Available online on 15.01.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

Composition and Drug Release Characteristics of Bi-layered and Multi-layered Tablets: A Comprehensive Review

Fatiha Momtaz Ferdousi [1], Farhani Safrin [2], Md. Nawshed Ali [3]*, Abdullah Al Juhan [4], Priyanka Akter [5]

[1] Department of Chemistry, Bhasha Soinik Ajit Guha Mahabiddalay, Cumilla.

[2] Department of Chemistry, Gunabati Degree College, Cumilla.

[3] Department of Pharmacy, State University of Bangladesh, Dhaka.

[4] Department of Pharmacy, Jagannath University, Dhaka.

[5] Department of Pharmacy, Manarat International University, Dhaka.

Article Info:

Article History:

Received 12 Oct 2024
Reviewed 26 Nov 2024
Accepted 23 Dec 2024
Published 15 Jan 2025

Cite this article as:

Ferdousi FM, Safrin F, Ali MN, Juhan AA, Akter P, Composition and Drug Release Characteristics of Bi-layered and Multi-layered Tablets: A Comprehensive Review, Journal of Drug Delivery and Therapeutics. 2025; 15(1):169-176 *DOI: http://dx.doi.org/10.22270/jddt.v15i1.6936*

*Address for Correspondence:

Md. Nawshed Ali, Department of Pharmacy, State University of Bangladesh, Dhaka.

Abstract

Multilayer and Bilayer tablets are winning popularity over single-layer tablets because of their controlled release advantages. Since each layer of API must be compatible with the others and with excipients to extend the effects of the medication or drugs and improve patient compliance, technology for creating multilayers and bilayers is less widespread than that for single-layer tablets. Hydrophilic polymers are more frequently employed in the formulation of biliary and multilayer tablets as both medication carriers and release barriers. But the ratio of using polymer is different from each other in the drug barrier layer and carrier layer that can make alteration by a researcher to develop a difference in the release rate of different APIs in a single unit of the tablet. With a larger surface area and a faster rate of drug release over time, multilayer and biliary tablets can help mitigate the non-linearity and drug interactions that arise with diffusion-controlled matrix devices. This review article covers the different techniques used to create biliary and multilayered tablets as well as the challenges associated with their formulation.

Keywords: Multi-layer tablets, Bi-layer tablets, Drug release, Tablet manufacturing

Introduction:

Bi-layer & Multi-layer tablets, which combine two or more Active Pharmaceutical Ingredients (API) in a single dosage form, have gained popularity in the pharmaceutical industry over the past ten years as a way to improve patient convenience and compliance. [1] This tablet formulation technique enhances the drug's availability in the body for a longer period of time and helps achieve zero-order release and pulsatile release rate. Film coating pellets, osmotically driven systems for advanced tablet and capsule materials, controlled ion exchanging systems, three-dimensional printing technology, and electrostatic deposition technology can all be used to customize the drug release rate. [2] The aspire of modifying the discharge rate of the drug is to make the best use of therapeutic effects, and increase the therapeutic regimen by controlled and slow release of the drug to ensure greater compliance to the patients.

The ingredients in multi-layered tablets may be released in different ways or at different rates; for example, each layer may have a distinct sustained-release substance, or one layer may contain a loading dosage and the other a sustaining dose of the same medication. These multi-layer tablets can be formulated in a number of ways. [3] Hydrophilic polymers are appropriate for multilayer and bi-layer tablets because it has demonstrated that hydrophilic polymer has a time-dependent curve in dissolution testing parameters. In the initial layer of the multilayer tablet, drug particles illustrate nearly first-order diffusion of tablet particles and swiftly dissolve the drug particle in the tablet surfaces. Improved drug discharge which is seen in the prior stage of tablet dissolution, is decreased with time. [4]

Extended drug release is necessary to sustain the therapeutic effect in certain pathological circumstances, while prompt release of the dose is necessary to offer a

quick commencement of action. [5] A multi-layer an bi-layer tablet preparation is one way to implement the dual drug release notion.[6,7] Whether as a controlled-release or oral immediate-release system, multi-layer tablets have grown in popularity during the past few years .[8,9] The goal of the multi-layer and bi-layer tablet is to either administer two or more medications at separate rates or release two or more medications at the same time with a chosen release rate. [8,10] Multi-layer tablets are favored due to the controlled release profiles of the active ingredients. [11,12] Modified/ controlled release formulations offer more benefits than immediate release dosage forms with the same active substance. [13] Products with modified/controlled drug release are designed to optimize the treatment regimens and provide greater patient convenience and compliance. [14]

This review article aims to evaluate the composition of different multilayer and bilayer tablets and technologies used by different scientists for formulating multilayer and bilayer solid dosage forms. The objectives of this article are to assess different polymer and their impact on the formulation of multilayer and Bilayer tablets, to estimate different pharmacokinetics shown by Multilayer and Bilayer tablets, and to understand the drug discharge mechanism of multilayer and bilayer from the solid unit of dosage form, to reckon different technologies followed for different formulation with different API, to evaluate different factors and challenges in the formulation of multilayer and bilayer tablets.

