



Design, Formulation and Evaluation of Alpha Lipoic Acid and Metformin Bilayer Tablet Dosage Form

Mayur Patni^{1*} and Swati Rawat²

¹ Y. B. Chavan College of Pharmacy, Aurangabad, INDIA

² R P College of Pharmacy, Osmanabad, INDIA

* Correspondence: E-mail: myur_121@yahoo.co.in

(Received 03 Aug, 2018; Accepted 09 Oct, 2018; Published 27 Dec, 2018)

ABSTRACT: The expense and complications in new drug entities have increased since last 3 decades, with concomitant recognition of the therapeutic advantages of controlled drug delivery. So focus has been given on development of sustained or controlled release drug delivery systems. Bilayer tablet is new novel of tablet for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. For promoting patient convenience and compliance pharmaceutical industries interested in developing a combination of two or more API's in a single dosage form. Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles using DUREDAS technology (immediate release with extended release/ both layer extended release). The objective of the present study was to prepare the bilayer tablets of alpha lipoic acid incorporated as immediate release layer while metformin HCl as sustain release layer for the treatment of type II diabetes. The immediate release alpha lipoic acid layer was designed and optimized in the first step using crosscarmellose as superdisintegrant followed by sustained release layer of metformin HCl and optimized using 3² factorial design as well as compressed using 16-station double rotary tablet machine and evaluated. All the pre-compression and post-compression parameters were obtained within acceptable limits. Both the layers exhibited more than 85% drug release. Moreover, bilayer tablets were found stable as evident from drug content and drug release study. The bilayer tablets of alpha lipoic acid and metformin HCl with acceptable hardness, friability, drug content and more than 85% drug release were designed, prepared and evaluated.

Keywords: Bi-layered tablet; immediate release; Controlled release; Tablet; Metformin and Alpha lipoic acid.

INTRODUCTION: In the modern era frequently and habitually used route to deliver drugs due to ease of administration and flexibility is solid oral dosage forms. Since, the compressed tablet is one of the most popular and acceptable dosage forms because of certain known advantages over other dosage forms. Furthermore, a controlled release oral dosage form is a main choice for drug delivery at controlled manner to achieve predetermined parameter, which makes it more popular. Since, it contribute to a better patient compliance and maintaining uniform dose levels even offer to reduce dose frequency, as well as possible side effects.¹⁻³

Now a day's two layered dosage form is one of the major choice in some particular pathological conditions, it include one layer of immediate release (IR) of the dose which generally intended to achieve and provide a rapid onset of action, followed by extended or

controlled drug release to maintain the therapeutic effect for longer duration of time (SR).^{4,5}

Bilayer tablet is new era of the solid dosage form, for the successful formulation and development of controlled release formulation along with various predetermined features to provide a way of successful drug development even delivery system. Controlled release dosage forms have been extensively used intended to improve therapy with several important drugs mainly anti-diabetic. Use of bilayer tablet is a very different approach and aspect for diabetic conditions. Bi-layer tablet technology is found to be most suitable for sequential release of two drugs in combination, separate two incompatible drug substances even also for sustained release tablet in which one Layer is immediate release as initial dose of one drug component and second layer is maintenance dose of another drug component. Bilayer tablet is improved beneficial

technology used in present days to overcome the shortcoming of the single layered tablet.⁶⁻⁸ Formulation of both the layers are done by using one or more than one rate controlling polymer, hence, enabling different types of drug delivery of one or more drugs at predetermined rate of release. There is a variety of application of the bi-layer tablet technology used in current era consist of either monolithic partially coated or multilayered matrices. Since, there are number of issues associated with the production of bi-layered tablets. But, the mechanical strength of bi-layered tablets technology has been observed not to be a controlling factor in drug release pattern. The determination of this property of bi-layered tablets could be useful in understanding the adhesion between various layers that are incorporated. Some of the other challenges associated with this technology are occurs during development of bi-layer tablets include the order of layer sequence, layer weight ratio, elastic mis-match of the adjacent layers, first layer tamping force and cross contamination between layers. If these factors not well controlled during the formulation in one way or other will be definitely effect the bi-layer compression perse (insufficient or uncontrolled process) and some the quality attributes like mechanical strength and individual layer weight control. Therefore care must be taken during the formulation and development of bi-layered tablet to enable design of a vigorous product and process.⁹⁻¹⁶

