RESEARCH PAPER

Fabrication of cardiovascular drug combination as Bilayer tablets: A Strategy for 24-Hour Hypertension Management

Swati S. Gaikwad[1]*, Hina D. Mehta[1], Vinayak S. Walhekar[2], Mansi L. Patil[3], Pratibha Waghale[4] and Vinod M. Thakare[1]

[1]Nagpur College of Pharmacy, Wanadongri, Hingna road, Nagpur-441110
[2]Dnyaan Prasad Global University School of Pharmacy and Research Pimpri Pune- 411018
[3]TSSM's Jayawant institute of Pharmaceutical Sciences and Research Bavdhan Pune 411021
[4]Yeshwantrao Chavan College of engineering, Wanadongri, Hingna road, Nagpur-441110
[1] swati.gaikwad05@gmail.com*
[1]Orcid id: https://orcid.org/0000-0002-7896-063X.*

Received: 15th Sep, 2025; Revised: 14th Oct 2025; Accepted: 6th Nov, 2025; Available Online: 1st December, 2025

ABSTRACT

Combination antihypertensive drug therapy is frequently recommended for patients with cardiovascular disorders. A persistent issue with current therapies is morning hypertension, as the therapeutic effect of the drugs does not extend for 24 h, necessitating repeated dosing. A bilayer tablet comprising Olmesartan medoxomil and Azelnidipine was developed to facilitate a rapid onset of action through the immediate release of an Olmesartan medoxomil inclusion complex and a floating sustained release of Azelnidipine.

In this study, an OLM: HP βcd (1:2) inclusion complex was utilized alongside various superdisintegrants, namely sodium starch glycolate, croscarmellose sodium, and crospovidone, to ensure rapid disintegration of the immediate-release dose. Polyethylene oxide (PEO) WSR 303 was employed as a sustained-release hydrophilic polymer, in conjunction with potassium bicarbonate as a gas-generating agent for the floating layer. Design Expert software was used to formulate and evaluate the various batches.

The in vitro drug release profile demonstrated the immediate disintegration of the OLM layer within 5 min, with a lag time of 45 s for the floating layer following the disintegration of the immediate-release layer. The floating layer exhibited in vitro and in vivo buoyancy for 8-10 hours. An in vivo pharmacokinetic study in rabbits indicated enhanced bioavailability of these drugs through the maintenance of steady-state plasma concentrations compared with conventional tablets.

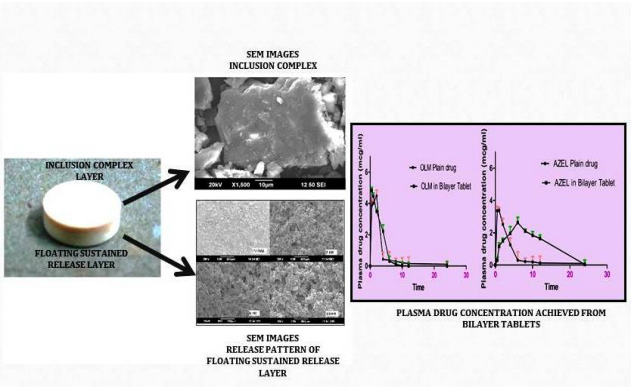
Based on the observed results, it can be concluded that floating bilayer tablets can enhance the bioavailability of the formulated antihypertensive drugs. Furthermore, the novel bilayer tablet design approach could provide consistent drug release over a 24-hour period.

Keywords: Bilayer tablet; Cardiovascular; Olmesartan medoxomil; Azelnidipine; Pharmacokinetics; Bioavailability

How to cite this article: Gaikwad SS, Mehta HD, Walhekar VS, Patil ML, Waghale P, Thakare VM; Fabrication of cardiovascular drug combination as Bilayer tablets: A Strategy for 24-Hour Hypertension Management. Int J Drug Deliv Technol. 2026;16(1): 466-471. DOI: 10.25258/ijddt.16.1.49

Source of support: Nil.

