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A Review on Bilayered Tablets

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ABSTRACT

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. Now a days the use of bilayered tablets has been increased. Bilayer tablet is more suitable for gradual release of two active ingredients in combination. Bilayered 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

These are developed in order to achieve modified release of a drug. In case of conventional dosage forms, there will be a wide range of fluctuations in the drug concentration, which therefore results in unwanted toxicity & low efficiency [1,2].

Advantages

- It helps in avoiding chemical incompatibilities between API's by physical separation.
- Suitable for sequential release of two drugs [3,4].
- Repetitive dosing is required in conventional dosage forms which can be avoided by bilayer tablet.
- Lower dose of drug is required compared to conventional dosage forms.
- It is the most preferred & convenient route of administration.
- Chemical & microbial stability is more compared to other oral dosage forms.
- Taste & odor can be masked by coating technique.
- They show highest dose precision & low content variability.
- Easy to swallow [5,6].

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Disadvantages

- Drugs with objectionable odour & with bitter taste cannot be formulated.
- Swallowing is difficult for children & for unconscious people [7,8].
- Formulation is difficult for drugs with poor wettability, slow dissolution rate & high absorption in the GIT.
- Cross contamination may occur between the 2 layers.
- Individual layer weight is inaccurate.
- Low yield, insufficient hardness & the layers gets separated [9,10].

IDEAL CHARACTERISTICS

- It should be elegant & free from chipping, cracking, discoloration and contamination [11].
- It ought to have adequate quality to with stand mechanical shock during its tablet formulation process [12].

CHALLENGES

Tablet breaks in to pieces when the two parts of the tablet don't bond totally. The two granulations should adhere properly when compressed into a bilayer tablet [13].

- At the point when the granulation of the main layer blends with the granulation of the second layer or vice versa, cross-contamination happens.
- Much expensive compared to conventional dosage forms or single layer dosage forms.
- The equipment used for formulation of bilayer tablet i.e., tablet press costs high [14-16].
- Development of two compatible granulations is must, which implies additional time spent on formulation, analysis & validation [17].

TECHNIQUES

Several techniques are used for bilayer tablets. They are as follows [18]
En So Trol Technology
Oros® Push Pull Technology
L-Oros Tm Technology
Duros Technology

TYPES OF BILAYER TABLET PRESSES

Various types of tablet presses are given below:

Single Sided Tablet Press

This is the simplest design containing two chambers which are separated from each other. Both the chambers are fed with different type of powders hence producing the two individual layers of a tablet [19-21]. Whenever the die goes under the feeder, the die is first filled with the first layer powder and then with the second layer powder [22,23].

Limitations

Exact weight of the individual medicament cannot be obtained. Discrimination of the two layers is difficult by visual observation [24]. As the compression roller is small, the dwell time of the first layer is very low which results in capping and variation the hardness. To extend the dwell time the torrent rotation speed is reduced which results in low tablet output [25,26].

Double Sided Tablet Press (Or) "Compression Force" Controlled Tablet Presses

Double sided tablet press contains an individual fill station. For each layer it offers pre-compression and main compression. Therefore each bilayer tablet undergoes four compression stages before ejecting from the tablet press [27,28]. In double sided tablet press with automated production control, compression force is used to check and control the weight of the tablet. Control system measures the peak compression force exerted on every individual layer or tablet. Out of tolerance tablets are rejected by the control system. The control system utilizes

the peak compression force as the sign to reject out of tolerance tablet and corrects the die fill depth when necessary [29-32].

Limitations

The 2 individual layers are separated because of insufficient bonding between them during final stage of compression [33]. For correct bonding the first layer should be compressed at a low compression force, hence therefore during final compression the first layer continues its interaction with the second layer. Accordingly the lower compression force diminishes the accuracy of the weight [34-37].

Bilayer Tablet Press With Displacement Monitoring

The principle of displacement tablet weight control varies from the compression force. While measuring displacement, control system sensitivity depends on the pre compression force but not on the operation point. For good inter layer bonding of bilayer tablet the lower the pre-compression force the more is the monitoring control system [38-40].