Since the adjacent compacted layers of a bi-layer tablet that are bonded together by some mechanical means, it is necessary to understand what influences the stress state, the mechanical properties of each layer and the resultant bilayer tablet, and compression parameters along with specialized techniques to forecast failure as a function of layer properties of bi-layered tablet and compression conditions are primary requirements for successful formulation and development of bilayer tablets.^{17,18}

Type 2 diabetes is a progressive disorder and most patients will need more than two oral agents to maintain sufficient glucose control. Shifting from one drug to another in a patient with poorly controlled glycemia or increasing the dose of an existing drug is not helpful always. Existing regimen needs to be modified by adding medications from different groups for glyce-mic control effectively. Several of the available oral agents have been studied in combination and have been shown to further improve glyce-mic control when compared with monotherapy.¹⁹

Metformin hydrochloride is an orally administered drug, which is widely used in the management of type

2 diabetes, a common disease that combines defects of both insulin secretion and insulin action. Alpha Lipoic acid responsible for oxidative glucose metabolism and cellular energy production.^{20, 21} Metformin and Alpha Lipoic acid combination is used for diabetic polyneuropathy, Type 2 diabetes, weight loss and other conditions. Side effects and the frequency of administration (two or three times per day) when larger doses are required can decrease patient compliance. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliance. Moreover, the broad spectrum effects of Alpha lipoic acid make the combination of metformin and alpha Lipoic acid a promising treatment option not only for optimizing management of glyce-mic control but also for prevention of the cardiovascular complication. Fixed-dose formulation Metformin and Alpha lipoic acid offers an effective option for the management of patients with type 2 diabetes when monotherapy fails in the achievement of the recommended standards of care. Hence, the present research was undertaken to formulate bilayer tablet of alpha lipoic acid (immediate release) and metformin hydrochloride (sustained release) using 3² factorial design.²²⁻²³

MATERIALS AND METHODS:

Materials: Metformin HCl and alpha lipoic acid were received from Lyka Lab Pvt Ltd, India, as a gift sample. HPMC K 100M and eudragit polymers was a gift sample received from M/S Colorcon Asia Pvt. Ltd., Mumbai, India. All other chemicals/reagents used were of analytical grade.

Design of alpha lipoic acid IR layer: In the first step, IR formulation of alpha lipoic acid was designed. Three formulations of alpha lipoic acid layer were designed by varying the concentration of superdisintegrant crosscarmellose sodium and based on evaluation results optimized formula is given in Table 1. All the excipients were passed through sieve no 60. An accurately weighed quantity of drug was mixed thoroughly with excipients except magnesium stearate in mortar and pestle for 20 min. Magnesium stearate was added at last and mixed to prepare final blend. Final weight of IR layer of alpha lipoic acid was 330 mg.²⁴

Table 1: Composition of alpha lipoic acid layer.

Sr. No	Ingredients	Quantity
1.	Alpha lipoic acid	200
2.	Microcrystalline cellulose PH-102	69

3.	Aerosil	3
4.	Dibasic Calcium Phosphate	27.60
5.	Crosscarmellose sodium	26.40
6.	Magnesium Stearate	4
Total		330

Design, formulation and optimization of metformin HCl SR layer using 3² factorial design: Full factorial design was employed to optimize the metformin SR formulation. The 3² factorial design was used to optimize the variables by Design Expert software. Nine

possible formulations were designed by considering two factors at three levels. The concentration of release retarding polymer HPMC K-100 M (mg) (X1) and binder PVP K-90 (mg) (X2) were set as independent variables. Dependant variables were drug release (Y1) and hardness (Y2) of the prepared formulations. Based on the design experimental trials were conducted for all nine possible combinations.²⁵ The composition of factorial design formulations is given in Table 2.

Table 2: Composition of factorial design batches.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	500	500	500	500	500	500	500	500	500
HPMC K-100M	100	90	90	90	100	80	80	80	100
Carboxy methyl cellulose	30	40	60	50	40	50	70	60	50
PVP K-90	30	30	10	20	20	30	10	20	10
Magnesium Stereate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total (mg)	670	670	670	670	670	670	670	670	670

Evaluation of factorial design formulations: The developed formulations were evaluated for drug release and hardness to select optimized formulation for the preparation of bilayer tablet.

