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Review Article

A Review on Applications of Bilayer Tablet Technology for Drug Combinations

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Abstract

Bilayer tablets are novel drug delivery systems where combination of two drugs in a single unit having different release profiles can be delivered. Bilayer tablets improve patient compliance, prolong the drug(s) action and can deliver two incompatible drugs in a single formulation. Bilayer tablets have one layer of active ingredient for immediate release and a second layer for delayed release, either as a second dose or in an extended release fashion. Bilayer tablets are advancing helpful technologies to overcome the disadvantages of single-layered tablets. However, bilayer tablet technology is resource-intensive. A thorough selection of excipients and manufacturing conditions for each technical stage is also required. Patients with high blood pressure often have difficulty or are unable to regulate their BP with just a single medication. The majority of hypertension patients will need to take two or more antihypertensive medicines in order to meet treatment goals. Combinations of antihypertensive drugs from various categories have been found to be more effective than either drug alone in treating hypertension in people whose blood pressure cannot be maintained satisfactorily with monotherapy. Combining two antihypertensive medications with mutually beneficial mechanisms of action may result in much greater blood pressure lowering efficacy than any of these components alone. The goal of this review is to discuss the use of bilayer tablets to administer fixed antihypertensive drug combinations for the treatment of high blood pressure.

Keywords: Bilayer tablet, blood pressure, antihypertensive drugs, Sustained release, maintenance dose.

INTRODUCTION

Oral administration is the most prevalent and preferred method of drug administration. This route is widely recognised due to its ease of administration, self-medication, patient compliance, and versatility in terms of accessible dosage forms. Tablets are the most convenient oral dosage form available and are chosen by both patients and clinicians. To fulfil current requirements, novel formulations with changed drug release patterns are being researched. Among these are controlled release formulations. They distribute the medication at a predetermined rate and at a predetermined spot in order to prolong or sustain the release of the formulation¹⁻³.

Bilayered tablets are the most appropriate formulation for delivering multiple drugs via a drug delivery system. Bilayer tablets herald a new era in the successful development of controlled release formulations, incorporating a variety of features to facilitate drug delivery. Bi-layer tablets may be the best option for avoiding chemical incompatibilities between APIs and enabling the development of multiple drug release profiles. Bilayered tablets are used to deliver two drugs sequentially, with one layer providing sustained release and the other providing immediate release⁴⁻⁵. The use of bi-layer tablets is quite different for antihypertensive, diabetic, anti-inflammatory, and analgesic medications, which frequently require combination therapy to be effective⁶.

Bilayer tablets are a cutting-edge tablet technology that enables the simultaneous delivery of one or two drugs with different release rates. By forming layers of multiple drugs and polymers, it is possible to manipulate more than one rate-controlling polymer, allowing for the delivery of various drugs⁷. Due to the exposed edges of each layer, they resemble a sandwich. Bi-layer tablets may be the optimal choice for avoiding chemical incompatibilities across APIs and allowing for the development of different drug release profiles. Bi-layer tablets are appropriate for the sequential release of two combined drugs. In Sustained-release tablets one layer contains the loading dose, and the second layer contains the maintenance dose⁸. For antihypertensive, diabetic, anti-inflammatory, analgesic, and antibiotic drugs, the use of bi-layer tablets is considerably different, as these drugs frequently require combination therapy to be effective⁹.

The bilayer tablet is a versatile product of monolithic partially coated or multilayered matrices. Medication release can be made practically unidirectional in the case of bi-layered tablets by putting the drug in the upper non-adhesive layer, where it is transported throughout the oral cavity¹⁰. The floating bilayer drug delivery system is a hybrid of the bilayer tablet and floating mechanism. Floating bilayer matrix tablets are ideal for sequential release of two drugs in combination, for separating incompatible substances, and for sustained release tablets in which one layer is immediate released as the initial dose and the second layer is either the same drug's

maintenance dose or another drug's sustained-release dose. Bilayered layers comprising floating systems are intended to aid in the formulation's retention in the stomach and are particularly effective for insoluble or unstable medications in intestinal fluids. Floating drug delivery systems float in the stomach and release the drug at a controlled rate over an extended period of time¹¹.

TYPES OF BILAYER TABLETS

Bilayer tablets may be identical (homogeneous) or dissimilar (heterogeneous).