Advantages

As the compression force is low on the first layer capping can be avoided. Sufficient hardness can be obtained with maximum turret speed. Cross contamination is prevented between the two layers. Maximum yield can be obtained. Visual separation of the layers is very clear [41-45].

CHARACTERIZATION OF BILAYER TABLET

Particle Size Distribution

Sieving is used to determine particle size distribution [46].

Angle of Repose

Angle of repose was calculated by measuring the diameter of the powder cone.
Tan θ=h/r [47]

Where “r” is the radius and “h” is height of the powder cone.

Moisture Sorption Capacity

Disintegrates are capable of absorbing moisture from the atmosphere and thus affects the hygroscopic drugs. Moisture sorption capacity is carried out by taking 1g of disintegrate in a petridish by distributing evenly over it and is placed in stability chamber at 37±1°C with 100% relative humidity for about 2 days. Moisture uptake is measured by calculating the difference in weights [48,49].

Density

Ratio of mass to volume for an untapped powder is known as the bulk density. A graduated cylinder containing sample is tapped mechanically until volume changes and thus tapped density is obtained [50].

Compressibility

It is the indirect measure of bulk density. To determine compressibility of the disintegrate carrs compressibility index [51].
Carr’s Index = (tapped density – bulk density) x 100 / tapped density [52]

Hausner’s ratio

It is used to determine powder flow.
Hausner’s ratio = tapped density / pour density [53]

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EVALUATION TESTS

Tablet Thickness and Size

Diameter & thickness are important for tablet uniformity. Vernier calipers are used for the determination of tablet thickness & diameter [54].

Tablet Hardness

Tablet hardness is measured by using Monsanto hardness tester. It is performed to find out the tablet breaking point and to test the structural integrity during handling, storage & transportation [55].

Friability

It is used to measure the mechanical strength of the tablet or granules. The equipment used for determining friability is friabilator [56]. 20 tablets are accurately weighed and placed in the friabilator which revolves at 25rpm by dropping the tablets from a height of 6" in each revolution. Tablets are then weighed after 4min to determine the percentage loss [57,58].

Uniformity of weight

Randomly 20 tablets are collected and the average weight is calculated. Weight variation is calculated and compared with the I.P. standards [59].

Dissolution Studies

Tablets are subjected to in vitro drug dissolution studies in simulated gastric & intestinal fluid to evaluate the controlled drug delivery potential [60]. Dissolution studies are carried out using USP I dissolution apparatus at 100 rpm at 37±0.5°C with 900ml pH 1.2 buffer for 2 hours. Later on the dissolution medium is replaced with900ml of pH 6.8 phosphate buffer. This is continued for other 10 hour. Drug samples of about 5ml are withdrawn and replaced with the drug free dissolution medium. The samples are analysed using UV spectrophotometer [61-65].

Advancement in the Field of Bilayer Tablets

Development of predetermined release profiles of active ingredients. Incorporation of incompatible active ingredients into single dosage form. Following are the few recent findings [66-69].

Tramadol and Acetaminophen - synergistic effect in pain

Cefixime trihydrate and Dicloxacilline sodium – synergistic effect in bacterial infections.

CONCLUSION

Bilayer tablet is the beneficial technology when compared to single layered tablet. By this technique even the incompatible drugs can be compressed into a single tablet. Bilayer tablet helps in sequential release of two drugs in which one as the immediate release and the other as the controlled release. The quality & GMP requirements of bilayer tablet vary widely. This explains why different kinds of tablet presses are used to produce bilayer tablets starting from single sided press to highly sophisticated machines.

REFERENCES

1. Madhavi BR, et al. Buccal Film Drug Delivery System-An Innovative and Emerging Technology. J Mol Pharm Org Process Res. 2013;1:107.
2. Pawar Harshal A, et al. Development and Evaluation of Mucoadhesive Patch Using a Natural Polysaccharide Isolated from Cordia dichotoma Fruit. J Mol Pharm Org Process Res. 2014;2:120.
3. Abbas-Aksil T, et al. Matrix Tablets from Algerian Lyophilized Berries (LB) (Arbutus unedo L.) Date (Phoenix dactylifera L.). Nat Prod Chem Res. 2016;4:207.