Bulk Density: Bulk density is defined as the ratio of mass of a powder to the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to stick to one another. Accurately weighed quantity of sample (10 gm) was placed in 50 ml measuring cylinder. The volume occupied by powder was determined without disturbing the cylinder. Bulk density for pure drug and all solid dispersion was calculated using following equation.

Bulk density = Weight of powder / Bulk volume

Tapped Density: Accurately weighed quantity of sample (10 gm) was placed in 20 ml measuring cylinder. The measuring cylinder was tapped for fixed number of taps to obtain constant volume of powder bed. The final volume was noted and tapped density was determined by using following equation.

Tapped density = Weight of powder / Tapped volume

Loss on drying (LOD): Weighed quantity of granules (2 gm) was added in previously weighed and dried glass bottle which was placed in drying chamber of LOD moisture analyzer. The temperature was maintained at 105 °C for 5 min until constant weight was

obtained. Sample was weighed after drying and moisture content was determined.

Drug release study: Dissolution of all the formulations was performed in 900 ml of phosphate buffer pH 6.8. The temperature of the dissolution media was maintained 37±0.5 °C at 100 RPM.

At each time interval 5 ml of sample was collected and replaced with fresh dissolution media. Sampling was done at 1 hr, 3hr and 10 hr time interval and analyzed by UV spectrophotometer at 232 nm. Cumulative drug release after 10 hr was calculated.

Hardness: Hardness of all the factorial formulations was determined. The term hardness indicates the ability of a tablet to withstand mechanical shocks while handling. It is generally expressed in Kg/cm² or in Newton (N). Hardness of a tablet was measured using Monsanto hardness testers (26).

Drug content: Twenty tablets were weighed and crushed in the mortar and pestle. Powder equivalent to 670 mg was transferred to 100 ml volumetric flask and volume was made with phosphate buffer pH 6.8. For drug extraction, it was sonicated for 15 min. The sample was filtered after sonication through 0.45 µm filter, suitably diluted and analyzed for drug content for both drugs using UV spectrophotometer (10).

Preparation and evaluation of bilayer tablets: The bilayer tablet of optimized IR layer and SR layer was designed. The composition of the bilayer tablet is

given in Table 3. The blend of IR layer and granules of SR layer were compressed into 1000 mg tablet. 16-station double rotary tablet machine at speed of 30

RPM and 14 mm flat concave faced punches was used for compression.

Table 3: Composition of bilayer tablet.

IR Layer		
Sr No	Ingredient	Quantity (mg)
1	Alpha lipoic acid	200
2	Microcrystalline cellulose PH-102	69
3	Aerosil	3
4	Dibasic Calcium Phosphate	27.44
5	Crosscamellose sodium	26.56
6	Magnesium Stearate	4
Total (mg)		330
SR layer		
1	Metformin HCl	500
2	HPMC K-100M	90
3	Carboxy methyl cellulose	50
4	PVP K-90	20
5	Magnesium Stereate	5
6	Talc	5
Total (mg)		670

Pre-compression parameters: Alpha lipoic acid IR blend and metformin SR granules were evaluated for bulk density, tapped density, angle of repose, Hausner's ratio and compressibility index according to standard procedures.

Post-compression parameters:

Thickness: Thickness of the tablets was measured using vernier caliper and average thickness was calculated. Ten tablets were selected at random to determine thickness. Test passed if none of the tablets deviated by $\pm 5\%$.

Weight variation: Twenty tablets were selected randomly and weighed individually on electronic balance. Average weight of the tablets was determined. Individual weight of the tablet was compared with the average weight. Since weight of the tablets is greater than 250 mg, test passed if none of the individual weight deviates by $\pm 5\%$ of the average weight.

Hardness: Crushing strength or hardness of the tablet is the force required to break the tablets diametrically. Six tablets were taken at random to determine hardness. Monsanto hardness tester was used to measure the tablet hardness. The hardness is measured in Kg/cm².

Friability: Ten tablets were taken (as the weight of the tablet is >650 mg) and used to determine friability. Tablets were weighed accurately (W1), dedusted and placed in the rotating chamber of Roche friabilator.

