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REVIEW ARTICLE

MULTILAYER TABLET- THE WAY OF DELIVERY OF INCOMPATIBLE DRUGS

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ABSTRACT

Layer tablet is an emerging technology for the development of controlled release & immediate release formulation of different drugs or drug with different release profile. In the last decade, pharmaceutical companies have shown keen interest in layer tablet technology. Layer tablets are used for preventing any type of incompatibilities between drugs & also for sustained release in which one layer serves as immediate release “initial dose” layer & other layer serves as “maintenance dose” layer. This technology has advantages over single layer conventional tablets as conventional tablets produce have variable drug release profile resulting in fluctuations in plasma drug concentrations. Layer tablet also is forerunners in the field of drug delivery technology due to their advantageous properties like better patient compliance, decrease drug resistance due to less frequent dosing & different release profile with different release mechanism in a single dose. There are various advantages of the layered tablet it consist of monolithic partially coated or multilayered matrices.
KEYWORDS- Trilayer Tablet, Bilayer Tablet, Patient Compliance, Incompatiblity, Sustained Release

INTRODUCTION

Nowadays various developed & developing countries move towards combination therapy for treatment of various diseases & disorders requiring long term therapy such as hypertension, diabetes and Cardio vascular diseases. Combination preparation plays an important role in clinical treatment because of its better and wider curative synergism and weaker side effects. Combination therapy may be achieved by giving separate drugs or where available by giving combination drugs (monolithic or bilayer dosage forms) which are dosage forms that contain more than one active ingredient. In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet and multilayered tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance [1]. Several pharmaceutical companies are presently developing layered tablets for a variety of reasons: better patient compliance, decrease drug resistance, patient extension & different release profile with different release mechanism in single dose. Multi-layered tablets are novel drug delivery systems where combination of two or more drugs in a single unit.

Benefits of Multi-layer tablet:
To control the delivery rate of either single or two different active pharmaceutical ingredient(s).

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- 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 such as chewing device, buccal/ mucoadhesive delivery systems, and floating tablets for gastro-retentive drug delivery [2].

The advantages of the multilayered 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 [3].

1. Lighter and compact.
2. Easiest and cheapest to package and strip.
3. Easy to swallowing with least tendency for hang-up.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Suitable for large scale production.
6. Greatest chemical and microbial stability over all oral dosage form.

IDEAL PROPERTIES OF MULTILAYER TABLETS:

- Drugs should not be affected by compaction of each layer and physically stable and Withstand the mechanical shock.
- Separation of layers should not occur during various stages such as compression, coating, packing, shipping and storage.
- Layer should not fuse into non-disintegrating matrix, should have clear, parallel, visual separation in final compressed tablets.
- If it consists of disintegrating matrix, it should be disintegrated within GIT, modified release part should not be affected dissolution profile of IR part and slow and gradual erosion.
- Layer tablet should have chemical & physical stability to maintain its physical attributes over time either if drugs are physical & chemical incompatible [4,5].

TYPE OF LAYERED TABLETS

1. Multi Layered tablets – two to three component systems.
2. Compression coated tablets – tablet within a tablet.
3. Inlay tablet – coat partially surrounding the core.

MULTILAYERED TABLETS

BILAYER TABLET

Bilayer tablets are suitable for sequential and simultaneous release of two different API's. In this one layer is immediate release and another layer is sustained release act as maintenance dose shown in figure 1. Bilayer tablet is suitable mean of to deliver two drugs at one time without any

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dynamic and pharmacological interaction. The bilayer tablet containing subunits that may be either the same drug (homogeneous) or different drugs (heterogeneous) [6].

Homogenous type

Bilayer tablets are preferred when the release profiles of the drugs are different from one another. Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layerof drug for immediate release while second layer designedto release drug, later, either as second dose
or in an extended release manner [7].

Heterogeneous type

Bilayer tablet is suitable for sequential release of two drugsin combination, separate two incompatible substances [8].

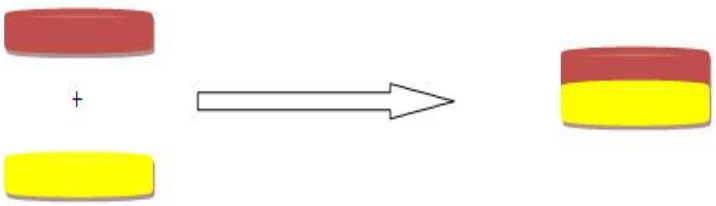

Figure 1 Bilayer tablet

Advantages

- They are used as an extension of a conventional technology
- Ability to combine different release rate.
- IR and SR in the same tablet for chronic condition requiring repeated dosing.