4. Banala N, et al. Design and Evaluation of Floating Multi Unit Mini Tablets (MUMTS) Muco Adhesive Drug Delivery System of Famotidine to Treat Upper Gastro Intestinal Ulcers. J Pharmacovigil. 2015;3:179.
5. Akram MA, et al. Designing, Development and Formulation of Mouth Disintegrating Telmisartan Tablet with Extended Release Profile Using Response Surface Methodology. J Bioequiv Availab. 2015;7:262-266.
6. Jethara SI and Patel MR. Development and Evaluation of Bilayer Tablet of Metoclopramide HCl and Aceclofenac. Intel Prop Rights. 2015;3:138.
7. Hu L, et al. A Novel Approach to Formulate and Optimize Orally Disintegrating Tablets of Bambuterol Hydrochloride. Pharmaceut Anal Acta. 2013;4:216.
8. Madhavi N, et al. Formulation and Evaluation of Phenytoin Sodium Sustained Release Matrix Tablet. J Bioequiv Availab. 2012;4:128-133.
9. Abdul Althaf S, et al. Formulation, Evaluation and Mathematical Modelling of Clopidogrel Bisulphate & Aspirin Immediate Release Bilayer Tablets. Pharmaceut Anal Acta. 2012;3:194.
10. Ratnaparkhi MP. Formulation and Development of Taste Masked Orally Disintegrating Tablets of Perindopril Erbumine by Direct Compression Method. Pharmaceut Anal Acta. 2012;3:162.
11. Usman M, et al. Preparation and Evaluation of Controlled Release Tablets Containing Mefenamic Acid. Clin Exp Pharmacol. 2012;2:107.
12. Valenzuela F, et al. Relative Bioavailability of Chewable and Conventional Film-Coated Tablet Formulations of Sildenafil 100 mg in Healthy Volunteers Under Fasting Conditions. J Bioequiv Availab. 2011;3:207-210.
13. Damodar R and Movva B. Preparation and *In-vitro* Evaluation of Metformin HCl Tablets Containing Sustained Release Beads for Increasing Therapeutic Window. J Bioequiv Availab. 2014;6:091-095.
14. Malvey S, et al. Formulation and Evaluation of Acyclovir Orodispersible Tablets Using Sublimation Method. J en Pract. 2015;3:208.
15. Gul S and Sajid S. Formulation of Improved Norfloxacin HCl Tablets: Quality Control Assessment and Comparison Study of Acidic and Basic Form of Norfloxacin in Tablet Formulation. J Develop Drugs. 2015;5:145.
16. Akram MA, et al. Designing, Development and Formulation of Mouth Disintegrating Telmisartan Tablet with Extended Release Profile Using Response Surface Methodology. J Bioequiv Availab. 2015;7:262-266.
17. Hart A. Effect of Particle Size on Detergent Powders Flowability and Tabletability. J Chem Eng Process Technol. 2015;6:215.
18. Gopinath C, et al. An Overview On Bilayered Tablet Technology. Journal of Global Trends in Pharmaceutical Sciences. 2013;4:1077-1085.
