REVIEW ARTICLE JPAR 2020

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Recent Approaches and Challenges in Bilayer Tablet Technology

Bibaswan Mishra*, Bhabani Shankar Nayak, Biswaranjan Mohanty, Satyajit Panda

Faculty of Pharmacy, Department of Pharmaceutics, Institute of Pharmacy and Technology, Salipur, Cuttack-754202, Odisha, India.

Received: 01.12.2020 Revised: 14.12.2020 Accepted: 22.12.2020 Published: 30.12.2020

ABSTRACT: The present basis for drug delivery system is to deliver the medicament rapidly so as to attain the quick therapeutic effect and maintain the effect for an extended period time through releasing the drug in a controlled manner. Bilayer tablet technology is one of those technique that contains an immediate release layer and an extended release layer. The technology has proven tremendous accessibility to counter several diseases and ailments that require both functionality. It is also possible to deliver multiple drug to achieve different therapy using a single dosage form. Bilayer tablet system has successfully used in the treatment of diabetes, cardiovascular and inflammatory diseases. The aim of the present study is to discuss about various approaches to bilayer tablet technology and a detailed recent characterization technique in analyzing its parameters.

Corresponding author*
Dr. Bibaswan Mishra
Assistant Professor
Institute of Pharmacy and Technology,
Salipur, Cuttack, Odisha, India.
Tel: +91-98613 38249
Mail ID: drbibaswanmishra@gmail.com

Keywords: Bilayer, Tablet Technology, Dissolution, Stability, Incompatible, Bioavailability.

INTRODUCTION:

Oral drug delivery system covers a majority proportion of the total modern formulations. Solid orals are the preferred route of drug administration because of better patient compliance and ease manipulation in the dosage regimen. Several novel drug delivery systems have gained acceptance and researchers still show interest in modified tablets such as controlled/sustained release tablets, delayed release tablets, compression coated tablets and oral osmotic pumps [1-3]. For better therapeutic activity immediate attainment of effective serum concentration is required to get immediate relief

from symptoms. Similarly the sustained action is required though constant release of medication to maintain the plasma concentration within the therapeutic window. Hence bilayer tablets are developed to manufacture both the approaches into a single tablet as a fixed dose combination as shown in Fig 1 [4].

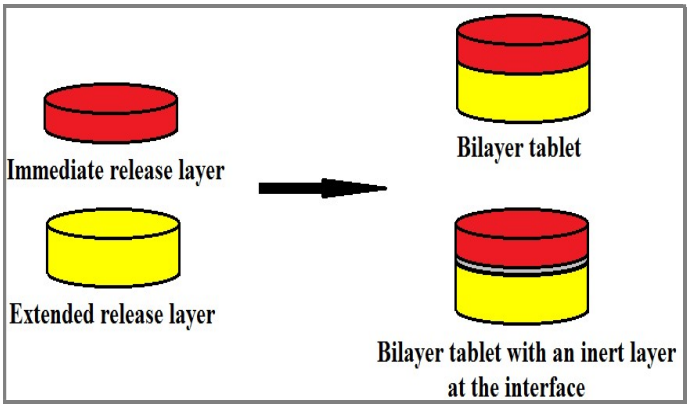

Fig 1. General appearance of bilayer tablets.

The important advantages associate with bilayer tablet are A single API can be administered with two different release profile to get immediate and sustained effect [5]; Two different APIs can be administered with dissimilar therapeutic activity [6]; Physical separation between two physically or chemically incompatible medicaments can be achieved [7]; The reduction in units of daily dose is possible [8]; Synergistic effect can be accomplished in right combination of drugs [9]; The design of bilayer tablet is very simple over other complex-configuration dosage form and Patient compliance can be improved; vii) Manufacturing is cost effective and easy for large scale manufacturing [10].

Despite the several advantages, few challenges are associated with the suitability of the final product. The characterisation of tablet is important to ensure the optimum tablet properties as the failure in the dosage form may lead to suboptimal or toxic effect in patients. The study also emphasizes the recent novel approaches that can be applicable to this dosage form. The review contains a detailed evaluation procedure to study all empirical parameters related to bilayer tablets [4].

MAJOR CHALLENGES AND REMEDIES ASSOCIATED TO BILAYER TECHNOLOGY:

It is evident that bilayer tablets carry some major advantages over the conventional tablet and sustained release tablet when used alone. But researchers find several issues associated with the development of a robust bilayer tablet manufacturing techniques [11-15].