General properties of bi-layer tablet dosage forms

- It should have graceful product identity free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to with stand mechanical shock during its production and packaging.
- Should have physical and chemical stability.
- The bi-layer tablet must release drug in an expectable and reproducible manner.
- Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents [9].

BI-LAYER TABLET PRESSES:

1. Single sided tablet press.
2. Double sided tablet press.

Bi-layer tablet press with displacement.

Single Sided Tablet Press

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

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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 [10].

Double Sided Tablet Press

A double sided press offers an individual fill station, pre – compression and main compression for each layer. Infact 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 [11].

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 depend on the applied precompression force. In fact the lower the precompression force, the more the monitoring control system and this ideal for good interlayer bonding of the bilayer tablet [12].

TRIPLE LAYER TABLET

Triple layer tablet consist of three layer of which first layer is for immediate release of drug and the second layer is for sustained release. These two layersare separated with the middle barrier layer. This is more suitable for the delivery of two drugs which have interactions in them. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different colour to produce a distinctive looking tablet. Dust extraction is essential during compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down [13].

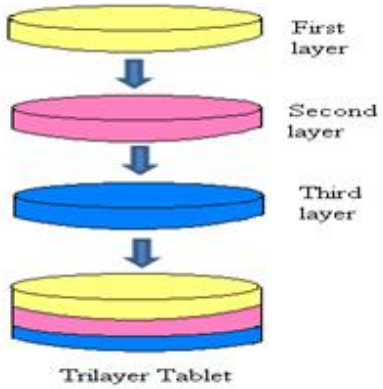

Figure 2 Trilayer tablet

COMPRESSION COATED TABLETS

This type of tablet has two parts, internal core and surrounding coat. The core is small porous tablet andprepared on one turret. For preparing final tablet, a biggerdie cavity in another turret is used in which first the coat material is filled to half and then core tablet is

mechanicallytransferred, again the remaining space is filled with coatmaterial and finally compression force is applied shown in figure 3. This tablet readily lend itself in to a repeat action tablet as the outerlayer provides the initial dose while the inner core releasethe drug later on. But, when the core quickly releases thedrug, entirely different blood level is achieved with the riskof over dose toxicity.

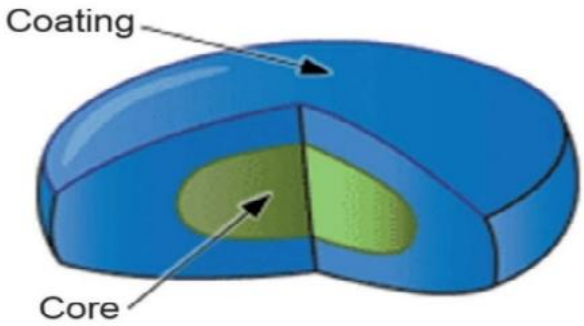

Figure 3 Compression coated tablet

To avoid immediate release of boththe layers, the core tablet is coated with enteric polymer sothat it will not release the drug in stomach while, the firstdose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner coremay be of liquid formulation to provide immediate release of core after the coat gets dissolved [14].

INLAY/CORE COATED TABLETS

In this type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed shown in figure 4. While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet [14-15].

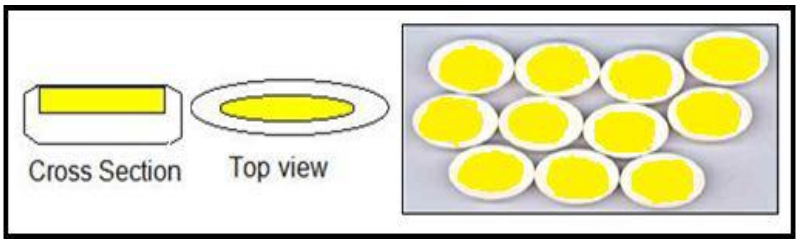

Figure 4 Core coated tablet

EVALUATION OF LAYER TABLET FORMULATION

Preformulation Evaluation

1. Particle size distribution: The particle size distribution was measured using sieving method [16].

2. Photo-microscope study: Photo-microscope image of TGG and GG was taken (X450 magnifications) by Photomicroscope [16-17].