Drug Release Profile by Multilayer and Bi-layer tablets:

Multilayered and Bi-layered tablets are classically categorized as per layering constitution into a tablet in tablet, triple-layered tablets, bi-layer tablets, and while drug release kinetics are categorized into zero-order controlled release profile, surrounded coated core tablets, time programmed release profile, bimodal release profile, and quick/slow delivery system. [15] Tablets with inconsistent drug discharge profiles can be fashioned by the changeable composition of formulation, design of individual layers, and geometry of dosage form. For instance, in zero-order prolonged formulations [16], tablets typically consist of a hydrophilic/hydrophobic polymer matrices structure or protective layers wherein the discharge of drug pattern is monitored either by the develop of coated later in the central of hydrophilic matrix tablet on both split ends with polymers which are hydrophobic to accomplish sustainable discharge, or by coating the core part of the tablet with Lipsome matrix on each sides with acquaphobic polymers to attain sustainable discharge of drug, either by just coating single side of acquaphobic polymers and parting the another side opened to permit restricted release of the active ingredient in diverse discharge medias; while in quick/slow drug delivery systems [17], tablets illustrate an initial fast drug release, following the second phase of delayed discharge profile to keep a consistent plasma levels; and in the case of time-programmed delivery systems [18], tablets generally consists of a lastly, in bimodal controlled release [5], tablets display sigmoidal releasing patterns, with an early quick release of drug, a retarded distribution of the drug ingredient, and a third period of rapid drug release.

Table 1: Polymers used as barrier and drug carrier in multilayer matrix tablet [17]

Desired drug release kinetics	Polymers are used as a barrier layer	Polymers used as drug carrier
zero-order or nearly zero order	Hydrophilic (Xanthan gum from Locust bean)	Hydrophilic (anionic SCMC)
Zero-order release kinetics	Hydrophilic (Carbopol) Hydrophobic (EC) Hydrophilic (SCMC) Hydrophilic (Guar gum)	Hydrophilic (Carbopol) ` Hydrophilic (HPMCA&HPMC) Hydrophilic (Xanthan gum) Hydrophilic (Guar gum)
Zero-order release	Hydrophilic (HPMC K4M, HPC, NaCMC	Hydrophilic (Guar gum)
Zero-order drug release kinetics	Hydrophilic (Methocel®K15M) and Hydrophobic (Carnauba wax)	Hydrophobic (Carnauba wax)
Non-linear drug release	Hydrophobic (Carnauba wax)	Hydrophobic (Carnauba wax)
Retarded to a lesser extent drug release	Hydrophobic	Hydrophilic
Retarded drug release	Hydrophobic	Hydrophilic

Characteristics of multilayer and bi-layer tablets [19]

- ✓ Delayed discharge of drug in the upper gastrointestinal tract.
- ✓ The major constituent in multilayer tablets is polysaccharides which are biodegradable.
- ✓ A number of species of microorganisms' has the aptitude for disgrace multilayer tablets.

- ✓ Can be prepared using conventional pharmaceutical tablet preparation techniques**.**
- ✓ Since having a large total of polysaccharides in multilayer tablets, the discharge rate of drug-enhanced the in the colon.

Advantages of using multilayer and bi-layer tablets [17]

- Fluctuation of drug label concentration is reduced by using multilayer and bi-layer tablets because sustained is achieved and minimum concentration is maintained in the blood and plasma.
- Intake of the drug in the nighttime can be avoided with multilayer and bi-layer tablets by sustained release of the drug.
- Patient reliability is augmented by using multilayer and bi-layer drugs.
- Intake of drug with an interval of time is abridged because of having sustained release characteristics in multilayer and bi-layer tablets.
- Because of sustained-release characteristics in multilayer and bi-layer safety areas of highly potent drugs can be enhanced

Disadvantages of using multilayer and bi-layer tablets [17]

- **Poor result between in-vivo and in-vitro studies**: Due to using different technology and different hydrophilic polymer in the matrix system and their characteristics, in-vivo and in-vitro results cannot be predicted.
- **Dumping of dose**: Carrying modified or sustained release characteristics in regular dosing of drugs can be dumped and the pharmacological effect of drugs can be seen for a longer time.
- **Adjustment of dose**: Potential effect of dosage adjustment will be reduced.
- **Poor availability**: Using barriers in multilayer and bi-layer tablet preparation causes poor availability of the drug in the systemic circulation
- **Drug clearance**: Having variation in release rate in multilayered tablets results in first-pass clearance of drugs.
- **Dose preparation**: Minimal dose preparation like 1gm of API cannot be prepared by using multilayer technologies. Because compression of tablets in a different layer is harder due to having a low quantity of drugs.