19. Mehraj UD, et al. An overview on bilayered tablet technology. Inov J Sci. 2013;1.
20. Jaldhara SP, et al. A review on bilayer tablets. Journal of Drug Discovery and Therapeutics. 2013;1:40-48.
21. Niranjan K, et al. Evaluation of the Performance Characteristics of Bilayer Tablets: Part I. Impact of Material Properties and Process Parameters on the Strength of Bilayer Tablets. AAPS PharmSciTech. 2012;13:1236-1242.
22. Yatin ND, et al. Design and optimization of bilayered tablet of Hydrochlorothiazide using the Quality-by-Design approach. Int J Pharm Investig. 2014;4:93-101.
23. Divya A, et al. Bilayer tablet technology: An overview. J App Pharm Sci. 2011;1:43-47.
24. Ijaz H, et al. Formulation and in-vitro evaluation of floating bilayer tablet of lisinopril maleate and metoprolol tartrate. Pak J Pharm Sci. 2015;28:2019-2025.
25. Papós K, et al. Effect of the surface free energy of materials on the lamination tendency of bilayer tablets. Int J Pharm. 2015;496:609-613.
26. Oh JH, et al. Designing of the fixed-dose gastroretentive bilayer tablet for sustained release of metformin and immediate release of atorvastatin. Drug Dev Ind Pharm. 2016;42:340-349.
27. Momin MM, et al. Formulation and evaluation of bilayer tablet for bimodal release of venlafaxine hydrochloride. Front Pharmacol. 2015;6:144.
28. Dey S, et al. Formulation and evaluation of fixed-dose combination of bilayer gastroretentive matrix tablet containing atorvastatin as fast-release and atenolol as sustained-release. Biomed Res Int. 2014:12.
29. Abebe A, et al. Review of bilayer tablet technology. Int J Pharm. 2014;461:549-558.
30. Busignies V, et al. Role of the elasticity of pharmaceutical materials on the interfacial mechanical strength of bilayer tablets. Int J Pharm. 2013;457:260-267.
31. Klinzing G and Zavaliangos A. Understanding the effect of environmental history on bilayer tablet interfacial shear strength. Pharm Res. 2013;30:1300-1310.
32. Hiten AP and Ajay kumar T. Novel Approach of Bilayer tablet Technology: An Review. Journal of Pharmaceutical Science and Technology 2012;4:892-904.
33. Rohan DD, Gowda DV, et al. Bi-layer tablets- an emerging trend: a review. International journal of pharmaceutical sciences and research. 2011;2:2534-2544.
34. Ajit KK and Manish SB. Design of Floating Bilayer Tablets of Diltiazem Hydrochloride and Lovastatin. journal of pharmaceutical science and technology. 2008;62:344-352.
35. Uttam M and Tapan KP. 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 development and industrial pharmacy. 2008;34:305-313.