Conflict of interest: None



Graphical Abstract

1. INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. It is responsible for 17.3 million annual deaths, and by 2030, this number is anticipated to exceed 23.6 million.[1.] Various therapies are available for the treatment of hypertension and cardiovascular diseases [2]. However, there are limited ranges of drugs that can be used in patients with nephropathy. One such drug combination is olmesartan medoxomil and azelnidipine. A literature survey revealed that azelnidipine, a calcium channel blocker, has Cardioprotective and Nephroprotective activities compared to other available calcium channel

**Author for Correspondence: swati.gaikwad05@gmail.com*

blockers[3]. Despite these benefits, this combination has limitations, such as low solubility and bioavailability [4,5]. Therefore, a drug delivery system that can enhance the solubility and bioavailability of this drug combination is required.

Floating oral drug delivery systems (FDDS) are useful for medications that are insoluble or unstable in the intestinal tract because they are retained in the stomach fluids. The floating drug delivery system (FDDS), which has a lower density than gastrointestinal juices, remains in the stomach, feeling buoyant without changing a person's gastric emptying rate. This results in controlled variability in plasma drug concentration and a higher residence time.

A bi-layer tablet is a potential device for the simultaneous release of two drugs. Two incompatible drugs can be incorporated into the same dosage form without much interaction, and a dual release mechanism from a single tablet can be achieved by formulating the initial dose as an immediate-release layer and the maintenance dose as a second sustained-release layer. There are various applications of bi-layer tablet [6,7.] In addition, bilayer technology is an easier technique than cup-and-core technology.

The studies envisage developing a bilayer gastro-retentive drug delivery system of drug combination Olmesartan medoxomil and Azelnidipine to increase its gastric retention time and, therefore, its absorption and bioavailability for a longer duration of time. This study includes the fabrication of bilayer tablets of Olmesartan Medoxomil and Azelnidipine consisting of an olmesartan medoxomil inclusion complex with HP β-cyclodextrin in the immediate-release layer and an azelnidipine gastro-retentive sustained-release layer, which will serve as a boon for patients suffering from cardiovascular disease along with nephropathy.

2. MATERIAL AND METHODS

2.1. Material

Various drugs and excipients were procured from industries. Azelnidipine (AZD) and olmesartan medoxomil (OLM) were provided by Mylan Laboratories Ltd. (Hyderabad, India) for research purposes. Colorcon Asia Pvt. Ltd. (Goa, India) generously provided the Polyethylene oxide WSR 303. Ankit Pulps (Nagpur, India) supplied Avicel (PH 101) (microcrystalline cellulose) (Goa, India). Evonik Degussa India Pvt. Ltd. (Mumbai, India) provided the Aerosil. Croscarmellose sodium, sodium starch glycolate, polyplasdone, aerosil, and magnesium stearate were obtained from the Chemical Store of the Department of Pharmaceutical Sciences, RTMNU, Nagpur.

2.2. Formulation development

To formulate a bilayer tablet inclusion complex of olmesartan medoxomil and HP β-cyclodextrin for immediate release and azelnidipine sustained-release layer with PEO WSR polymer. The following methods were used in the formulation.

2.2.1. Preparation of Olmesartan medoxomil: HP β-Cyclodextrin inclusion complex for Immediate Release Layer [8,9,22]

To form the inclusion complex, various ratios of OLM and HPβ-CD (1:1, 1:2, and 1:3) were combined. To facilitate this process, an adequate amount of water was added to create a thick paste, which was subsequently kneaded for 15 minutes. The mixture was then subjected to drying in a hot-air oven. Upon drying, the substance was triturated using a mortar and pestle, passed through a #100 mesh sieve, and stored in a desiccator, as detailed in a previously published article.[24].