Objectives for designing multilayer and bilayer tablets [20,21,22]

1. To control the delivery rate of either single or two different active pharmaceutical ingredients(s).

2. To separate incompatible APIs from each other, to control the release of one API from one layer by utilizing the functional property of other layers (such as osmotic properties).

3. To modify the total surface area available for API layer by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.

Reason for choosing multilayer and bilayer tablet over the conventional tablet

Factors making the multilayer tablet more convenient:

- In a multilayer tablet system, tablets are manufactured in different layers. Most of the tablets are compressed in more than one layer in which most inner layer is compressed with a larger force than the outer layer which helps in the retardation of drug release. [23] Moreover, using multiple layers in a tablet with more than an active ingredient can also be used in a single dosage unit. That is suitable for combination drug therapy. [24]
- Having multiple layers in a single tablet, it becomes easier to use incompatible API in a single unit of the dosage form with different release rates at different release sites by using physical characteristics of ingredients in a multilayer tablet for instance osmotic property of API.
- Modification of available total surface area for active ingredients in the tablets can be modified by increasing or decreasing compression force between different layers which will help in achieving an erodible barrier for the modified rate of drug content release. [21]
- Using multilayer tablets gives the facility of administrating multiple APIs at one time and due to the structure of the layer first-order release rate can also be achieved with prolonged life of drug product and facilitate the novel delivery system of a drug such as buccal delivery system [25], flotation of a tablet for gastro-retentive drug delivery system [26] and chewing device. [27]

Factors that make the bilayer tablet more convenient:

Bilayer tablets are also a single unit of dosage form and provide the maximum capability of all other oral dosage formulations in the market with greater precision of dose API content and lower variability. Moreover, at a lower cost than other oral dosage forms, bilayer tablets can be formed. They are also lighter and more compact than multilayer tablets and other conventional dosage forms.

Having the facility of formulating a combination of different API packing costs can also be reduced in the bilayer tablet. It is comparatively easier to mask unwanted odour or taste and also bring desired odour and taste using appropriate excipients in the dosage form. Bilayer tablets also provide greater microbial and chemical stability than other dosage forms. The release rate of bilayer tablets can be altered by altering

compression force and changing the face of the punches during tablet compression.

Methodology / Technology for multilayer and bilayer tablet

For the preparation of bi-layer tablets, granules of the tablet must be prepared with different sizes of powder particles. For proper dosing of the drug by tablet granules which going to be positioned in the bottom layer into the die from the first hopper. Different technologies used for layered tablets are discussed in following table

Table 2: Methodology / Technology for multilayer and bilayer tablet

Technology	Description
OROS® Push Pull Technology	Consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core. [28]
L-OROS™ Technology:	Lipid-containing soft gel carries drug contents in a dissolved form and complete coating with a barrier layer that retard the drug release which is followed by a semi-permeable membrane and osmotic push layer with a drilled orifice which permits to release of drug content from the system. [29]
EN SO TROL Technology:	This technology is mostly used for the controlled release of the drug from the system. In this technology, the core powder also carries wicking agents which allow drawing water from the surface to the inside of the core through the orifice. The core layer is also surrounded by a semi-permeable layer which delays the drug release. [30]
DUROS technology	The system consists from an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and reglious minute quantity of concentrated form in continues and consistent from over months or Year. [31]
DUREDAS™ technology (Dual release drug delivery system)	Two separate direct compression phases that combine the immediate release layer and the aquaphilic layer in a fixed tablet dosage form, culminating in a controlled aquaphilic matrix system that progressively consumes liquid from the gastrointestinal tract (GIT). [1,32] It transforms into a sticky, porous gel upon absorption, principally acting as a barrier between the dosage form and the nearby fluid. As the gel expands, the surrounding medium penetrates and disperses the pharmacological substance. [33]
Gemini technology	More than one active drug compound can be delivered with different release rates in a single unit of the dosage form. [34]
Programmable oral drug absorption system (PRODAS)	This technique, which is a hybrid of blend membranes and hydrophilic composite tablet technologies, is generally utilized to deliver a medication combination in a single dose. [35]
Erodible moulded multilayered tablets	The drug release from a highly permeable moulded multilayered tablet is driven primarily by the erosion of the polymeric matrix, which is controlled by the right selection of coating materials and the optimum design of the matrix geometry. [36]
Glueing pills technology (GPT)	Gluing Pills Technology (GPT) active drugs are blended with necessary excipients and compacted into a monolayer tablet. Both are cemented together through the GPT, which employs a viscous solution of gelatin or PVP (polyvinylpyrrolidone) K-90 as a bonding agent. Raman microscopy research is used to qualitatively evaluate the function of the glue layer as a barrier against cross-contamination among two monolayer tablets. [37]
SODAS® Technology: (Spheroidal Oral Drug Absorption System	This method is focused on the formation of sustained-release beads and is distinguished by its adaptive nature, allowing the production of bespoke pharmaceutical formulations that react directly to the needs of unique drug candidates. [38]