Tablets were exposed to shock for 4 min (25 RPM). Tablets were reweighed and friability was calculated according given formula

$$\text{Friability} = (W1 - W2) / (W1) * 100$$

Where; W1 = Initial weight of the tablets

W2 = Final weight of the tablets

Drug content: Twenty tablets were powdered in mortar and pestle and powder equal to 1000 mg was transferred to 100 ml volumetric flask. The volume was made with pH 6.8 phosphate buffer and sonicated for 15 min. The resulting solution was filtered, diluted suitably and analyzed by UV spectrophotometer to determine the concentration of both the drugs present by simultaneous method.

Drug release: Dissolution study of the bilayer tablet was performed using 900 ml of phosphate buffer pH 6.8 as dissolution media at 37 ± 0.5 °C temperature and 100 RPM. At each time interval 5 ml of sample was collected and replaced with fresh dissolution media. Sampling was done at 1 hr, 3hr and 10 hr time interval and analyzed by UV spectrophotometer. Drug release was calculated for both the drugs. The mechanism of drug release from the metformin SR layer was determined by fitting the data to various equations like zero order, first order, Higuchi equation, Koresmeyer's equation.

Stability study: The bilayer tablets were subjected to accelerated stability study according to ICH guidelines. The study was performed at room temperature

and 40 °C by maintaining 75% RH for three months. Sampling was done at one month interval for three months. The samples were analyzed for drug content and dissolution.¹¹

RESULTS AND DISCUSSION:

Preparation of alpha lipoic acid IR layer: The alpha lipoic acid IR layer was optimized by designing three formulations containing different concentrations of superdisintegrant crosscarmellose sodium. The developed formulations were evaluated for drug release, drug content, disintegration time, and bulk density and tapped density. The formulation (alpha lipoic acid IR

layer) containing 8% crosscarmellose sodium was selected for the development of bilayer tablets.

Design, formulation and optimization of metformin HCl SR layer using 3² factorial design: This study was undertaken to optimize the metformin HCl SR layer for the preparation of bilayer tablets through 3² factorial design. Total nine formulations were designed by varying the concentrations of two variables, HPMC K-100 M and PVP K-90. The developed formulations were evaluated for pre-compression and post-compression parameters. The results are provided in Table 4.

Table 4: Compilation data of stability studies.

Parameters	Factorial formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (g/ml)	0.48	0.49	0.51	0.50	0.52	0.53	0.49	0.56	0.58
Tapped density (g/ml)	0.61	0.63	0.64	0.67	0.69	0.72	0.64	0.67	0.70
Loss on drying	3.8	4.1	3.9	4.8	4.3	4.5	5	4.4	4.6
Hardness Kg/cm ²	4.5	4.7	4.3	4.2	4.4	4.6	4.7	4.5	4.8
Drug content (%)	90.64	88.12	93.52	98.56	91.67	93.72	89.23	96.82	94.20

Bulk and tapped density of the formulation is important during the compression of the tablets. Both the densities were within limits and matches with the literature value. The LOD parameter is critical for the preparation of the metformin tablets and was obtained in the acceptable range of 3.8 to 4.8. These values are closer to the reported values. Hardness of the tablets is an important during handling and shipping. All the formulations exhibited sufficient hardness between 4.2-4.8 kg/cm². The formulations were assayed and drug content of all formulations was between 88-99%. The F4 formulation was having greater drug content of 98.56%.¹²

Drug release study: The developed formulations were subjected to dissolution study for 10 hrs. The percent drug release from various formulations was determined and reported in Table 5. The drug release profiles are presented in Figure 1 for various formulations.

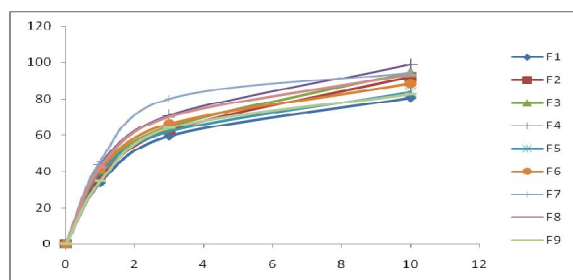


Figure 1: Dissolution profile of factorial formulations.