Homogenous type: Bilayer tablets having same drug in two layers but drug release profile is different from one another. These bilayer tablets contain one layer of the immediate release and second layer is extended release manner¹².

Heterogeneous type: Bilayer tablet is suitable for continuous release two drugs in combination, separate two incompatible substances.

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bi-layer tablet press capable of:

- High yield.
- Preventing capping and separation of the two individual layers that form the bilayer tablet.
- Preventing cross-contamination between the two layers.
- Producing a clear visible separation between the two layers.
- Accurate and individual weight control of the two layers¹³⁻¹⁴.

ADVANCED TECHNIQUES USED IN PREPARATION OF BILAYER TABLET:

- OROS Push Pull Technology
- L-OROS Technology
- EN SO TROL Technology
- DUROS TROL Technology
- Elan Drug Technology' Dual release Drug Delivery System

OROS Push Pull Technology:

This approach comprises mainly two or three layers, one or more of which must contain the drug, and the other is a push layer. Generally, it consists of a drug and two or more agents utilized in the drug layer such as suspending and osmotic agents. A semipermeable membrane surrounds the core of the tablet¹⁵.

L-OROS Technology:

This system is used to resolve the solubility problem associated with the drug. L-OROS system contains a lipid soft gel product holding drug in a dissolved state and an osmotic push layer with semi permeable membrane and a drilled for exit orifice¹⁶.

EN SO TROL Technology:

Increased solubility by an order of magnitude or creation of an optimal dose form Shire's drug delivery laboratory takes an integrated strategy, concentrating on the identification and implementation of discovered enhancers into controlled release technologies¹⁷.

DUROS Technology:

The system is comprised of an outer cylindrical titanium alloy reservoir and an inner cylindrical titanium alloy reservoir. This reservoir is extremely robust and effectively protects the drug molecules from enzymes. The DUROS technology is a small medicine delivery system that resembles a miniature syringe and continuously and consistently releases minute amounts of concentrated medication over months or years.

DUREDAS™ Technology

This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers¹⁸.

CHALLENGES INVOLVED IN MANUFACTURING OF BILAYER TABLET:

Due to insufficient hardness, layer sequence, layer weight ratio, an elastic mismatch between neighbouring layers and an excessive tamping force applied to the first layer, cross-contamination between layers can occur during manufacturing of bilayer tablets. Bi-layer compression pressure and qualitative properties like mechanical strength and layer weight regulation will be severely impacted if these factors are not properly regulated. It is therefore necessary to pay attention to a product's and process's strong design¹⁹. Despite the fact that two single-layer tablets have been compacted into one, the production of bilayer tablets is far more difficult than that of single-layer ones.

Bilayer tablet manufacturing largely relies on the physical and chemical properties of the active pharmaceutical ingredient (API) and excipients. The material composition of bilayer tablets has a significant impact on the tablet's strength and the manner in which it fractures. Plasticity, brittleness and viscoelasticity all have an impact on compression. It is important to consider how material plasticity and brittleness deform during compression. As long as the elasticity of the plastic material does not exceed the bond limit, plasticity has no effect on the compression process⁶.

A substance's material qualities must be evaluated before manufacturing bilayer tablets because particle breakdown is more substantial in the middle layer of the die than in the outer layer. There must be a suitable volume reduction and mechanical, durable, and coherent cohesion between each layer in a multilayer tablet formulation. Due to their compressibility and compatibility, they should be extremely compact (the ability of a substance to shrink in volume when compressed) (the ability of powdered substances to convert into tablets). Stacking tablets require careful control over the weight of each layer by optimising the particle size distribution, flow properties, and compression capabilities of the material⁶.

Bilayer tablet manufacturing has been found to be most successful when the first layer's compression force, which impacts interfacial strength and adhesion between the two layers, is precisely controlled. This allows for mechanical aeration to occur between the layers. To put it another way, if the first layer of a bilayer tablet is more elastic, the stress and strain generated throughout the system compromises the bilayer tablet's structural integrity. As a result, the layers' adhesion could be jeopardised by the breakdown of the contact between them. In terms of the die's compactability,

pressure and speed have a considerable impact. After a first layer of compression forces (typically between 2 and 18 KN) has been used to compact the powders and grains and smooth the surface of that layer, a void is created in which a second layer can be placed.

