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BILAYER DRUG DELIVERY SYSTEMS - A REVIEW OF NOVEL APPROACH

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ABSTRACT

Bilayer tablets are generating great interest recently as they can achieve controlled delivery of different drugs with pre-defined release profiles. Over the last three decades pharmaceutical industries interested in developing a combination of two or more API's in a single dosage form for promoting patient convenience and compliance. Bilayer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is immediate release as loading dose and second layer is maintenance dose. This bilayer technology is primary option to avoid chemical incompatibilities between API's by physical separation.

This article explains the need for development and production of quality bilayer tablets and how to overcome the common bilayer problems that may encountered during development.

KEY WORDS: Bilayered tablets, API, incompatibilities, immediate release layer, sustained release layer

INTRODUCTION[1,2,3]

oral route of drug administration have wide acceptance upto 50- 60% of total dosage forms and is most convenient and preffered route for systemic effects due to its ease of dosing administration, pain avoidance, accuracy in dose, flexibility in formulation and patient compliance.

Tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness, stability and ease of manufacturing.

Conventional release formulations offer disadvantages of repetitive dosing and unpredictable absorption window which may result in wide range of fluctuation in drug concentration in plasma, tissue with subsequent undesirable toxicity and poor therapeutic efficiency.

To avoid these challenges the concept of controlled drug delivery system was introduced. The aim in designing sustained or controlled delivery system is to decrease the repetition of dosing and to increase effectiveness of drug by localization of drug at the site of action.

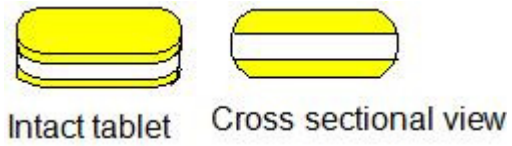
Immediate release drug delivery systems are designed to release the drug instantly which may be associated with fluctuations in plasma concentration due to metabolism and excretion.

Repetitive administration of immediate release dosage form may not achieve constant plasma level of drug with in therapeutic window.

On the basis of these considerations, bilayer tablets were proposed.

Bilayer tablet diagram

cross sectional view of a Matrix tablet



GOAL TO DESIGN BILAYER TABLETS[5,7]

- Bilayer tablet is suitable for sequential release of two API's which have different release profiles and physical incompatibilities. In this, the immediate release layer release the drug immediately where a s the sustained release layer releases the drug in controlled manner to maintain the therapeutic concentration for prolonged period. This also acts as maintenance dose.
- Control the delivery rate of either single or both the API's by utilizing the functional property of other.

ADVANTAGES

- ✓ Bilayer tablets offer better separation of incompatible components.
- ✓ Greatest chemical and microbial stability over all oral dosage forms.
- ✓ Frequency of administering dose can be reduced which improves patient compliance.
- ✓ It makes possible extended release preparations with the immediate release portion in one layer and control release portion in the second layer.
- ✓ Economical when compared to other oral dosage forms.
- ✓ Very advantageous for chronic condition where repeated dosing is required.

DISADVANTAGES

- Lack of sufficient bonding adhesion at the interface of two layers is the major problem in bilayer tablet which leads to separation.
- Flexibility on adjusting dose can't be achieved.
- Cross contamination may arise when granulation of first layer intermingles with the granulation of second layer.

TYPES OF BILAYER TABLET PRESS

1. **Single- sided tablet press**
2. **Double- sided tablet press**
3. **Bilayer tablet press with displacement monitoring.**

1. Single- sided tablet press[11,15,17]

Single sided bilayer tablet press is simple with both the chambers possessing double feeders separated from each other. Each chamber is gravity or forced fed with different powders, thus producing two individual layers of tablet.

When die passes under feeder the first layer will be loaded followed by the second layer. Then the entire tablet is compressed.

Limitations

- Weight monitoring/ control of individual layer is not possible.
- Separation between two layers cannot be distincted visually.
- Very short dwell time, resulting in poor de- aeration, capping and hardness problems.

2. Double- sided press

The problems of single sided press can be overcome in double sided press. Most double sided tablet presses posses automated production control and control over compression force. This will enable to monitor and control tablet weight.