Statistical analysis of factorial design and response surface plots: The response surface plots are presented in Figure 2. The selected independent variables significantly affected the dependant variables ($p < 0.05$). The desirability function was used to select optimize formulation. Based on the desirability function the F4 formulation was optimized. The F4 formulation possessed percent drug release of 98.82% and 4.2 Kg/cm² hardness. The desirability was found equal to one for this formulation.

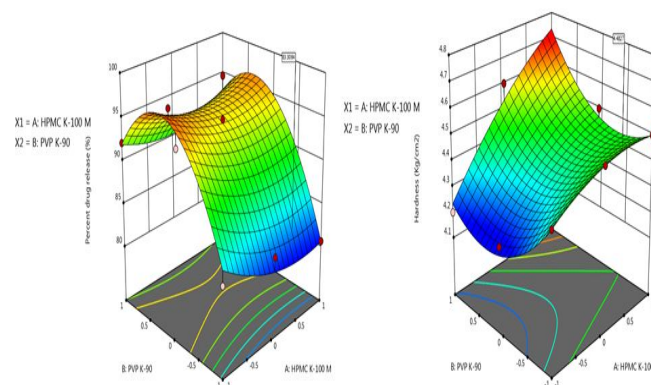


Figure 2: Response surface plots.

Preparation and evaluation of bilayer formulation: The bilayer tablets of optimized alpha lipoic acid IR layer and metformin HCl SR layer were prepared. The weight of the IR layer was 330 mg and SR layer 670 mg in the bilayer tablet. The designed formulation was evaluated for pre-compression and post-compression

parameters and results are given in Table 5. Bulk and flow properties of the formulation were good and passable as observed from the different parameters and closer to the previous results. The developed bilayer tablet showed uniform thickness. The weight variation for tablets having weight greater than 324 mg is $\pm 5\%$ allowed as per USP. The tablet passed the

test as weight variation was less than 5%. The friability was also observed less than 1% which is acceptable. The tablets exhibited sufficient hardness as reported in Table 5. The drug content for both the layers was greater than 98%. Overall, each evaluation parameter for bilayer tablets was obtained within prescribed limit.¹³

Table 5: Pre-compression and post-compression parameters.

Sample	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Carr's index	Hausner's ratio	Angle of repose (degree)
Alpha lipoic acid IR layer	0.43	0.52	17.30	1.20	24.58
Metformin HCl SR layer	0.51	0.63	19.04	1.23	25.72
Post-compression parameters					
Bilayer tablet	Thickness	Hardness	Friability	Weight variation	Drug content
	6.45 \pm 0.32	5.8 \pm 0.49	0.48 \pm 0.059	0.67 \pm 0.014	98.67 \pm 1.24 (ALA) 99.02 \pm 1.56 (Metformin HCL)

In vitro dissolution study of bilayer tablets: The amount of drug release from the bilayer tablet was within acceptable limit. Both the layers showed greater than 85% drug release within prescribed time. The amount of drug released at 1 hr and 10 hr was considered. The drug release from the immediate release alpha lipoic acid layer was 97.81 % within 1 hr. The metformin HCl SR layer also showed drug release of 96.27 at the end of 10 hr. It was a challenge to retard the drug release from the metformin SR layer due to its freely water soluble nature. But selected polymer HPMC K-100 M provided the required drug release control during selected time. This could be due to the optimum concentration of the HPMC K-100 M selected through optimization [14]. The drug release profile from bilayer tablets given in Figure 3 and Table 6.

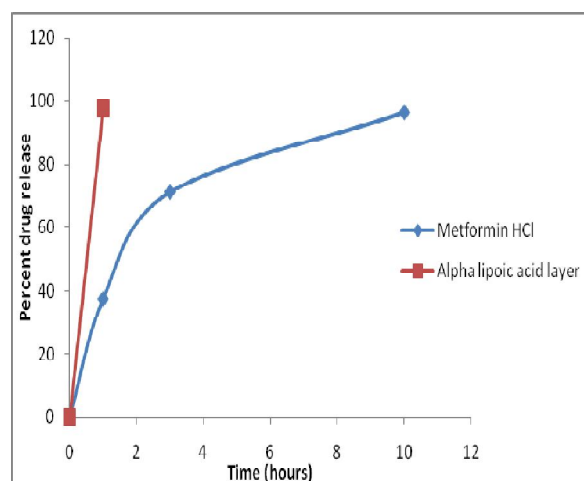


Figure 3: Dissolution profile of bilayer tablet.