Tensile strength and surface roughness are both improved by compression. Smoothing the initial layer's surface may improve delamination by lowering intermolecular adhesion between adjacent layers. At a modest compression force, the tablet's first layer interacts with the second layer during the final compression of the tablet, resulting in proper bonding. If the first layer is crushed with a high compression force, bonding is substantially impeded⁶.

There is less friction between the particles of a lubricant and the die with which it comes into contact because the lubricant is more evenly disseminated. A lower lubricant component is needed in bilayer formulations to improve the contact and strength between the two layers. For Bilayer tablets, lubricant levels are more important than brittle materials because they have a higher impact.

As part of the product development process, the amount of lubricant needed to prevent the first layer from picking up and sticking must be estimated. Blended lubricant is dispersed or "coated" on the granules' surface as they come into contact with die and punches during compression. This provides the necessary lubrication to reduce friction and wear on the parts. This helps reduce intergranular adhesion, which affects quality factors like tablet breaking force and dissolving. Instead of using it directly on the granules, researchers applied lubricant to dies and punches to see how it affected important tablet quality aspects. This is known as external lubrication in the literature. Crushing strength can be increased by 40% with external lubrication, which involves spraying lubricant on the die and punches during each compression cycle rather of incorporating it into the bulk powder combination. The presence of a magnesium stearate layer on the tablet was confirmed using a scanning electron microscope. In spite of the fact that this unique technique is best suited for monolayer tablets, it could be used to better understand the influence of lubricant on bilayer tablet quality characteristics¹⁵.

While designing a bilayer tablet, the weight of the two layers may not always be equal. Most of the time, their weight ratios will be rather different. There is evidence that the first and second layers often have a 1:1, 1:2, or even 1:3 ratio to each other. When creating bilayer medicines, keeping the weight of the second layer constant with that of the first might be a challenge.

The compactness of bilayer tablets is greatly affected by environmental variables such as humidity and moisture during the formulation process. It's surprising how little research has been done on how moisture affects bilayer tablet strength. Tablets with hygroscopic materials in the bilayer layer absorb and desorb water from their pore structure according to the relative humidity of the air.

Water can also permeate compacts made from sodium starch glycolate, starches, microcrystalline cellulose and crospovidone as well as polyvinylpyrrolidone and colloidal silicon dioxide. Moisture seeps into porous compacts and/or particles, causing them to expand. Delamination occurs as a function of time when the contact between the layers is reduced due to changes in layer thickness. Material preconditioning to match the humidity level in the manufacturing region was recommended, as was the packaging of compacts in airtight, moisture-resistant blisters¹⁵.

It is important to address the physical stability of bilayer tablets alongside formulation design and manufacturing process factors during product development because it can affect quality parameters such as tensile strength, layer adhesion, friability, and dissolution. It was found that the interfacial strength of bilayer tablets containing lactose decreased with increasing humidity and storage time, whereas that of bilayer tablets having MCC in the first layer increased with increasing humidity and storage time.

Material flow properties, particle size distribution, and the ability of the bilayers to press effectively all play a role in achieving uniform dispersion of active medicinal components in bilayer tablets. For the instrumented bilayer press, each vendor has its own method of balancing the weight. The first and second bilayers of existing development and commercial presses are weighed. A mechanism for measuring the second layer's weight is not accessible on any commercially marketed bilayer press. With this, the manufacturing of bilayer tablets becomes a substantial challenge^{6,15}.

Commercially accessible bilayer presses for bilayer tablet formulators include the Kilian, Oystar Manesty, Hata, Korsch, Courtoy, Fette, Kilian, and Piccola. In most instrumented bilayer presses, compression force and punch displacement are automatically calculated. Compression machine design and accessory technologies have advanced to the point where it is now possible to tailor the features of a product (initial layer sampling, sealed feeders, precompression rolls, layer strain gauge sensitivity, and maximum upper punch penetration). It's important to take into account factors like precompression force and punch velocity as well as time needed for consolidation and relaxation. The quality of the dose can be improved or harmed by compression machines¹⁸.

Additional factors influence the development of bilayer tablets of the appropriate quality, notwithstanding the theoretical advantages of a material that compresses without distortion and compacts independently. This includes the particle size distribution, angle of response, photomicroscopic examinations, densities, compressibilities, and moisture sorption capacity of the sample⁶.