Difficulties in manufacturing multilayer and bilayer tablet tablets

Multilayer and bilayer tablet tablets might be composed of a core and one or more barrier layers and/or a core and outer shell in the case of press-coated tablet. As they are not easy to design and manufacture, several problems that affect the properties of the dosage form may emerge during production. Some of the principal difficulties include: inadequate hardness [39], imprecise regulation of layers and tablet weight [40], elastic mismatch between conterminous layers [41], and susceptibility to delaminate [39] during the various stages of manufacture.

Inadequate manufacturing process of multi-layer tablets may contribute to the delamination (distinct separation of layers along the interface). The delamination may occur directly after compression, at a subsequent step of technological process, or during storage [10,42] and could take place between adjacent layers (interlayer delamination) or within one of the layers (intralayer delamination). [43] As a consequence, the patient cannot receive one of the intentional substances or receives an improper dosage. Therefore, to minimize the possibility of their occurrence, it is necessary to pay particular attention to the applied substances properties and formulation process parameters. These include the tools and materials which may be incorporated in the design of multi-layer tablets, the factors that cause delamination, the order and weight proportion of layers, the mechanical strength of tablet and each layer, and the interphase adhesion of the layers. [44]

Table 3: Various works in the field of multilayered tablets

Drugs	Dosage form	Method of preparation	Uses	Ref
Atorvastatin immediate-release layer, Ezetimibe sustained-release layer.	Modified-Release Bilayer Tablets	Compaction	Hyperlipidemia	45
Atorvastatin calcium immediate release layer, Metformin hydrochloride sustained release layer.	Bilayered tablet	Compaction	Anti-hyperglycaemic agent in patients with type 2 diabetes.	46
Aspirin immediate release layer, Isosorbide 5-mononitrate sustained release layer.	Sustained bilayer tablets	wet granulation and compression technique	Angina and heart disease	47
Cyclobenzaprine hydrochloride sustained release layer, Diclofenac potassium immediate release layer.	Bilayered tablet	wet granulation method	Severe pain due to inflammation and muscle spasms.	48
Cefixime trihydrate immediate release layer, Dicloxacillin sodium Sustained release layer.	Bilayered tablet	wet granulation process	Bacterial infections	49
Cefuroxime and clavulanic acid are both fast-release layers.	Bilayered tablet	Dry Granulation and Compression	Uncomplicated urinary tract infections and reproductive tract infections	50
Amoxycillin immediate release layer, Potassium Clavulanate sustained release layer.	Bilayered tablet	Dry Granulation and Compression	Bacterial infections	51
Rifampicin and pyrazinamide are both immediate-release layers, Isoniazid sustained release layer.	Fixed-Dose Combination Bilayer Tablets	wet granulation method and direct compression	Tuberculosis.	52
Tramadol 35% immediate-release layer and a 65% sustained release layer.	Bilayered sustained release tablet	Compaction	Cancer pain	53
Salbutamol and theophylline both sustained release layers.	Bilayered sustained release tablet	Wet granulation method and direct Compression	Used in asthma for prolonged bronchodilation	54