Table 6: Pre-compression and post-compression parameters.

Month	Drug content		Percent drug release	
	Alpha lipoic acid layer	Metformin HCl layer	Alpha lipoic acid layer	Metformin HCl layer
First	97.85 \pm 1.31	99.12 \pm 1.65	96.81 \pm 1.57	95.07 \pm 2.45
Second	97.53 \pm 1.72	98.20 \pm 2.14	95.11 \pm 2.09	95.29 \pm 2.19
Third	98.07 \pm 2.04	98.04 \pm 1.93	95.46 \pm 1.89	94.17 \pm 1.67

Stability study: The bilayer tablets were subjected to accelerated stability study according to ICH guidelines for three months. The drug content and dissolution study was performed for three months after one month interval. The results indicate no significant changes in both the parameters estimated. The slight changes in drug content and drug release from the

bilayer tablet indicates the stability of the prepared tablets even after three months.²⁶⁻³⁰

CONCLUSION: The bilayer tablets of alpha lipoic acid (IR layer) and metformin HCl (SR layer) with acceptable hardness, friability, drug content and more than 85% drug release were designed, prepared and

evaluated. This may lead to reduction of dosage, dosing frequency and improve therapeutic effectiveness in type II diabetes with reduced side effects.

REFERENCES:

- Shinde, P. R. An overview on bilayered tablet technology. *Int J Pharma Bio Sci.* 2014, 5(2), 5496.
- Sarma, A. Bilayer tablet and duredas technology-a Review. *Int J Pharm Biol Sci.* 2013, 3(2), 554–63.
- Anuradha D. An overview in bilayered tablets. *Int J Pharmacy&Technology.* 2016;8(1):3554–70.
- Satpute, V. M.; Tuljapur, N. T. Bi-layer tablet: A controlled release dosage form. *Int J Res Anal Rev.* 2020, 7(7), 175–82.
- Avinash, Sharma; Pravin, Kumar; Sharma, G. D. Formulation and eveluation of bilayer tablet of metronidazole and dicyclomine hydrochloride for treatment of irritable bowel disease. *J Drug Deliv Ther.* 2017, 7(7), 56–8.
- Devталu, S. V.; Patil, A. E.; Bari, M; M. A review on novel approach – bilayer tablet technology. *Int J Pharm Sci Rev Res.* 2013, 21(1), 46–52.
- Namrata, M.; Sirisha, V. N. L.; Sruthi, B.; Harika, I. B.; Kirankumar, P.; Rao, Y. K. K. et al. A review on bi-layer tablets. *Int J Pharm Phytopharm Res.* 2013, 2(4):240–6.
- Syed, M. S.; Anjaneyulu, M. V.; Anusha, C.; Shekar, V.; Chejeti, R. A review article on bilayer tablets. *Int J Res Pharm Nano Sci.* 2013;2(4):417–22.
- Gaikwad, S.S.; Chafle, S. A.; Morris, P. S.; Avari, J. G. Development and evaluation of bilayer tablets of combination of antibiotics for the treatment of sexually transmitted disease. *Brazilian J Pharm Sci.* 2016, 52(3), 555–66.
- Vishal, M.; Anuj, K.; Pankaj, P.; Deepti, P.; Shraddha, S.; Mansee, S. et al. Formulation development and evaluation of bilayer tablets of lornoxicam. *Int J Drug Dev Res.* 2012, 4(2), 173–9.
- Hephzibah, K.; Sangeetha, S. Review on: Solid dispersion bilayer tablet. *Drug Invent Today.* 2020, 14(2), 200–3.
- Tanvir, Kabir M.; Sahab, Uddin M.; Al Mamun, A.; Jeandet, P.; Aleya, L.; Mansouri, R.A. et al. Combination drug therapy for the management of alzheimer's disease. *Int J Mol Sci.* 2020, 21(9), 1–23.
- Bailey, T. Options for combination therapy in type 2 diabetes: Comparison of the ADA/EASD position statement and AACE/ACE algorithm. *Am J Med [Internet].* 2013;126(9 SUPPL.1):S10–20. Available from: <http://dx.doi.org/10.1016/j.amjmed.2013.06.009>
- Rameshwar, V.; Kishor, D.; Tushar, G. Bi-layer tablets for various drugs: A review. *Sch Acad J Pharm.* 2014, 3(3), 271–9.
- Rao, S.V.; Priyanka, B.; Padmalatha, K. Bilayer tablet technology : A novel approach. *GSC Biol Pharm Sci.* 2019, 07(02), 22–8.
- 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.* 2019, 32(4), 229–35.
- Shiyani, B.; Gattani, S.; Surana, S. Formulation and evaluation of bi-layer tablet of metoclopramide hydrochloride and ibuprofen. *AAPS PharmSciTech.* 2008, 9(3), 818-27.
- Nirmal, J.; Saisivam, S.; Peddanna, C.; Muralidharan, S.; Godwinkumar, S.; Nagarajan, M. Bilayer tablets of atorvastatin calcium and nicotinic acid: formulation and evaluation. *Chemical and Pharmaceutical Bulletin.* 2008, 56(10), 1455-8.
- Patra. C.; Kumar, A.; Pandit, H.; Singh, S.; Devi, M. Design and evaluation of sustained release bi-layer tablets of propranolol hydrochloride. *Acta Pharmaceutica.* 2007, 57(4), 479-89.
- He, W.; Huang, S.; Zhou, C.; Cao, L.; Yao, J.; Zhou, J.; Wang, G.; Yin, L. Bilayer matrix tablets for prolonged actions of metformin hydrochloride and repaglinide. *AAPS PharmSciTech.* 2015, 16(2), 344-53.
- Oh, J. H.; Eun, Lee J.; Jeong, Kim Y.; Oh, T.O.; Han, S.; Jeon, E. K.; Shin, K.; Kim, D.H.; Hye, Park C.; Lee, Y. J. Designing of the fixed-dose gastroretentive bilayer tablet for sustained release of metformin and immediate release of atorvastatin. *Drug development and industrial pharmacy.* 2016, 42(2), 340-9.
- Ranade, A. N.; Wankhede, S. S.; Ranpise, N.S.; Mundada, M. S. Development of bilayer floating tablet of amoxicillin and Aloe vera gel powder for treatment of gastric ulcers. *AAPS PharmSciTech.* 2012, 13(4), 1518-23.
- Sonar, G. S.; Jain, D.K.; More, D. M. Preparation and in vitro evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate. *Asian J Pharm Sci.* 2007, 2(4), 161-9.
- Jadhav, R. T.; Patil, P. H.; Patil, P. R. Formulation and evaluation of bilayered tablet of Piracetam and Vinpocetine. *J Chem Pharm Res.* 2011, 3(3), 423-31.
- Dey, S.; Mahanti, B.; Khila, S.; Mazumder, B.; Gupta, S. D. Formulation development and opti-