APPLICATION OF BILAYER TABLET TECHNOLOGY IN ANTIHYPERTENSIVE DRUG COMBINATION THERAPY

A monotherapy approach to controlling high blood pressure is usually ineffective because of its complex character. Most people require a combination of two or more medicines from various classes in order to reach their goal blood pressure. When a second blood pressure medication is used in conjunction with the first, the results can be much better. People with moderately high blood pressure may not respond to one drug even if the dosage is increased¹⁸.

The primary factors affecting blood pressure are renal sodium excretion and the resulting plasma and total body volume, cardiac function, and vascular tone. Intravascular volume, cardiac output, and systemic vascular resistance are the direct hemodynamic drivers of blood pressure (BP). RAAS and the sympathetic nervous system (SNS) both have a role in changing these parameters in real time. Although it is possible to identify a specific cause for hypertension in certain people, BP elevation is frequently complex, making it difficult, if not impossible, to normalise pressure by interfering with only one presser mechanism¹⁹.

Rationale of combination therapy

- If these criteria are met, the use of two medications from distinct classes in a low-dose combination has a number of potential benefits.
- Because hypertension responds differently to treatment, combining two medicines increases the likelihood of response in a particular individual.
- There may be an increase in the antihypertensive effect of each medicine, which in perfect combinations may be synergistic rather than additive.
- Because the two medications exert their antihypertensive effects in distinct ways, there is a possibility for a more gradual beginning and a longer duration of action.
- By maintaining a modest dose of each treatment, side effects can be minimized.
- In many circumstances, the combination of the two medications might somewhat counteract the adverse effects of the other, e.g., palpitations caused by certain CCBs may be alleviated with β -blocker therapy.
- Different processes may have a variety of favorable impacts on target organs in addition to the benefits of blood pressure reduction. When hypertension patient sustains damage to their cardiac, renal, or cerebral end organs, their prognosis deteriorates. Combination therapies may slow the course of the disease. Combination medicines, particularly at low doses, can typically be administered once a day to increase patient compliance.
- Dose changes and titration will be simplified, blood pressure targets will be met more rapidly, and fewer clinic or physician visits will be necessary to reach targets. This results in more straightforward and successful solutions. Initiating antihypertensive treatment in primary care
- The treatment's overall cost can be decreased. Low-dose combination medicines may be less expensive than the constituents prescribed separately. In some countries, the cost of prescribing a single medication may be cheaper than the cost of prescribing two different drugs.²⁰⁻²¹

Fixed-dose combination therapy has several advantages over conventional monotherapy, including a simplified dosage schedule that results in increased patient compliance and, consequently, improved treatment outcomes, fewer side effects, decreased development of resistance in the case of antimicrobials, and potentially lower manufacturing, handling, packing, and shipping costs when compared to the costs of producing individual products. The usual dosage form results in an extensive range of drug concentrations in the bloodstream, which prompted the development of sustained drug delivery. The purpose of developing sustained delivery systems is to reduce dose frequency, increase the effectiveness of the treatment, or provide uniform drug distribution²².

Specific Drug Combinations²³

a. β Blockers with diuretics

Addition of diuretics has been shown to improve the antihypertensive efficacy of β 1-blockers with low-renin hypertension. Examples are atenolol/chlorthalidone, bisoprolol fumarate/ HCTZ.

b. Angiotensin-converting enzyme (ACEIs) inhibitor and angiotensin receptor blocker (ARB) with Diuretics

Hydrochlorothiazide and ARB together are more effective and have a lower risk of side events than either drug alone. The metabolic consequences of thiazide diuretics, notably hypokalemia and hyperglycemia, will likewise be reduced by an ARB.

c. Renin-angiotensin system (RAS) and Calcium channel blocker (CCB)

The synergistic or complimentary effects of CCBs, ARBs, and ACE inhibitors are most likely due to the diverse mechanisms of action. An RAAS blocker may reduce dose-dependent CCB-induced peripheral edema.

d. Angiotensin-converting enzyme inhibitor/Calcium channel blocker (ACEI/CCB)

The therapeutic advantages of ACEIs in people with both diabetes and hypertension appear to be independent of BP decrease. For hypertension patients who do not respond well to amlodipine or who develop intolerable edema, the results of the trial on amlodipine/benazepril combination therapy suggest it is an effective, safe, and well-tolerated medication.