3.1. Preparation of Bilayer tablets

3.1 Preparation of the immediate release layer

Experimental design:

The compositions listed in Table 1 were used. For the production of IR tablets, three distinct superdisintegrants were utilised at variable levels: sodium starch glycolate, cross carmellose sodium, and crosspovidone. Olmesartan Medoxomil ICs and Microcrystalline cellulose (MCC) were thoroughly mixed with Superdisintegrants for 15 minutes using a mortar and pestle followed by addition of lubricant and glidant. In order to analyse the flow property of blend, evaluation of precompression parameters were performed prior preparation of tablets.[8]

The specified quantity of the lubricated mixture was accurately weighed and manually introduced into a pilot-scale tablet compression machine (Chamunda Pharma Machinery Pvt. Ltd.). The mixture was then subjected to direct compression using 7 mm flat-faced, round-shaped punches, resulting in tablets with a mass of 100 mg.[9,11].

3.2. Preparation of the Floating sustained release layer

Experimental design:

In this study, batches were formulated using a Central Composite factorial design, incorporating 13 full factorial design points, as illustrated in Table no. 2. In the referenced table, the letter Y denotes the dependent variables, while X1 and X2 represent the independent variables. The independent formulation factors selected were X1, potassium bicarbonate, and X2, PEO WSR 303. Table 1 presents the levels of the independent variables. The dependent variables are identified as Floating Lag Time, the percentage of drug released at 1 hour (D1h), and the time required for 90% of the drug to be released.

Table no. 3. shows the direct compression process used to make Azelnidipine Gastro retentive (GR) tablet formulations (F1–F9). The powders were all sieved using an ASTM 40 mesh sieve (425). For 10 minutes, precise amounts of the drug Azelnidipine and PEO WSR 303 were carefully combined. Subsequently, Avicel PH 101 and potassium bicarbonate were added, and the mixture was stirred for 5 minutes. To lubricate the blend, magnesium stearate (0.5 percent w/w) and Aerosil (0.5 percent w/w) were incorporated for 3 minutes. Tablets were compressed on a pilot press tablet compression machine equipped with 7 mm diameter beveled flat-faced punches, at a weight of 200 mg. [22.]

The specified quantity of the lubricated mixture was accurately measured and manually introduced into a pilot press tablet compression machine (Chamunda Pharma Machinery Pvt. Ltd.). Subsequently, it was compressed using 10 mm flat-faced, round punches at a weight of 200 mg, ensuring a consistent compression force across all formulations[12], as detailed in the published article.[13].

3.3. Preparation of Bilayer tablets

The optimized batch was selected from immediate release and Sustained release formulations on the basis of evaluation results. These optimized batches were used for the Bilayer tablet formulation.

Bilayer tablets were developed utilizing optimized immediate release (O9) and sustained release (F3) layers. Specifically, 100 mg of Olmesartan Medoxomil was incorporated into an immediate release blend, while 200 mg of Azelnidipine was included in floating sustained release granules, both of which were precisely weighed. In accordance with the formulation detailed in Table No.3, various batches of bilayer tablets were manufactured using the direct compression method. To ensure uniformity of the layers, the immediate release powder blend was manually introduced into the die of a pilot press tablet compression machine and compressed at a low compression force. Subsequently, a sustained release layer mixture was applied over the precompressed immediate release layer and compressed using 10 mm round-shaped concave facing punches [13,14].

4. EVALUATION OF BILAYER TABLET FORMULATION

4.1 Post compression evaluation parameters

Post compression characteristics such as diameter, thickness (n = 20), hardness (n = 6), friability (n = 20), weight variation (n = 20), drug content (n = 6) and percent drug release (n = 6) were studied for prepared bilayer tablet formulation. Disintegration time (n = 6) of immediate release tablets whereas, floating lag time (n = 6) and *in vivo* buoyancy time (n = 2) of floating sustained release tablets were determined[14].

4.2 In-vitro drug release study

An in vitro drug release study was conducted in accordance with Pharmacopoeial specifications. At predetermined intervals, a 5 mL sample was withdrawn and replaced with an equivalent volume of the dissolution medium. The sampling time points were set at 5, 10, 15, 30, 45, and 60 minutes for OLM immediate-release tablets, and at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours for AZD floating sustained-release tablets. The collected samples were filtered through a 0.45 µm membrane filter and analyzed using a UV spectrophotometer (UV Shimadzu 1700) at λmax 257 nm and 269 nm for OLM and AZD, respectively. The test was performed on three tablets, and the mean ± SD was calculated[15,16].