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3. Angle of repose: In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plan [18-19].

$$\text{Angle of repose} = \text{Tan}^{-1}(h/r)$$

Where, h= height, r = radius

4. Determination of bulk density and tapped density: A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas [20-21].

$$\text{Bulk density} = W / V_b$$

$$\text{Tapped density} = W / V_T$$

Where, W = weight of the powder, V_b = bulk volume, V_T = tapped volume

5. Compressibility index (carr's indices): Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material [22].

$$CI = 100\ (V_b - V_T)/V$$

Where, CI = Compressibility index, V_b = bulk volume, V_T = tapped volume.

6. Hausner's ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density [22].

7. 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 [19].

Formulation Evaluation

1. **Thickness:** Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using venire calliper [23].
2. **Hardness:** The limit of hardness of MDT is usually kept in lower range to facilitate early disintegration in mouth. The hardness of MDTS may be measured using hardness tester (Monsanto Hardness tester). It is expressed in kg or pound [24].
3. **Size and Shape:** Size and shape of the tablet can be dimensionally described, monitored and controlled [24].
4. **Uniformity of weight:** Weight variation test is done as per standard procedure. Ten tablets from each formulation are weighed using an electronic balance and the average weigh are calculated [24].
5. **Friability:** Friability is the measure of tablet strength. 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 [25].

   % loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100.
6. **Wetting time:** Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to

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petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [26] .

7. **Water Absorption Ratio:** A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$$R = 10 (Wa /Wb)$$

Where- Wb is weight of tablet before water absorption & Wa is weight of tablet after water absorption [27].

8. **Dissolution Study:** Bilayer tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis [23].

DESIGN OF MULTI-LAYERED TABLETS

The design of multi-layer through modulating layers which allows different tablet designs for the production with specific release to achieve different dissolution patterns like bimodal, delayed and multi modal delivery have been given below [28]:

- Zero order sustained release
- Time programmed delivery system
- Bimodal release profile

Zero order sustain release

It comprises either a hydrophilic or hydrophobic intermediate layer containing the active drug or one or two barrier layers which are press coated to the faces of the tablet core, leaving the sides of the core exposed. Many authors have evaluated this design. The widely usedbarrier polymers for sustaining the drug delivery are either hydrophilic and/or hydrophobicmaterials. In general linear release profiles can be obtained by applying hydrophilic barrier layers on both the faces of a hydrophobic matrix tablet or by applying a hydrophilic barrier layer on one face and hydrophobic barrier layer on the other face of the matrix tablet.However, net formulation and variables within the matrix and barrier layers is important to be controlled rather carefully in order to achieve zero-order drug release from hydrophobic matrix tablet coated with hydrophobic barrier layers on both the faces.

Time Programmed Delivery System

Time programmed followed by time controlled release, when the delivery of drug is required in a time controlled fashion in the gut, rather than release of drug in continuousmanneraccording to circadian rhythm. This system consists of core which is coated with different polymeric barriers. The release of drug, from the core tablet after swelling or after eroding of hydrophobic or hydrophilic barrier of coating that's how pulsatile release of the drug followed by extended or prolonged release of the drugdelivery system provides immediaterelease of the drug.

Bimodal Release Profile

Bimodal release profile show an initial rapid release followed by slow release and again a second phase of rapid drug release i.e. sigmoidal release profile. This system compensates the slow absorption in the stomach and small intestine and for programmed pulse releases that perform more effectively at the site of action to undertake periodic changes.

CONCLUSION

Layer tablet is improved beneficial technology to overcome the limitation of the single layered tablet. Layer tablet is suitable for sequential release of more than one drug in combination, separate incompatible substances and also 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.