e. Combination ARB with CCB

Combination therapy with RAAS inhibitors and either a CCB or a diuretic has a solid justification. Antihypertensive drugs amlodipine, valsartan, and hydrochlorothiazide (approved in 2009) are a fixed dose combination.

f. ACEIs with ARB

It's possible that an ACEI/ARB regimen could provide the advantage of a more complete RAAS blockage. The ACEI escape phenomenon, in which angiotensin II levels revert to pretreatment levels despite ongoing ACEI treatment, will be less common with ARB. ARBs will also impede the production of angiotensin II via ACEI-independent mechanisms.

g. Combination of CCBs and diuretics

In comparison to diuretics and blockers, the use of calcium channel blockers and diuretics for hypertension may increase the risk of myocardial infarction but not of stroke.

Currently available antihypertensive bilayer tablets

When two antihypertensive drugs with different mechanisms of action are combined in one dosage form and taken once or twice daily, the goal is to improve blood pressure control. The clinical and metabolic effects of high doses of the individual components of the combination tablet can be lessened by using moderate doses of two different drugs. Some researchers have advised the use of combination antihypertensive medication in individuals with target organ damage or greater baseline levels of hypertension²⁴. Table 1 is a list of antihypertensive combinations.

Table 1: Antihypertensive bilayer tablets available in market²⁵

S. N.	Category	Drugs	Brand Name
1.	Diuretic combinations	Amiloride and hydrochlorothiazide (5 mg/50 mg)	Moduretic
		Spironolactone and hydrochlorothiazide (25 mg/50 mg, 50 mg/50 mg)	Aldactazide
		Triamterene and hydrochlorothiazide (37.5 mg/25 mg, 50 mg/25 mg)	Dyazide
		Triamterene and hydrochlorothiazide (37.5 mg/25 mg, 75 mg/50 mg)	Maxzide-25 mg, Maxzide
2.	Beta blockers and diuretics	Atenolol and chlorthalidone (50 mg/25 mg, 100 mg/25 mg)	Tenoretic
		Bisoprolol and hydrochlorothiazide (2.5 mg/6.25 mg, 5 mg/6.25 mg, 10 mg/6.5 mg)	Ziac
		Metoprolol and hydrochlorothiazide (50 mg/25 mg, 100 mg/25 mg, 100 mg/50 mg)	Lopressor HCT
		Nadolol and bendroflumethazide (40 mg/5 mg, 80 mg/5 mg)	Corzide
		Propranolol and hydrochlorothiazide (40 mg/25 mg, 80 mg/25 mg)	Inderide
		Propranolol ER and hydrochlorothiazide (80 mg/50 mg, 120 mg/50 mg, 160 mg/50 mg)	Inderide LA
		Timolol and hydrochlorothiazide (10 mg/25 mg)	Timolide
3.	ACE inhibitors and diuretics	Benazepril and hydrochlorothiazide (5 mg/6.25 mg, 10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg)	Lotensin HCT
		Captopril and hydrochlorothiazide (25 mg/15 mg, 25 mg/25 mg, 50 mg/15 mg, 50 mg/25 mg)	Capozide
		Enalapril and hydrochlorothiazide (5 mg/12.5 mg, 10 mg/25 mg)	Vaseretic
		Lisinopril and hydrochlorothiazide (10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg)	Prinzide
		Lisinopril and hydrochlorothiazide (10 mg/12.5 mg, 20 mg/12.5 mg, 20 mg/25 mg)	Zestoretic
		Moexipril and hydrochlorothiazide (7.5 mg/12.5 mg, 15 mg/25 mg)	Uniretic
		Angiotensin-II receptor antagonists and diuretics	
		Losartan and hydrochlorothiazide (50 mg/12.5 mg, 100 mg/25 mg)	Hyzaar
		Valsartan and hydrochlorothiazide (80 mg/12.5 mg, 160 mg/12.5 mg)	Diovan HCT
4.	Calcium channel blockers and ACE inhibitors	Amlodipine and benazepril (2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg)	Lotrel
		Diltiazem and enalapril (180 mg/5 mg)	Teczem
		Felodipine and enalapril (5 mg/5 mg)	Lexxel
		Verapamil and trandolapril (180 mg/2 mg, 240 mg/1 mg, 240 mg/2 mg, 240 mg/4 mg)	Tarka
5.	Miscellaneous combinations	Clonidine and chlorthalidone (0.1 mg/15 mg, 0.2 mg/15 mg, 0.3 mg/15 mg)	Combipres
		Hydralazine and hydrochlorothiazide (25 mg/25 mg, 50 mg/50 mg, 100 mg/50 mg)	Apresazide
		Methyldopa and hydrochlorothiazide (250 mg/15 mg, 250 mg/25 mg, 500 mg/30 mg, 500 mg/50 mg)	Aldoril
		Prazosin and polythiazide (1 mg/0.5 mg, 2 mg/0.5 mg, 5 mg/0.5 mg)	Minizide