- The non-uniformity in the weights of two individual layers is observed.
- Ineffective binding results at the interface of the two layers because of the high elastic modulus ratio.
- Release of part of the sustained release layer along with the immediate layer may be possible.
- Contamination at the adjacent layer may occur.
- The tablet has a tendency to delaminate at the non-planer interface.
- The tablet hardness is insufficient.
- Due to the large size of the particle, it is difficult to swallow.

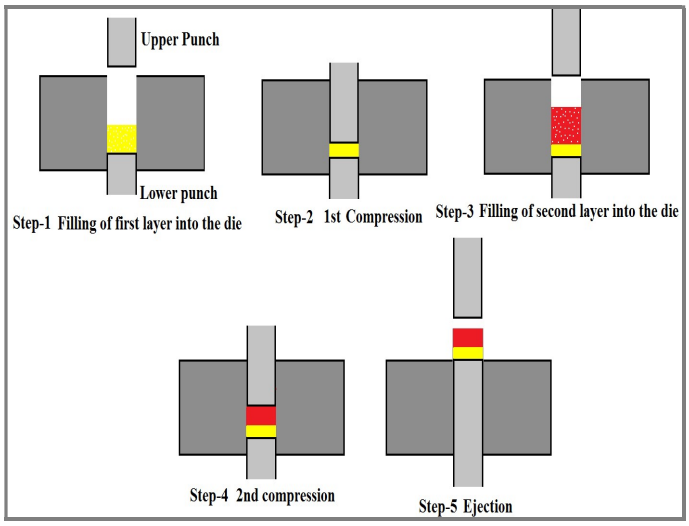

Fig 2. Step by step approach of bilayer tablet manufacturing.

Effect of material properties:

The material properties such as plasticity, viscoelasticity and brittleness largely affect the bilayer tablets. The compression behaviour depends on the plastic/elastic characteristics of the API and/or the excipients. In such cases, the plastic flow or the elastic recovery should not surpass the bond strength [16].

Effect of compression forces:

The mechanical integrity of a bilayer tablet is a function of the compression force applied for the adhesion of two layers at the interface. Inappropriate compression force may result in delamination and reduction of tensile strength. If the ingredients of the first layer tablet is more elastic than the second layer, compression force weakens the strength of bilayer tablet during unloading phase and ejection of tablet [17].

Effect of lubricating agent:

Lubricating agents are mixed in the tablet excipients to reduce the friction between the powder/granules, and

punch and/or die cavity during the compaction process. The coating of lubricants on the powder particles hinders an optimum interfacial interaction between the two layers. Kottala, *et al*. (2012a) suggested in his study that an increased concentration of magnesium stearate in bilayer tablet formulation decreases the interfacial strength [13].

Effect of environmental factor:

Hygroscopic porous particles in the tablet excipients absorb moisture and lead to layer expansion during storage. It also changes the Young's modulus of elasticity. Such deviations may weaken the interface between the layers leading to time dependent delamination. Examples of such hygroscopic substances showing this behavior are Poly Vinyl Pyrrolidine, Sodium starch glycolate, Microcrystalline Cellulose and colloidal silicon dioxide [18-20].

CHARACTERIZATION OF BILAYER TABLET:

General appearance and organoleptic characteristics:

The general appearance of the bilayer tablet has an important feature in patient compliance. The tablet size, shape, colour, odour, taste and surface texture should be evaluated for general acceptability of patients. A tablet's shape and size should be dimensionally stated.

Thickness of bi-layer tablets:

The tablet thickness is measured using a standard slide calliper or using a micrometre instrument for ten tablets. The uniformity of thickness within the statistical limit is the prerequisite ensuring the content uniformity and consistency of applied compressional force for each unit of bilayer tablets [21].

Weight variation:

For the weight variation evaluation procedure, standard procedures recommended in the official books to be followed. The appropriate result of this study ensures an approximation of content uniformity [22].

Friability:

Friability of bilayer tablets is determined as a measure of sustaining the integrity of the tablet or resistance to loss in weight due to shock and friction during its handling and transportation. Roche friabilator is used to determine the friability using standard procedure specified in official books. The limit for acceptance is weight loss within 1 % of initial weight for 20 tablets 4 min [23].