Atorvastatin calcium, immediate release layer, and Nicotinic acid sustained release layer.	Bilayered tablets	Aqueous and non-aqueous granulation method.	Reduce the low-density lipoprotein cholesterol	25
Metoclopramide hydrochloride immediate release layer and Ibuprofen sustained release layer.	Bilayered tablets	Direct compression	Migraine	55
Atenolol immediate release layer and Amlodipine sustained release layer.	Bilayered tablets	Dry granulation technique	Antihypertensive	56
Glipizide immediate release layer and Metformin hydrochloride sustained release layer.	Bilayer matrix tablet	Direct compression technique	Type 2 diabetes.	57
Atenolol sustained release layer and Lovastatin immediate release layer.	Bilayer floating tablets	Direct compression method	Hypertension and hypercholesterolemia.	23
Montelukast sustained release layer and levocetirizine immediate release layer.	Bilayered tablets	wet granulation method	Allergic rhinitis and bronchial asthma.	58
Simvastatin Immediate release layer and Atenolol sustained release layer.	Gastro-bilayer Floating Tablets	Direct compression method	Combination therapy for hypertension and dyslipidaemia	59
Aspirin and isosorbide 5-mononitrate are both sustained release layers	Sustained bilayer tablet	wet granulation and compression technique	Prevention of angina and heart disease	60
Ziprasidone HCl and trihexyphenidyl HCl both sustained release layers.	Bi-layer floating tablets	Direct compression method	Schizophrenia	61
Metformin HCl sustained release layer and Evogliptin tartrate immediate release layer.	Bilayer tablet	Direct compression method	Type 2 diabetes	62

Conclusion

Both Bi-layer and multi-layer tablets can help producers differentiate themselves from rivals, increase the potency of their goods, and protect themselves from counterfeiters. Several pharmaceutical industries and formulating scientists across the globe are working on the production of bi-layer and multi-layer tablets with the ultimate aim of a better health care system

Conflicts of Interest: None

Ethical approval: Not Applicable

Authors contribution

Fatiha Momtaz Ferdousi: Conception & Supervision.

Farhani Safrin: Investigation and Execution.

Md. Nawshed Ali: Drafting and construction of the body of the manuscript.

Abdullah Al Juhan: Critical Review & Processing.

Priyanka Akter: Literature Review & Interpretation.

Funding: Nil

Source of Support: Nil

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting in this paper are available in the cited references.

References:

1. Gopinath C, Bindu VH, Nischala M. An overview of bilayered tablet technology. Journal of Global Trends in Pharmaceutical Sciences. 2013;4(2):1077-85.

2. Abdul S, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. J Control Release [Internet]. 2004;97(3):393-405. https://doi.org/10.1016/j.jconrel.2004.03.034 PMid:15212872

3. Warnke G, Carpanzano T. Layer by Layer: The Fundamentals of Multi-Layer Tableting. https://www.jrspharma.com/pharma-wAssets/docs/technical-information/ti-layer-by-layer.pdf

4. Narasimhan B, Langer R. Zero-order release of micro- and macromolecules from polymeric devices: the role of the burst effect. J Control Release [Internet]. 1997;47(1):13-20. https://doi.org/10.1016/S0168-3659(96)01611-2

5. More S, Ghodekar S, Rane B, Bavaskar K, Patil M, Jain A. Multilayered tablet: a novel approach for oral drug delivery. International journal of pharmaceutical sciences and research. 2018;9(3):872-82.

6. Dey S, Mahanti B, Khila S, Mazumder B, Gupta SD. Formulation development and optimization of bilayer tablets of aceclofenac. Expert Opin Drug Deliv [Internet]. 2012;9(9):1041-50. https://doi.org/10.1517/17425247.2012.707187 PMid:22788786

7. Patra CN, Kumar AB, Pandit HK, Singh SP, Devi MV. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride. Acta Pharm [Internet]. 2007;57(4):479-89. https://doi.org/10.2478/v10007-007-0038-0 PMid:18165191

8. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM. Review of bilayer tablet technology. Int J Pharm [Internet]. 2014;461(1-2):549-58. https://doi.org/10.1016/j.ijpharm.2013.12.028 PMid:24370841

9. Al-Zoubi N, Malamataris S. Three-layer matrix tablets and simple approach of drug release programming. J Drug Deliv Sci Technol [Internet]. 2008;18(6):431-7. https://doi.org/10.1016/S1773-2247(08)50083-9

10. Klinzing G, Zavaliangos A. Understanding the effect of environmental history on bilayer tablet interfacial shear strength. Pharm Res [Internet]. 2013;30(5):1300-10. https://doi.org/10.1007/s11095-012-0969-0 PMid:23334778

11. Anuar MS, Briscoe BJ. Interfacial elastic relaxation during the ejection of bi-layered tablets. Int J Pharm. 2010;387(1-2):42-7. https://doi.org/10.1016/j.ijpharm.2009.11.031 PMid:19963050