CONCLUSIONS

Monotherapy is widely acknowledged to be ineffective in many patients, and many individuals will develop severe side effects at larger doses of a single medication.. In this broad population of patients, fixed-dose combination antihypertensive medicines are an appropriate and beneficial therapeutic option. Bi-layer tablets present an ideal chance for producers to differentiate themselves from competitors,

increase the efficacy of their products, and safeguard against counterfeit items. Bilayer layer tablets have been proposed, consisting of two layers, one of which is gradual release and the other of which is immediate release, with the goal of achieving a high serum concentration in a short period of time. The second layer is a hydrophilic matrix with a controlled release that is designed to sustain an effective plasma level for an extended period of time. Significant advancements in the

manufacture of tablets have been made recently. This has resulted in an improvement of the tablets' physicochemical qualities and the capability of generating tablets with modified/controlled release. However, a number of technological difficulties must be solved before a multilayer tablet with the same level of reliability as monolayer tablets can be achieved. The variability of adjacent layers is a significant source of design and production issues for multilayer tablets.

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REFERENCES

- Rathore R, Gupta AK, Parashar AK. Formulation and Evaluation of fast dissolving films of Granisetron Hydrochloride. *J Drug Delivery and Therapeutics*. 2019; 9(2-A):36-38.
- Gaikwad SS, Chafle SA, Morris PS, Avari JG. Development and evaluation of bilayer tablets of combination of antibiotics for the treatment of sexually transmitted disease. *Brazilian Journal of Pharmaceutical Sciences* [Internet]. 2016 Sep [cited 2022 Jan 11];(3):555-66. Available from: <http://dx.doi.org/10.1590/s1984-82502016000300020>.
- Davis JR. Handbook of materials for medical devices. ASM International; 2003.
- Malviya Y, Kondalkar A. Formulation development and evaluation of gastroretentive floating tablets of ambroxol hydrochloride. *JDDT* [Internet]. 23Nov.2019; 9(4-s):1016-21.
- Sangeetha R, Pillai MK, Haribabu Y. Bi-layer tablets: A flexible technology for oral drug delivery-An updated review. *Res J Pharm Technol* [Internet]. 2021; 14(1):547-51. Available from: <http://dx.doi.org/10.5958/0974-360x.2021.00099.8>
- Singh A, Das S, Gupta S, Ghosh S. The challenges of producing bilayer tablet: A review. *J Drug Deliv Ther* [Internet]. 2021; 11(4-S):171-5. Available from: <http://dx.doi.org/10.22270/jddt.v11i4-s.4922>.
- 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. Available from: <http://dx.doi.org/10.2478/v10007-007-0038-0>.
- Joseph D, Thomas GM. A review on current applications of bilayer tablets. *Res J Pharm Technol* [Internet]. 2019; 12(5):2539. Available from: <http://dx.doi.org/10.5958/0974-360x.2019.00427.x>
- Parashar AK, Patel P, Gupta AK, Jain NK, Kurmi BD. Synthesis, characterization and in vivo evaluation of PEGylated PPI dendrimer for safe and prolonged delivery of insulin. *Drug Deliv Lett*. 2019; 9(3):248-63. Available from: <http://dx.doi.org/10.2174/2210303109666190401231920>.
- 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. Available from: <http://dx.doi.org/10.1016/j.jddst.2020.102079>
- Agiba AM, Abul-Ella SS, El-Monem RAA. Pharmacotechnical development and optimization of multilayered tablets: An updated industrial review with emphasis on bilayer tablets. *Int j appl pharm* [Internet]. 2021; 55-64. Available from: <http://dx.doi.org/10.22159/ijap.2021v13i4.41528>