Hardness:

The resistance to capping, abrasion and breakage during handling, shipping and storage can be assessed by performing the hardness test of the tablet. Monsanto and Pfizer hardness testers are used for this purpose. This helps in determining the requirement of adjusting compression force during manufacturing of bilayer tablets at different steps. The tablet should not be excessively hard which might not disintegrate and the release of medicament of immediate release layer is delayed. As per the Indian Pharmacopoeia, acceptable hardness of tablet is considered to be 4 kg/cm^2 [24].

Dissolution:

Dissolution is determined as the percent of drug dissolve per unit time in a particular solvent system under a condition as specified in the official monograph for that particular drug.

The two layers of bilayer tablets may contain the same drug or different drug substance. The study is performed at least in triplicate and the result is expressed with standard deviation [25].

Drug content:

The drug content of the drug substances present in different layers can be determined by taking the sample of the solvent in which the dissolution study is performed after completion of dissolution. Appropriate calculation is made to compensate loss due to sampling during dissolution study. The study is performed at least in triplicate and the result is expressed with standard deviation [26].

Stability:

ICH guidelines specify the appropriate condition for the long term stability testing for drug products. After a period of 15 days of storage under these conditions, the bilayer tablets are tested for physical characterizations i.e. hardness, drug content, dissolution and friability [27].

RECENT APPROACHES TO BILAYER TECHNOLOGY:

Researchers and pharmaceutical manufacturers have found interest in the development of bilayer tablets in recent years. Various approaches such as floating, swelling and mucoadhesive can be incorporated to bilayer tablets in addition to variable release profiles from two layers. Some of the novel ideas identified so far are discussed as follows.

Intra gastric buoyant approach:

There are low density tablets that upon oral administration floats over the gastric content of the stomach. The immediate release layer delivers the drug rapidly so as to get rapid onset of action. On the other hand the drug releases from the controlled release layer in a controlled manner to maintain the serum drug concentration steady. Subsequently the system absorbs fluid and breaks down to smaller particles that can be easily passed from the stomach. Complete drug release within the gastric emptying time is the prerequisite for the fate of the system [28].

Mucoadhesive approach:

In this approach, after administration of the dosage form, the immediate release layer delivers the API to attain the minimum effective concentration in the blood. But the extended release layer absorbs the biological fluid and becomes viscous, tacky and sticky. Such a system has special affinity to the mucous of gastric layer whereby it attaches and discharges the drug to maintain the effective serum level. However this approach is yet to be administered to humans because it is unsuccessful due to rapid shading and inconsistent incidence of mucous in GIT [29].

Table 1. Examples of some bilayer tablets for common rationale.

Drugs	Rationale of bilayer tablet
Diclofenac Sodium, Paracetamol	Synergistic effect for pain [31]
Metformin HCl, Pioglitazone	Synergistic effect for diabetes mellitus [32]
Pioglitazone HCl, Gliclazide	Synergistic effect for Type II Diabetes treatment [33]
Losartan potassium	Biphasic release for hypertension treatment [34]
Misorostol, Diclofenac	For minimizing contact between drugs [35]
Metformin, Glipizide	Synergistic effect for diabetes [36]
Atorvastatin, Atenolol	Hypercholesterolemia and hypertension treatment [37]
Indomethacin	Biphasic drug release [38]
Atenolol, Lovastatin	Synergistic effect for biphasic release profile and hypertension [39]

Swellable unit approach:

After administration, these types of system disaggregate, unfold as swellable units that restrict their passage through pylorus till a programmable period. Once the drug is released completely, these are degraded by breaking down further and are cleared by the gastric emptying. These are considerably small in size and comprise both immediate and extended release layer [30].

CONCLUSION:

Bilayer tablet is a suitable technique for the sequential release of the same or two different drug desiring varied release profiles. Instant drug release is achieved from the immediate layer followed by a sustained release for an extended time period. Though few challenges are there in developing a robust bilayer tablet, meticulous study of the parameter described in this review may enlighten the pharmaceutical scientist in the development of bilayer tablets with optimum characteristics. The various recent novel approaches discussed in the review with the characterization study definitely draw the attention of researchers adding newer concepts and discoveries to the bilayer technology.

ACKNOWLEDGEMENT:

Authors thank to Institute of Pharmacy & Technology, Salipur, Cuttack, for providing library facility to carry out this review study.