12. Maurya SD, Prajapati S, Gupta A, Saxena G, Dhakar RC, Formulation Development and Evaluation of Ethosome of Stavudine, Indian J.Pharm. Educ. Res. 2010;44(1)

13. Mcginity JW. Aqueous polymeric coatings for pharmaceutical dosage forms. Marcel Dekker; 1997.

14. Adepu S, Ramakrishna S. Controlled drug delivery systems: Current status and future directions. Molecules [Internet]. 2021;26(19):5905. https://doi.org/10.3390/molecules26195905 PMid:34641447 PMCid:PMC8512302

15. Gavate NT, Gondkar SB, Saundagar RS. Multilayer tablet: a new trend in solid dosage forms. World Journal of Pharmaceutical Sciences. 2013;2:271-84.

16. Qiu Y, Chidambaram N, Flood K. Design and evaluation of layered diffusional matrices for zero-order sustained-release. J Control Release [Internet]. 1998;51(2-3):123-30. https://doi.org/10.1016/S0168-3659(97)00119-3 PMid:9685909

17. Yadav GS, Bansal M, Thakur N, Khare P. Multilayer tablets and their drug release kinetic models for oral controlled drug delivery system. Middle East J Sci Res [Internet]. 2013;16(6):782-95. Available from: https://www.idosi.org/mejsr/mejsr16(6)13/7.pdf

18. Maroni A, Zema L, Cerea M, Sangalli ME. Oral pulsatile drug delivery systems. Expert Opin Drug Deliv [Internet]. 2005;2(5):855-71. https://doi.org/10.1517/17425247.2.5.855 PMid:16296783

19. Gauri B, Singh SK, Mishra D. Formulation and evaluation of colon targeted oral drug delivery systems for metronidazole in the treatment of amoebiasis. International Journal of Drug Delivery. 2011;3(3):503-12.

20. Jangid V, Chatterjee DA, Agrawal DV, Kumar Gupta M, Garg P. A review on bilayer tablet technology for multi modal drug delivery. J Biomed Pharm Res [Internet]. 2022;11(6). https://doi.org/10.32553/jbpr.v11i6.947

21. Efentakis M, Peponaki C. Formulation study and evaluation of matrix and three-layer tablet sustained drug delivery systems based on Carbopols with isosorbite mononitrate. AAPS PharmSciTech [Internet]. 2008;9(3):917-23. https://doi.org/10.1208/s12249-008-9084-2 PMid:18686040 PMCid:PMC2977044

22. Phaechamud T. Variables influencing drug release from layered matrix system comprising hydroxypropyl methylcellulose. AAPS PharmSciTech [Internet]. 2008;9(2):668-74. https://doi.org/10.1208/s12249-008-9085-1 PMid:18500559 PMCid:PMC2976919

23. Kulkarni A, Bhatia M. Development and evaluation of regioselective bilayer floating tablets for biphasic release profile. Iranian Journal Of Pharmaceutical Research. 2009;8:15-25.

24. Nirmal J, Saisivam S, Peddanna C, Muralidharan S, Godwinkumar S, Nagarajan M. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. Chem Pharm Bull (Tokyo) [Internet]. 2008;56(10):1455-8. https://doi.org/10.1248/cpb.56.1455 PMid:18827389

25. Park CR, Munday DL. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int J Pharm [Internet]. 2002;237(1-2):215-26. https://doi.org/10.1016/S0378-5173(02)00041-8 PMid:11955819

26. Sungthongjeen S, Sriamornsak P, Puttipipatkhachorn S. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur J Pharm Biopharm [Internet]. 2008;69(1):255-63. https://doi.org/10.1016/j.ejpb.2007.09.013 PMid:17967527

27. Maggi L, Segale L, Conti S, Ochoa Machiste E, Salini A, Conte U. Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. Eur J Pharm Sci [Internet]. 2005;24(5):487-93. https://doi.org/10.1016/j.ejps.2005.01.010 PMid:15784338

28. Mishra P, Sharma PK, Malviya R. A review on bi-layer tablets - an emerging trend. J Drug Deliv Ther [Internet]. 2014;4(4). https://doi.org/10.22270/jddt.v4i4.900

29. Rekhi GS. Advances in solid dose oral drug delivery. ON Drug Delivery: Oral Drug Delivery and Advanced Excipients. 2010;14-8.