36. Girish SS, et al. Preparation and in vitro evaluation of bilayer and fl oating-bioadhesive tablets of rosiglitazone maleate. Asian J Pharm Sci. 2007;2:161-169.
37. Samiran D and Pranjal Kumar S. Bilayer and floating-bioadhesive tablets: innovative approach to gastroretension. Journal of drug delivery and therapeutics. 2011;1:32-35.
38. Franck J, et al. Axial strength test for round flat faced versus capsule shaped bilayer tablets. Pharm Dev Technol. 2015;20:139-145.
39. Yang YP, et al. Effect of release of hydroxypropylmethyl cellulose on single and bilayer sustained-release matrix tablets. Beijing Da Xue Xue Bao. 2013;45:291-296.
40. Sohn Y, et al. Development of self-microemulsifying bilayer tablets for pH-independent fast release of candesartan cilexetil. Pharmazie. 2012;67:917-924.
41. Ranade AN, et al. Development of bilayer floating tablet of amoxicillin and Aloe vera gel powder for treatment of gastric ulcers. AAPS Pharm Sci Tech. 2012;13:1518-1523.
42. Shirsand S, et al. Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method. Int J Pharm Investig. 2012;2:34-41.
43. Patel D, et al. Formulation and evaluation of bilayer tablet by using melt granulation technique for treatment of diabetes mellitus. J Pharm Bioallied Sci. 2012;1:37-39.
44. Kottala N, et al. Evaluation of the performance characteristics of bilayer tablets: Part I. Impact of material properties and process parameters on the strength of bilayer tablets. AAPS PharmSciTech 2012;13:1236-1242.
45. Dey S, et al. Formulation development and optimization of bilayer tablets of aceclofenac. Expert Opin Drug Deliv. 2012;9:1041-1050.
46. Kottala N, et al. Influence of compaction properties and interfacial topography on the performance of bilayer tablets. Int J Pharm. 2012;1:171-178.
47. Gattani SG, et al. Formulation and evaluation of bilayer tablets of metoclopramide hydrochloride and diclofenac sodium. PDA J Pharm Sci Technol. 2012;66:151-160.
48. Yedurkar P, et al. Mucoadhesive bilayer buccal tablet of carvedilol-loaded chitosan microspheres: in vitro, pharmacokinetic and pharmacodynamic investigations. J Microencapsul. 2012;29:126-137.
49. Bi M, et al. Enhancing and sustaining AMG 009 dissolution from a bilayer oral solid dosage form via microenvironmental pH modulation and supersaturation. AAPS PharmSciTech. 2011;12:1401-1406.
50. Podczeck F. Theoretical and experimental investigations into the delamination tendencies of bilayer tablets. Int J Pharm. 2011;408:102-112.
51. Chaudhary A, et al. Microporous bilayer osmotic tablet for colon-specific delivery. Eur J Pharm Biopharm. 2011;78:134-140.
52. Rathod RT, et al. FDC of montelukast with levocetirizine: focus on bilayer technology. J Indian Med Assoc. 2009;107:562-564.
53. Akseli I, et al. Mechanical property characterization of bilayered tablets using nondestructive air-coupled acoustics. AAPS PharmSciTech. 2010;11:90-102.
54. Hinson VK, et al. Reducing dosing frequency of carbidopa/levodopa: double-blind crossover study comparing twice-daily bilayer formulation of carbidopa/levodopa (IPX054) versus 4 daily doses of standard carbidopa/levodopa in stable Parkinson disease patients. Clin Neuropharmacol. 2009;32:189-192.
55. Nirmal J, et al. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem Pharm Bull. 2008;56:1455-1458.
56. Kulkarni AS, et al. Design of floating bilayer tablets of diltiazem hydrochloride and lovastatin. PDA J Pharm Sci Technol. 2008;62:344-352.
57. Patra CN, et al. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Acta Pharm. 2007;57:479-489.
58. Liu L, et al. Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. Int J Pharm 2008;352:225-230.
59. Patel VM, et al. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS PharmSciTech. 2007;8: 203-208.
60. Narendra C, et al. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS PharmSciTech 2006;7:23-29.
61. Rahman Z, et al. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm. 2006;56:49-57.
62. Sanna V, at al. Bilayer tablets based on poly (epsilon-caprolactone) and polymethylmethacrilates as controlled-release systems for ruminants. Pharm Dev Technol. 2004;9:321-328.
63. Ozdemir N, et al. Studies of floating dosage forms of furosemide: in vitro and in vivo evaluations of bilayer tablet formulations. Drug Dev Ind Pharm. 2000;26:857-866.
64. Ohmori S, et al. Sustained-release phenylpropanolamine hydrochloride bilayer caplets containing the hydroxyl propyl methyl cellulose 2208 matrix. II. Effects of filling order in bilayer compression and manufacturing method of the prolonged-release layer on compactibility of bilayer caplets. Chem Pharm Bull. 2000;48:678-682.

65. Ohmori S, et al. Sustained-release phenylpropanolamine hydrochloride bilayer caplets containing the hydroxypropylmethylcellulose 2208 matrix. I. Formulation and dissolution characteristics. Chem Pharm Bull. 2000;48:673-677.
66. Mandal U, et al. 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 Dev Ind Pharm. 2008;34:305-313.
67. Jivani RR and Patel CN. Statistical Design of Experiments on Fabrication of Bilayer Tablet of Narrow Absorption Window Drug: Development and In vitro characterisation. Indian J Pharm Sci. 2012;74:302-311.
68. Niwa M, et al. Quantitative analysis of the layer separation risk in bilayer tablets using terahertz pulsed imaging. Int J Pharm. 2013;452:249-256.
69. Zacour BM, et al. Correlating bilayer tablet delamination tendencies to micro-environmental thermodynamic conditions during pan coating. Drug Dev Ind Pharm. 2014;40:829-837.