The effective peak compression force exerted on each individual tablet or layer is measured by control system. This measured peak compression force is the signal used by control system to reject out of tolerance and correct the die fill depth.

3. Bilayer tablet with displacement monitoring

The displacement tablet weight control principally is fundamentally different from principle based upon compression force. In this the control system sensitivity depends on applied compression force and not on tablet weight. Infact the lower the precompression force, the more the monitoring control system. And this ideal for good inter layer bonding of bilayer tablet

ADVANTAGES

- Provides sufficient hardness by increasing dwell time at precompression of both first and second layer.
- Weight monitoring / control for accurate and independent weight control of individual layeres.
- Cross-contmination can be avoided to maximum exent.
- Clear visual separation between two layers is possible.

EVALUATION OF BILAYER TABLETS

The compressed matrix tablets were evaluated for different official and non- official tests .i.e.

PRE-COMPRESSION PARAMETERS:[19,20]

PARTICLE SIZE DISTRIBUTION

Particle size distribution was measured using sievieng method.

PHOTO MICROSCOPY

Photo microscopy image of TGG and GG was taken (X450 magnifications) by photomicroscope.

ANGLE OF REPOSE

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

$\tan\theta = h/r$

where H and r are height and radius of the cone

MOISTURE SORPTION CAPACITY

All disintegrants have capacity to absorb moisture from atmosphere which effects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrate uniformly distributed in petridish and kept in stability chanber at 37 ± 1^0c and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

DENSITY

The loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated using the following formulations

Bulk density = weight of powder/ bulk volume

Tapped denity = weight of powder/ volume after tappings(tapped volume)

COMPRESSIBILITY INDEX

The compressibility index of disintegrate was determined by carr،s index compressibility index.

Carrs index (%) =(TBD-LBD)/TBD ×100

HAUSNER'S RATIO

Ratio of tapped to bulk density, calculated by following formula

Hausner's ratio = TBD/LBD

POST- COMPRESSION PARAMETERS

1) WEIGHT VARIATION TEST

Individual weights of 20 tablets were taken and the average weight was calculated by using the following formula. Weight variation should not be more than 5%.

2) HARDNESS

Hardness of the tablets was observed by the use of hardness tester. Desired hardness was 11 - 16Kp

3) THICKNESS

Thickness of the tablets was calculated by the use of Digital Vernier callipers. Desired thickness was 4.4 - 4.6 mm.

4) FRIABILITY

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. After 100 rotations (4 minutes), the tablets were taken out from the friabilator. Permitted friability limit is 1.0%.

The percent friability was determined using the following formula:-

Friability = W_2- W_1 /W_1 *100

Where, W1 = Weight of the tablet before test.
W2 = Weight of the tablets after test.

5) DISSOLUTION

The invitro dissolution testing requirement for bilayered tablets varies depending on intended dosage design and physic-chemical characteristics of drugs in each layer.

Dissolution conditions for immediate release layer

Apparatus: USP apparatus- II(paddle) **RPM**: 75
Medium: 900mL 0.01N HCl , **Temp:** 37^{0}C ±0.5 ^{0}C
Sampling Interval: 5, 10, 15,20,30,45 and 60 minutes
0.01N HCl Preparation: Dilute 8.5mL of Conc. HCl to 10,000mL with water.

Dissolution conditions for sustained release layer
apparatus: USP apparatus-II(paddle) **RPM**: 50
Medium: 900 ml p^H 6.8 buffer**, Temp:**37±0.5°C
Sampling interval: 2hr,4hr,6hr,8hr, and 12hr
Samples were analysed by U.V Spectrophotometer by simultaneous estimation method

CONTENT OF ACTIVE INGREDIENTS (ASSAY)

The amount of active ingredient(s) was determined and compared with standards stated in the monograph. Twenty tablets were used for assay. All the batches should fall within the limit of 95 - 105 %.

CONCLUSION

Bilayered tablet enables great advantage for manufacturers to separate themselves from their competetiors product and improve their product efficacy. this article explains advantages and disadvantages of bilayered tablets and and different types of tablet presses ranging from primitive to highly sophisticated. When a quality bi-layer layer tablet needs to be formulated in conjuction with accurate weight control can be achieved by displacement weight control system based presses

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