- mization of bilayer tablets of aceclofenac. *Expert opinion on drug delivery*. 2012, 9(9), 1041-50.
26. PV, S.; Kinagi, M.; Biradar, S.; Gada, S.; Shilpa, H. Formulation design and evaluation of bilayer buccal tablets of granisetron hydrochloride. *Ind J Pharm Edu Res*. 2011, 45(3), 242.
27. Deshmukh, M. T.; Kore, V. U.; Kshirsagar, P. K.; Jagtap, S. V.; Shete, R. V. Formulation and Evaluation of Sustained Release Matrix Tablet of Metformin Hydrochloride. *Current Pharma Research*. 2018, 8(3), 2403-12.
28. Momin, S.; Khan, S.; Ghadage, D. M.; Yadav, A. V.; Wagh, A. Formulation and evaluation of bilayer tablets of propranolol hydrochloride. *Journal of Drug Delivery and Therapeutics*. 2017, 7(2), 50-7.
29. Jayaprakash, S.; Halith, S. M.; Pillai, K. K.; Balasubramaniyam, P.; Firthouse, P. M.; Boopathi, M. Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate. *Der Pharmacia Lettre*. 2011, 3(4), 143-54.
30. Mandal, U.; Pal, T. K. Formulation and in vitro studies of a fixed-dose combination of a bilayer matrix tablet containing metformin HCl as sustained release and glipizide as immediate release. *Drug Dev Ind Pharm*. 2008, 34(3), 305-13.