4.3 Drug release kinetics models

Mathematical models, including zero-order, first-order, Higuchi, Hixon-Crowell, and Korsmeyer-Peppas, were utilized to characterize the kinetics of drug release from matrix tablet batches.[17]

4.4 *In-vitro* drug release study Olmesartan Medoxomil SD (IR) and Azelnidipine Gastro retentive (GR) bilayer tablets

The in vitro drug release study was conducted utilizing a type I (basket) apparatus (Electrolab TDT-08L plus, Dissolution tester USP Mumbai, India) operating at 100 rpm. The study employed an acid buffer with a pH of 1.2 for the immediate release layer of Olmesartan Medoxomil and for the gastroretentive (floating) sustained release layer of Azelnidipine. The temperature was maintained at 37.5±2°C. A 5 mL sample was collected at specified time intervals and was replenished with the same dissolving fluid to ensure both immediate release and floating sustained release. The withdrawn samples were diluted and analysed using HPLC at 255 nm. The test was performed on three tablets, with the mean and standard deviation computed.

HPLC analysis

The chromatogram was plotted for OLM and AZEL as concentration versus AUC using the mobile phase prepared for calibration (Table no. 5) [18]

1.5 *IN VIVO* STUDY

In vivo evaluation of prepared dosage forms

In the current in vivo clinical study, the prepared formulations, namely bilayer tablets and conventional tablets, were evaluated using healthy New Zealand White rabbits of either sex, weighing between 1.0 and 2.5 kg. The subjects were divided into two groups, each

comprising four animals. The first group received the conventional tablets, serving as the reference. The second group received the in-house bilayer floating formulation. Food was withheld from the rabbits for 12 hours prior to drug administration and for another 24 hours following administration. All rabbits had free access to water throughout the trial. The second group received the in-house bilayer floating formulation. Food was withheld from the rabbits for 12 hours prior to drug administration and for another 24 hours following administration. All rabbits had free access to water throughout the trial.[19] The procedure for this in vivo animal investigation was approved by the Institutional Animal Ethical Committee. (Approval no. CPCSEA/UDPS/2018/020).

5. STABILITY STUDIES AND STORAGE CONDITION

Stability tests were carried out as per ICH guidelines Q1A(R2) on the optimised formulation batches to see if environmental or storage conditions had an impact. The optimised batch O9F3 was held for six months in an environmental stability chamber (Remi Lab, Bombay) under accelerated stability conditions of 40ºC±2ºC temperature and 75% ± 5% relative humidity. After the samples were collected at the end of 1, 3, and 6 months, the Physical parameters, drug content, and in-vitro drug release were all evaluated.[20]

6. RESULTS

Evaluation of bilayer tablets

6.1 Post compression parameters of Bilayer Tablets

The post-compression features of the developed bilayer tablets have been studied and the results are shown in Table 6.

Weight variation, thickness hardness, friability, and medication content were all assessed of the compressed tablets. All of the weights, according to USP, were within a 10% deviation range and passed the weight variation test. The tablets had a hardness of 3.0–5.0 kg/cm2 when tested. The tablets' friability was found to be less than 0.33-0.56 percent, indicating that they passed the friability test

6.2 *In-vitro* dissolution test of bilayer tablet

The USP type I apparatus (Basket) was used to conduct the in-vitro dissolution research of bilayer tablets (Electrolab TDT- 08L plus, Dissolution tester USP Mumbai, India). Results of dissolution test for bi-layer tablet are represented in (Figure 5 and 6). Results were represented as mean ± SD. Bilayered tablets prepared with optimized formulation of immediate release layer (O9) have shown disintegration time (40 ± 5 sec.).

6.3 Stability Study

Stability testing was performed on optimum batches of bilayer tablets in accordance with ICH requirements. Physical parameters were evaluated, and no significant changes between batches before and after the stability investigation were observed.