REFERENCES

1. Yang L, Venkatesh G, Fassihi R. Compactionsimulator study of a novel triple-layer tablet matrix for industrial tableting. Int. J. Pharm. 1997; 152(1):45-52.
2. Pujara ND, Gokani R, Paun J. Bilayer Tablet – An Emerging Trend. Int. J. Pharm. Res. Dev. 2012; 4(4): 102 – 111.
3. Remya PN, Damodharan N, Kumar CV. Formulation and Evaluation of Bilayered Tablets of Ibuprofen and Methocarbamol. Int.J. Pharm Tech Res. 2010;2(2): 1250-55.
4. Rathod RT, Misra D. FDC of montelukast with levocetirizine: focus on bilayer technology. J Indian Med Assoc. 2009;107(8): 562-74.
5. Mishra P, Sharma PK, Malviya R. A review on Bi-layer tablets- An emerging trend. J. Drug Del. Tech. 2014; 4(2): 110-4.
6. Nagaraju R, Kaza R. Formulation and evaluation of bilayer sustained release tablet of salbutamol and theophylline. Int J Pharm Sci. Nanotech. 2009; 2(3): 638-46.
7. Krishnaiah YSR, Karthikeyan RS, GouriSankar V, Satyanarayana V. Three-layer guar gum matrixtablet formulations for oralcontrolled delivery of highly solubletrimetazidinedihydrochloride. J Control Rel. 2002; 81(2): 45-56.
8. Kulkarni A, Bhatia M. Development and evaluation of bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iran. J. Pharm. Res. 2009; 8(1): 15-25.
9. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur. J. Pharm. Biopharm. 2008; 69(1): 255-63.
10. Sowmya C. An overview on bi-layer tablets. Int. J. Pharm Tech. 2012; 2(4): 2143- 56.
11. Panchal HA, Tiwari AK. A Novel approach of Bilayer Tablet technology: A Review. Int. Res. J. Pharm. 2012; 3(5): 44-9.
12. Deshpande RD, Gowda DV, Mahammed N, Maramwar DN. Bi-Layer Tablets- An Emerging Trend: A Review. Int. J Pharm. Sci. Res. 2011; 2(10): 2534-44.
13. Singh PK, Kumar S, Shukla VK, Verma P, Dey S. Bilayer and Floating-Bioadhesive tablets: Innovative approach to Gastroretention. J. Drug Del. Ther. 2011;1(1): 32-35.

eISSN 2319-1074

14. Manidipta D. Bilayer Tableting Technology: An Overview. J. Pharma Res. 2012; 5(1): 310-4.
15. Patel M, Sockan GN, Kavitha MT. Challenges in the formulation of bilayered tablets: A Review. Int. J. of Pharm. Res. Dev. 2010; 2(5): 30-42.
16. Noor AV. Formulation design, characterisation and in vitro evaluation of bilayered tablets containing Telmisartan and Hydrochlorthizide. Int J Biopharm. 2013; 4(1): 29-36.
17. The Indian Pharmacopoeia, Vol. 2, 4th Ed. The Controller of Publication, Govt. of India, Delhi; 1996.
18. Aushutosh A, Arunanachalam A, Karkikeyan M, Mandipa S, Ravishankar V, Senthilaraj R. Design and evaluation of sustained release tablets of Telmisartan. Int J Pharm Sci. 2010; 8(1): 595-603.
19. The United States Pharmacopoeia, United states Pharmacopoeial convention, Inc., Rockville, MD; 2000.
20. Uttam M. Formulation and In Vitro Studies of a Fixed-Dose Combination of a Bilayer Matrix Tablet Containing Metformin Hcl as Sustained Release and Glipizide as Immediate Release. Drug Develop & Ind. Pharm. 2008; 34(3): 305-13.
21. Enose A A, Prithiviraj A, Kesavan B. Eudragit NE30D based metformin gliclazide extended release tablets: formulation, characterization and in vitro release studies. Chem. Pharm Bull. 2002; 50(11): 1495-98.
22. Defang O, Shufang N, Wei L. In vitro and in vivo evaluation of two extended release preparations of combination Metformin and Glipizide. Drug Dev. Ind. Pharm. 2005; 31(7): 677-85.
23. Saini S, Nanda A, Hooda M, Komal DJ. Formulation and evaluation of mouth dissolving anti-allergic tablets of Levocetrizine dihydrochloride. J Chem Pharm Res. 2011; 3(5): 450-5.
24. Lachman L, Liberman H, Kanig J. The theory and practice of industrial Pharmacy. Varghese publishing House Mumbai; 1976, 218-236.
25. Siddiqui MN, Garg G, Sharma PK. Fast dissolving tablet: prepration characterization and evaluation: an overview. Int. J Pharm Sci Review Res. 2010; 4(2): 87-96.
26. Amin AF, Shah T, Bhahdani M, Patel M. Emerging trend in the development of orally disintegrating tablet. Pharmainfo. net. 2006. Available from: http:// www. .net reviews/ mouth.
27. Mahaveer PK. Orally disintegrating tablets: A future prospectus. Int J. Pharm. Sci. Bio. 2010(1); 3: 71-9.
28. Manidipta D. Bilayer Tableting Technology: An Overview. J. Pharma Res. 2012; 5(1): 310-4.