30. Rayakwar N, Dangi YS. Development and characterization of controlled release bilayered tablets of Citicoline sodium. J Drug Deliv Ther [Internet]. 2019;9(2-s):125-31. https://doi.org/10.22270/jddt.v9i2-s.2471

31. Melocchi A, Parietti F, Loreti G, Maroni A, Gazzaniga A, Zema L. 3D printing by fused deposition modelling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs. Journal of Drug Delivery Science and Technology. 2015;30:360-7. https://doi.org/10.1016/j.jddst.2015.07.016

32. Nikam SD, Pagar RY, Gangurde AB, Khairnar NN, Hire MV, Joshi MK. DUREDAS Technology: A Cutting-Edge Bilayer tablet strategy. Journal of Chemical Health Risks. 2024;14(2):237-9.

33. Nagaraju R, Kaza R. Formulation and evaluation of bilayer sustained-release tablets of salbutamol and theophylline. International Journal of Pharmaceutical Sciences and Nanotechnology. 2009;2(3):638-46. https://doi.org/10.37285/ijpsn.2009.2.3.7

34. Kumar V, Prasad, Ganesh, Swathi, Rashmi, Reddy A. Development and evaluation of guaifenesin bilayer tablet. PCI- Approved-IJPSN [Internet]. 2010;3(3):1122-8. https://doi.org/10.37285/ijpsn.2010.3.3.10

35. Busignies V, Mazel V, Diarra H, Tchoreloff P. Role of the elasticity of pharmaceutical materials on the interfacial mechanical strength of bilayer tablets. Int J Pharm [Internet]. 2013;457(1):260-7. https://doi.org/10.1016/j.ijpharm.2013.09.009 PMid:24055440

36. Akhtar M, Jamshaid M, Zaman M, Mirza AZ. Bilayer tablets: A developing novel drug delivery system. J Drug Deliv Sci Technol [Internet]. 2020;60(102079):102079. https://doi.org/10.1016/j.jddst.2020.102079

37. Demiri V, Stranzinger S, Rinner P, Piller M, Sacher S, Lingitz J, et al. Gluing Pills Technology: A novel route to multilayer tablet manufacturing. Int J Pharm [Internet]. 2018;548(1):672-81. https://doi.org/10.1016/j.ijpharm.2018.07.004 PMid:30033397

38. Giannos SA. Biotherapeutics-from drug discovery to drug delivery. Control Release Society Newsletter. 2004;21(3).

39. Blicharski T, Swiader K, Serefko A, Kulczycka-Mamona S, Kolodziejczyk M, Szopa A. Challenges in technology of bilayer and multi-layer tablets: a mini-review. Curr Issues Pharm Med Sci [Internet]. 2019;32(4):229-35. https://doi.org/10.2478/cipms-2019-0039

40. 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 Release [Internet]. 2004;95(1):51-60. https://doi.org/10.1016/j.jconrel.2003.10.028 PMid:15013231

41. Akseli I, Dey D, Cetinkaya C. Mechanical property characterization of bilayered tablets using nondestructive air-coupled acoustics.

AAPS PharmSciTech [Internet]. 2010;11(1):90-102. https://doi.org/10.1208/s12249-009-9352-9 PMid:20063078 PMCid:PMC2850479

42. Talla S, Wadher K, Umekar M, Lohiya RT, Formulation, Optimization and Evaluation of Solid Dispersion of Deferasirox Using Factorial Design, Journal of Drug Delivery and Therapeutics. 2024;14(5):23-31 https://doi.org/10.22270/jddt.v14i5.6526

43. Inman SJ, Briscoe BJ, Pitt KG. Topographic characterization of cellulose bilayered tablets interfaces. Chem Eng Res Des [Internet]. 2007;85(7):1005-12. https://doi.org/10.1205/cherd06188

44. Desai D, Wang J, Wen H, Li X, Timmins P. Formulation design, challenges, and development considerations for fixed dose combination (FDC) of oral solid dosage forms. Pharm Dev Technol. 2013;18(6):1265-76. https://doi.org/10.3109/10837450.2012.660699 PMid:22339230

45. Mubeen I, Zaman M, Farooq M, Mehmood A, Azeez FK, Rehman W, et al. Formulation of modified-release bilayer tablets of atorvastatin and ezetimibe: An in-vitro and in-vivo analysis. Polymers (Basel). 2022;14(18):3770. https://doi.org/10.3390/polym14183770 PMid:36145914 PMCid:PMC9506081

46. Deshpande RD, Gowda DV, Vasanti S, Mahammed N. Design of polypill for treatment of type -II diabetes mellitus associated with dyslipidemia. Journal of Scientific & Industrial Research. 2012;71:556-61.

47. Hu L, Hu Q, Kong D. Formulation and in vitro evaluation of aspirin and isosorbide 5-mono-nitrate sustained bilayer tablets. International Journal Of Pharmaceutical Sciences And Research. 2014;5(3):799-804.