REFERENCES:

1. Abdul S, Poddar SS. A flexible technology for modified release of drugs:multi layered tablets. J Control Rel, 2004; 97: 393-405.
2. Wong PSL, Gupta SK, Stewart BE. Osmotically controlled tablets. In: Rath-bone MJ, Hadgraft J, Roberts MS, editors. Modified-Release Drug Delivery Technology. London: Informa Healthcare; 2002. pp. 101-114.
3. Ozeki Y, Ando M, Watanabe Y, Danjo K. Evaluation of novel one-step dry-coated tablets as a platform for delayed-release tablets. J Control Rel, 2004; 95: 51-60.
4. Abebea A, Akselib I, Sprockela O, Kottalaa N, Alberto MC. Review of bilayer tablet technology. Int J of Phar, 2014; 461: 549-558.
5. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layertablet of metoclopramide hydrochloride and ibuprofen. AAPS Pharm Sci Tech, 2008; 9: 818-827.
6. Nirmal J, Saisivam S, peddanna C, Muralidharan S, Nagrarajan M. Bilayertablets of atrovastatin calcium and nicotinic acid: formulation and evaluation. Chem Pharm Bull, 2008; 56: 1455-1458.
7. Vaithiyalingam SR, Sayeed VA. Critical factors in manufacturing multilayered tablets – assessing

material attributes, in-process controls, manufacturing process and product performance. Int J Pharm, 2010; 398: 9-13.
8. La Force C, Gentile DA, Skoner DP. A randomized, double-blind, parallel group, multicenter, placebo-controlled study of the safety and efficacy of extended release of guaifenesin/pseudo ephedrine hydrochloride for symptom relief as an adjunctive therapy to antibiotic treatment of acute respiratory infections. Post Grad Med, 2008; 120: 53-59.
9. Serebruany VL, Malinin AI, Sane DC, Jilma B, Takserman A, Atar D, *et al*. Aggrenox and aspirin in patients after ischemic stroke: the Aggrenox versus aspirin therapy evaluation trial. Eur J Pharmacol, 2004; 3: 315-324.
10. Niwa M, Hiraishi Y, Iwasaki N, Terada K. Quantitative analysis of the layer separation risk in bilayer tablets using terahertz pulsed imaging. Int J Pharm, 2013; 452: 249-256.
11. Charman SA, Charman WN. Oral modified-release delivery systems. In: Rathbone MJ, Hadgraft, J, Roberts MS, editors. Modified-Release Drug Delivery Technology. London: Informa Healthcare; 2002. pp. 1-19.
12. Akseli I, Abebe A, Sprockel O, Cuitino A. Mechanistic characterization of bilayer tablets. Powder Technol, 2013; 236: 30-36.
13. Kottala N, Abebe A, Sprockel O, Bergum J, Nikfar F, Cuitino A. Evaluation of the performance characteristics of bilayer tablets: Part I. Impact of material properties and process parameters on the strength of bilayer tablets. AAPS Pharm Sci Tech, 2012a; 13: 1236-1242.
14. Kottala N, Abebe A, Sprockel O, Nikfar F, Cuitino A. Influence of compaction properties and interfacial topography on the performance of bilayer tablets. Int J Pharm, 2012b; 436: 171-178.
15. Martin K, Abebe A, Raghavan K, Stamato H, Timmins P. Bilayer tablets: effects of upper punch penetration on the potency of the second layer. Chicago, IL: AAPS Annual Conference; 2012.
16. Eiliazadeh B, Briscose B, Sheng Y. Investigating density distributions for tablets of different geometry during the compaction of pharmaceuticals. Part Sci Technol, 2003; 21: 303-316.
17. Eiliazadeh B, Pitt K, Briscose B. Effects of punch geometry on powder movement during pharmaceutical tabletting. Int J Solids Struct, 2004; 41: 5967-5977.
18. Podczeck F, Al-Muti E. The tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. Eur J Pharm. Sci, 2010; 41: 483-488.
19. Klinzing G, Zavaliangos A. Understanding the effect of environmental history on bilayer tablet interfacial shear strength. Pharm Res, 2013; 30(5): 1300-1310.
20. Zacour B, Pandey P, Subramanian G, Gao Z, Nikfar F. Correlating bilayer tablet delamination tendencies to micro-environmental thermodynamic conditions during pan coating. Drug Dev Ind Pharm, 2014; 40(6): 829-837.
21. Akhtar M, Jamshaid M, Zaman M, Mirza AZ. Bilayer tablets: A developing novel drug delivery system. J Drug Del Tech, 2020; 60:102079.
22. India. Pharmacopoeia of India. 8th ed. Delhi: Controller of Publications; 2018.
23. John AS, Sathesh B, Divakar G, Jangid MK, Purohit KK. Development and evaluation of buccoadhesive drug delivery system for Atorvastatin calcium. J Curr Pharm Res, 2010; 1:31-38.
24. Karwa P, Kasture P. Formulation and *in-vitro* evaluation of Bilayer tablets of zolpidem tartrate for Biphasic drug release. Int J Parama Tech Res, 2011; 3 (4): 1919-1929.
25. Rahman Z, Ali M, Khar R. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm, 2006; 56 (1): 49-57.
26. Sharma V. Formulation, optimization and evaluation of bilayer tablet of antihypertensive drug. J Drug Deliv Therapeut, 2019; 9 (4): 704-708.
27. Podczeck F. Theoretical and experimental investigations into the delamination tendencies of bilayer tablets. Int J Pharm, 2011; 408 (1-2):102-112.
28. Karudumpala S, Gnanaprakash K, Venkatesh B, Sankar P, Balaji G, Vidya Sagar N. Formulation and evaluation of gastro-retentive floating bilayer tablets of nifedipine. Am J Alzhe Disease Dem, 2013; 3: 341-357.
29. Yadav A, Jain DK. Formulation development and in vitro characterization of bilayer and floating-bioadhesive tablets of propranolol hydrochloride. Asian J Pharm Life Sci, 2011; 1 (1): 1-12.
30. Ijaz H, Qureshi J, Danish Z, Zaman M, Abdel-Daim M, Bashir I. Design and evaluation of bilayer matrix tablet of metoprolol tartrate and lisinopril maleate. Adv Polym Technol, 2017; 36 (2):152-159.