6.4 Pharmacokinetic analysis

To forecast the augmentation of bioavailability of manufactured Bilayer tablets and Nanosuspension, an in vivo pharmacokinetics investigation was conducted. The HPLC analytical method was used to determine the concentrations of Olmesartan medoxomil and Azelnidipine medication in blood plasma taken from New Zealand white rabbits. Figure 7 shows the mean concentration time curves for Olmesartan medoxomil and Azelnidipine drugs and drug release from bilayer tablets, respectively.

In this research, PK solver software was used to determine Cmax, Tmax, half life, area under curve, and elimination rate constant.

In vivo Pharmacokinetic Study was carried out and values of Cmax and AUC0-24 for Olmesartan medoxomil and Azelnidipine medication in Bilayer tablets were found to be greater than Cmax of pure drug. In bilayer tablets, Olmesartan medoxomil bioavailability is over 1.57 times higher (Frelative percent =157.43). Azelnidipine bioavailability increases about 2.79 times in bilayer tablets (Frelative percent =279.89). This could be attributed to drug's improved solubility and dissolution in the form of HP-βCd inclusion complex and longer residence time in stomach.

7. DISCUSSION

Bilayer tablets were formulated by integrating an optimized immediate release layer (O9) with a GR sustained release layer (F3). Specifically, 100 mg of Olmesartan Medoxomil immediate release blend and 200 mg of Azelnidipine sustained release blend were precisely measured. A direct compression method was employed to produce various bilayer tablets. These tablets underwent evaluation for hardness, friability, disintegration time, drug content, percentage drug release, weight variation, thickness, in-vivo buoyancy, and in-vitro drug release. According to the dissolving investigation, the Olmesartan medoxomil IR layer released more than 85% of the medication after 5 minutes, which was desired. In pH 1.2, the Olmesartan medoxomil was entirely discharged within 30 minutes. While Azelnidipine released approximately (25.20%) within 1 hour in acid buffer, the rate of release increased significantly every hour, resulting in continuous Azelnidipine release and total drug release in 12 hours.

Stability testing was performed on optimised batches of bilayered tablets in accordance with ICH requirements. After examining the physical parameters, no significant differences were discovered in any of the batches before and after the stability testing.

An in vivo investigation implies that the greater Cmax values found were related to improved drug solubility and

longer retention time in the GIT due to the floating and mucoadhesive features of the Bilayer tablet (O9F3) formulation.

8. CONCLUSION

From the above research study it is clear that Bilayer tablet of olmesartan medoxomil and azelnidipine can be successfully formulated. Results showed formulation of inclusion complexes containing HP βCyclodextrin has shown most effectiveness not only in enhancing solubility of drug but also improved the bioavailability of drug. Also, comparing the role of three different superdisintegrants sodium starch glycolate, crosscarmellose sodium, and polyplasdone XL, it was observed that polyplasdone XL is most efficient in quick release of drug from immediate release tablets. Similarly, PEO WSR 303 has proved to be able polymer along with potassium bicarbonate to keep the tablet floating for longer duration of time in stomach. The results of drug release observed during optimization of immediate and gastric floating layer were closed enough to that in combined bilayer tablet. In vivo investigations have proved that there is enhanced bioavailability of drug compared to conventional dosage form. Thus, it can be concluded from the above verified results that mucoadhesive bilayer tablets can assist in bypassing extensive hepatic first-pass metabolism and improves bioavailability of the antihypertensive drugs formulated. Thus, with this research study we have developed alternative dosage form for the treatment of cardiovascular disease for effective therapy.

Ethics statement

The animal study protocol was approved by the Institutional Animal Ethics Committee of Department of Pharmaceutical Sciences, R. T. M. Nagpur University, Nagpur (Approval no. IACE/UDPS/2018/20).

Consent for publication

I hereby provide consent for the publication of the manuscript detailed above, including any accompanying images or data contained within the manuscript.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

FUNDING

No funding or any specific grant from funding agencies in the public, commercial, or not-for profit sectors for this research.

Competing interests

The authors have no competing interests to declare.

Declarations of interest

None.

Authors' contributions

Swati S. Gaikwad: Conceptualization, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. Mansi L. Patil: Visualization, Writing – review & editing Hina D. Mehta: Visualization, Writing – review & editing, Pratibha Waghale & Sonali wairagade: Writing – review & editing.. Vinod M. Thakare: Conceptualization, Methodology, Supervision.