48. Jamunadhevi V, Saho PK, Kailasam P. Formulation and in vitro evaluation of bi-layer tablet of cyclobenzaprine hydrochloride ER and diclofenac potassium IR -A novel fixed dose combination. International Journal Of Research in Pharmaceutical Sciences. 2011;2(2):170-8.

49. Kumar G, Anand Babu K, Ramasamy C. Formulation and Evaluation of Bilayered Tablets of Cefixime trihydrate and Dicloxacillin sodium. International Journal of PharmTech Research IntJ PharmTech Res. 2011;3(2).

50. Aggarwal KV, Goel S, Mishra U. An optimized bilayered tablet dosage form with two active antibiotics: clavulanic acid and cefpodoxime (Patent No. 2013001543:A1). 2013.

51. Mala D, Chudasama J, Narayan P, Rathore PS. Formulation and Evaluation of Amoxycillin and Potassium Clavulanate Bilayered Tablets. International Journal Of Pharmaceutical And Chemical Sciences. 2014;3(1):41-6.

52. Silva AM, Abrahim-Vieira B, Carmo FA, Amaral LH, Silva LC, Escudini CS, et al. Segregated Delivery of Rifampicin and Isoniazid from Fixed Dose Combination Bilayer Tablets for the Treatment of Tuberculosis". Journal of Pharmaceutical Research International. 2014;(4):1781-801. https://doi.org/10.9734/BJPR/2014/11525

53. Shinkai M, Katsumata N, Kawai S, Kuyama S, Sasaki O, Yanagita Y, et al. Phase III study of bilayer sustained-release tramadol tablets in patients with cancer pain: a double-blind parallel-group, non-inferiority study with immediate-release tramadol capsules as an active comparator. Support Care Cancer [Internet]. 2023;32(1):69. https://doi.org/10.1007/s00520-023-08242-z PMid:38157081 PMCid:PMC10756890

54. R. Nagaraju, Kaza R. Formulation and evaluation of bilayer sustained release tablets of salbutamol and theophylline. PCI-Approved-IJPSN [Internet]. 2009;2(3):638-46. https://doi.org/10.37285/ijpsn.2009.2.3.7

55. Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of metoclopramide hydrochloride and ibuprofen. AAPS PharmSciTech [Internet]. 2008;9(3):818-27. https://doi.org/10.1208/s12249-008-9116-y PMid:18612830 PMCid:PMC2977017

56. Kayes Y, Ahamed KM, Alam A, Sartker MM, Sajeeb R. Formulation and In-vitro Evaluation of Bilayer Tablets of Atenolol and Amlodipine. Bangladesh Pharmaceutical Journal. 2019;22(2):153-69. https://doi.org/10.3329/bpj.v22i2.42299

57. Bagyalakshmi J, Phani Krishna Y, Ravi TK. Bilayer tablet formulation of metformin hydrochloride and glipizide: A novel approach in the treatment of diabetes. International Journal Of Pharmaceutical Sciences Review And Research. 2011;8(2):209-15.

58. Md M, Srinivas P, Sadanandam M. Formulation and evaluation of bilayered tablets of montelukast and levocetirizine dihydrochloride Using natural and synthetic polymers. International Journal of Drug Delivery. 2011;3(4):597-618.

59. Swain RP, Pendela S, Panda S. Formulation and evaluation of Gastro-bilayer floating tablets of simvastatin as immediate release layer and atenolol as sustained release layer. Indian J Pharm Sci [Internet]. 2016;78(4). https://doi.org/10.4172/pharmaceutical-sciences.1000140

60. Hu L, Hu Q, Kong D. Formulation and in vitro evaluation of aspirin and isosorbide 5- mono-nitrate sustained bilayer tablets. International Journal Of Pharmaceutical Sciences And Research IJPSR. 2014;5(3):799-804.

61. Dinakaran SK, Kumar S, Banji D, Avasarala H, Rao V. Formulation and evaluation of bi-layer floating tablets of ziprasidone HCl and trihexyphenidyl HCl. Braz J Pharm Sci [Internet]. 2011;47(3):545-53. https://doi.org/10.1590/S1984-82502011000300012

62. Won DH, Park H, Ha E-S, Kim H-H, Jang SW, Kim M-S. Optimization of bilayer tablet manufacturing process for fixed dose combination of sustained release high-dose drug and immediate release low-dose drug based on quality by design (QbD). Int J Pharm. 2021;605(120838):120838. https://doi.org/10.1016/j.ijpharm.2021.120838 PMid:34197909