 1st layer slugs to the same thickness
- Pre-compression force Side B: 70 daN, i.e. lower than the 80 daN on side A
- Main-compression force Side B: whatever force is required to make the final bi-layer tablet at the correct thickness and hardness.

The above explanation suggests what is crucial with regard to individual layer weight control on a bi-layer press. Whether the press is a single or a double sided press, the final compression force exerted on the final bi-layer tablet is always higher than the compression force on first layer only. Otherwise both layers would not bond together. In the case of a compression force control system, the force signal measured in this final station reflects not only variations in weight of the second layer, but also of the first layer as this first layer is further compressed in the final compression station. The use of the air compensator avoids this problem as this system measures displacement on precompression, where the air pressure on side B can be set at a lower level then the air pressure in the first pre-compression station.

EVALUATION OF BILAYER TABLETS

Pre-compression evaluation: [1][2][5][6][7]

Particle size distribution

The particle size distribution is measured using sieving method

Photo-microscope Study

Photo-microscope image of TGG and GG was taken (X450 magnifications) by photomicroscope

Angle of Repose

The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where 'h' and 'r' are the height and radius of the powder cone.

Moisture Sorption Capacity

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate uniformly distributed in Petri-dish and kept in stability chamber at 37±1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

Density

The bulk density (BD) and tapped density (TD) were determined and calculated using the following formulas.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

Compressibility

The compressibility index of disintegrate was determined by Carr's compressibility index.

$$\text{Carr's Index (\%)} = \frac{(\text{TD-BD})}{\text{TD}} \times 100$$

Hausnser's ratio

It is calculated by the formula,

$$\text{Hausner's Ratio} = \frac{\text{TD}}{\text{BD}}$$

Post-compression parameter: [15][16]

General Appearance: The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness: Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer. Generally thickness should be within 30% to 50% of tablet dimension.

Weight variation: Standard procedures are followed as described in the official books.

Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up. Normally, when capping occurs, friability values are not calculated. A thick tablet may have less tendency to cap whereas thin tablets of large diameter often show extensive capping, thus indicating that tablets with greater thickness have reduced internal stress.

Hardness (Crushing strength): The resistance of tablets to capping**,** abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness**.** The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. The Strong-Cobb Pfizer and Schleuniger apparatus which were later introduced measures the diametrically applied force required to break the tablet. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 Kg is usually considered to be the minimum for satisfactory tablets.

IN VITRO PERFORMANCE [2]:

The *in vitro* dissolution testing requirement of the bi-layer tablets will vary based on the intended dosage design and the physico-chemical characteristics of the drug in each layer. This variability poses special challenges in the development of a meaningful dissolution procedure for bi- layer drug products, especially if drugs with different water solubility are incorporated in the bi-layer tablets. In general, attributes such as rate of swelling and rate of water uptake need to be assessed for the bi-layer tablets. For example, if the goal of bi-layer immediate tablet is to deliver two incompatible API, then the separation of these layers in the dissolution media may be of no significance as this would not have any impact on the product performance (*in vivo*).

However, if the bi-layer tablet is a modified release product, with the design feature to control the release rate of the API layer by compacting with placebo layer, the integrity of the layers in the dissolution media is critical to the performance of the drug product (*in vivo*). In the case of bi-layer drug products, a bio-

relevant dissolution test conditions would be more meaningful in evaluating product quality and product performance. For example, in vitro dissolution testing of bi-layer tablet made with water insoluble APIs need extensive use of simulated fluids on both fresh tablets and the long-term stability samples.

Having a sensitive, reliable and discriminating *in vitro* dissolution procedure to determine the product quality and to predict bioavailability is of primary interest to the agency. It is recommended that all studies done for the development of the dissolution method must be included in the filing to support the final method that will be used for release and stability of the drug product. In general, development of a meaningful dissolution procedure for APIs with limited water solubility is more challenging than for the drug product with a high water solubility API. Having both classes of drugs in the same unit presents additional challenges to both the pharmaceutical industry and the regulatory agency. To measure the in vitro drug release performance of the bi-layer drug product, well established techniques can be used to achieve adequate dissolution by understanding the solubility differences of the APIs (where applicable), use of relevant and appropriate amount of surfactants, composition and volume of dissolution test medium, pH, type of apparatus and rate of agitation.

STABILITY STUDY (TEMPERATURE DEPENDENT):

The bilayer tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

Table 1: ICH guideline for stability study

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25± 2^0C/60% RH ± 5% RH or 30^0C ± 2^0C/65% RH ± 5% RH. **If 30^0C ± 2^0C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Table 2: Research work done on Bilayer tablet containing same drug in both layers prepared with DUREDAS technology

Sl. No.	Drug	Disintegrant	Rate retarding polymer	Reference
1	Aceclofenac sodium	Sodium starch glycolate	Eudragit RL100	18
2	Ambroxol hydrochloride	Sodium starch glycolate	Methocel K4M, Ethyl cellulose	19
3	Amoxicillin trihydrate	Sodium starch glycolate	HPMC K4M, HPMC K 15M, SCMC	20
4	Baclofen	Crospovidone, Croscarmellose	HPMC K 4M, PEO WSR N10	21
5	Guaifenesin	Sodium starch glycolate	Metalose 90 SH and Carbopole 934	22
6	Lornoxicam	ac-di sol	HPMC K4M and HPMC K100M	23
7	Metoprolol tartrate	Sodium starch glycolate, cross carmellose sodium and kyron T 314	HPMC K15 M] and Polyoxy ethylene (PEO) WSR 303	24
8	Propranolol hydrochloride	Sodium starch glycolate	Ethylcellulose, Eudragit RLPO and Eudragit RSPO	25

Table 3: Research work done on Bilayer tablet containing two different drugs in both layers prepared with DUREDAS technology

Sl. No.	Drug		Disintegrant	Polymer used	Reference
	IR layer	SR layer			
1	Amlodipine Besilate	Metoprolol Succinate	Sodium starch glycolate and pregelatinised starch	HPMC K100, HPMC K4M	26
2	Lovastatin	Atenolol	Sodium starch glycolate and Tablettose 80	HPMC K100M and xanthan gum	27
3	Atorvastatin	Nicotinic acid	Croscarmellose sodium and Cross-Povidone	HPMCK100M	28
4	Ranitidine HCl	Diclofenac Sodium	MCC	HPMC E15, HPMC K4M, K100M, and Ethyl Cellulose	29
5	Glimepiride	Metformin HCl	Sodium starch glycolate	Polyox WSR N80, Polyox WSR 303	30
6	Ramipril	Metoprolol succinate	Cross Carmellose sodium	HPMC K100M and Sodium Carboxymethylcellulose	31
7	Pioglitazone HCl	Metformin HCl	Cross Povidone	PEO-303	32

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