- Kasperek R, Zimmer L, Zun M, Dwornicka D, Wojciechowska K, Poleszak E. The application of povidone in the preparation of modified release tablets. *Curr Issues Pharm Med Sci* [Internet]. 2016; 29(2):71-8. Available from: <http://dx.doi.org/10.1515/cipms-2016-0015>.
- Reddy M. S, Department of Pharmaceutics, Institute of Science and Technology, JNTUH, Kukatpally, Hyderabad, 500085, Telangana, India, Muppa L, Department of Pharmaceutics, Institute of Science and Technology, JNTUH, Kukatpally, Hyderabad, 500085, Telangana, India. A review of challenges and possibilities of bilayer tablet technology. *Int J Adv Res (Indore)* [Internet]. 2021; 9(08):676-81. Available from: <http://dx.doi.org/10.21474/ijar01/13315>
- Annapurna U, Priyanka KS. Bilayer Tablets-A Review. *Research Journal of Pharmacy and Technology*. 2019; 12(1):385-90.
- Kottala N, Abebe A, Sprockel O, Akseli I, Nikfar F, Cuitiño AM. Influence of compaction properties and interfacial topography on the performance of bilayer tablets. *Int J Pharm* [Internet]. 2012; 436(1-2):171-8. Available from: <http://dx.doi.org/10.1016/j.jipharm.2012.05.026>.
- Kalra S, Kalra B, Agrawal N. Combination therapy in hypertension: An update. *Diabetol Metab Syndr* [Internet]. 2010;2(1):44. Available from: <http://dx.doi.org/10.1186/1758-5996-2-44>
- Patel DM, Trivedi R, Patel H. Formulation and evaluation of bilayer tablets of Ketorolac Tromethamine. *J Drug Deliv Ther* [Internet]. 2021; 11(1):36-41. Available from: <http://dx.doi.org/10.22270/jddt.v11i1.4487>
- Nguyen NNT, Pham DT, Nguyen DT, Trinh TTL. Bilayer tablets with sustained-release metformin and immediate-release sitagliptin: preparation and in vitro/in vivo evaluation. *J Pharm Investig* [Internet]. 2021; 51(5):579-86. Available from: <http://dx.doi.org/10.1007/s40005-021-00533-z>
- Chun M-H, Kim JY, Park E-S, Choi DH. Development of a robust control strategy for fixed-dose combination bilayer tablets with integrated quality by design, statistical, and process analytical technology approach. *Pharmaceutics* [Internet]. 2021; 13(9):1443. Available from: <http://dx.doi.org/10.3390/pharmaceutics13091443>
- Sandhya T. Formulation and Evaluation of Sustained Release Bilayer Tablets of Losartan Potassium. *Asian Journal of Pharmaceutics*. 2021; 15(2).
- Tuyen NTL, Nghiem LQ, Tuan ND, Le PH. Development of a Scalable Process of Film-Coated bi-Layer Tablet Containing Sustained-Release Metoprolol Succinate and Immediate-Release Amlodipine Besylate. *Pharmaceutics* [Internet]. 2021; (11):1797. Available from: <http://dx.doi.org/10.3390/pharmaceutics13111797>
- Niranjan AK, Singh A. Formulation, development and evaluation of bilayer floating tablets of antihypertensive drug Bosentan. *J Drug Deliv Ther* [Internet]. 2021; 11(6):167-72. Available from: <http://dx.doi.org/10.22270/jddt.v11i6.5113>
- Wright JM, Musini VM, Gill R. First-line drugs for hypertension. *Cochrane Database Syst Rev* [Internet]. 2018; 4(4):CD001841. Available from: <http://dx.doi.org/10.1002/14651858.CD001841.pub3>
- Garg A, Mishra A. Preparation and Evaluation of Bilayer Tablet For The Treatment Of Hypertension. *NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal* NVEO. 2021; 9098-115.
- Fong B, Cornett G. Cicletanine in combination with oral antidiabetic and/or blood lipid-lowering agents as a combination therapy for diabetes and metabolic syndrome. *US Patent*. 20050113314:A1, 2005.