31. Gohel M, Parikh R, Nagori S, Jethwa B. Fabrication and evaluation of bilayer tablet containing conventional paracetamol and modified release diclofenac sodium. Indian J Pharm Sci, 2010; 72 (2): 191-196.
32. Rajendran N, Natarajan R, Subhashini R, Patel H. Formulation and evaluation of sustained release bilayer tablets of metformin HCl and pioglitazone HCl. Int J Curr Pharm Res, 2011; 3 (3): 118-122.
33. Saif AA, Alburyhi MM, Noman MA, Almaktari AM. Formulation and evaluation of trimetazidine hydrochloride and clopidogrel bisulphate multi-unit solid dosage forms. J Chem Pharmaceut Res, 2014; 6(2): 421-426.
34. Hiremath D, Goudanavar P, Azharuddin M, Udupi R, Sarfaraz M. Design and characterization of bilayer controlled release matrix tablets of losartan potassium. Int J Pharmacol Res, 2010; 2(4): 34-39.
35. Deshpande RD, Gowda DV, Mahammed N, Maramwar DN. Bi-Layer Tablets - An Emerging Trend: A Review. Int J Pharm Sci Res, 2011; 2(10): 2534-2544.
36. Bagyalakshmi J, Krishna YP, Ravi TK. Bilayer tablet formulation of metformin hydrochloride and glipizide: A novel approach in the treatment of diabetes, Int J Pham Sci Rev Res; 2011; 8(2): 209-215.
37. Dey S, Chattopadhyay S, Mazumder B. Formulation and evaluation of fixed-dose combination of bilayer gastroretentive matrix tablet containing atorvastatin as fast-release and atenolol as sustained-release. Bio Med Res Int, 2014; 2014: 396106.
38. Jain J, Marya B, Mittal R, Patel M. Formulation and evaluation of indomethacin bilayer sustained release tablets. Int J Pharm Tech Res, 2011; 3 (2): 1132-1138.
39. Kulkarni A, Bhatia M. Development and Evaluation of Regioselective Bilayer Floating Tablets of Atenolol and Lovastatin for Biphasic Release Profile. Ira J Pharm Sci, 2009; 8 (1): 15-25.

Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Mishra B*, Nayak BS, Mohanty B, Panda S. Recent Approaches and Challenges in Bilayer Tablet Technology. J Pharm Adv Res, 2020; 3(12): 1080-1085.