ACKNOWLEDGEMENT

The authors would like to thank Mylan Laboratories ltd, Hyderabad for providing gift sample of Olmesartan medoxomil and Azelnidipine.

REFERENCES

1. Heart disease and stroke statistics—2015 update: a report from the American Heart Association.https://www.researchgate.net/publication/311469386_Heart_disease_and_stroke_statistics-2015_update_a_report_from_the_American_Heart_Association
2. Rabito MJ, Kaye AD. Complementary and alternative medicine and cardiovascular disease: an evidence-based review. Evidence-Based Complementary and Alternative Medicine. 2013;2013(1):672097
3. Shinohara K, Hirooka Y, Ogawa K, Kishi T, Yasukawa K, Utsumi H, Sunagawa K. Combination therapy of olmesartan and azelnidipine inhibits sympathetic activity associated with reducing oxidative stress in the brain of hypertensive rats. Clinical and Experimental Hypertension. 2012;34(6):456-62 .
4. Laeis P, Puchler K, Kirch W. The pharmacokinetic and metabolic profile of olmesartan medoxomil limits the risk of clinically relevant drug interaction. Journal of Hypertension. 2001;19:21-32
5. Rashad AA, Nageeb EL-Helaly SA, Abd El Rehim RT, El-Gazayerly ON. Core-in-cup/liquisol dual tackling effect on azelnidipine buccoadhesive tablet micromeritics, in-vitro release, and mucoadhesive strength. Acta Pharmaceutica. 2019;69(3):381-98 .
6. Mishra P, Sharma PK, Malviya R. A review on Bi-layer tablets-An emerging trend. Drug Deliv Therapeut. 2014;4(4):110-4 .
7. Rajinikanth PS, Mishra B. Floating in situ gelling system of acetohydroxamic acid for clearance of H. pylori. Drug Dev Ind Pharm. 2008;34(6):577-87.

8. Gabriel OK, Yvonne TF, Kok-Khiang P, Enhancement of norfloxacin solubility via inclusion complexation with β-cyclodextrin and its derivative hydroxypropyl-β-cyclodextrin. Asian J Pharm Sci. 2016;11:536–546.

9. Jallo LJ, Ghoroi C, Gurumurthy L, Patel U, Davé RN. Improvement of flow and bulk density of pharmaceutical powders using surface modification. Int J Pharm. 2012; 423: 213–25.

10. Bayas JP, Sumithra M. QbD method to the formulation and development of a spironolactone immediate-release tablet with enhanced dissolving research. Materials Today: Proceedings. 2022;51:2539-49 https://doi.org/10.1016/j.matpr.2021.12.347

11. Gaikwad SS, Avari JG. Improved bioavailability of Azelnidipine gastro retentive tablets-optimization and in-vivo assessment. Mater Sci Eng: C. 2019;103:109800.

12. Han JK, Kim JY, Choi DH, Park ES. A formulation development strategy for dual-release bilayer tablets: An integrated approach of quality by design and a placebo layer. Int J Pharm. 2022;618:121659.

13. Akhtar M, Jamshaid M, Zaman M, Mirza AZ. Bilayer tablets: A developing novel drug delivery system. J Drug Deliv Sci Technol. 2020;60:102079 .

14. Nagarsheth A, Patel D, Thakkar H. Formulation and evaluation of proliposomal tablet of Diclofenac sodium. J Drug Deliv Sci Technol. 222;71:103353 .

15. Pan Y, Pang W, Lv J, Wang J, Yang C, Guo W. Solid state characterization of azelnidipine–oxalic acid co-crystal and co-amorphous complexes: The effect of different azelnidipine polymorphs. J Pharm Biomed Anal. 2017;138:302-15

16. Zhang Q, Ren W, Dushkin AV, Su W. Preparation, characterization, in vitro and in vivo studies of olmesartan medoxomil in a ternary solid dispersion with N-methyl-D-glucamine and hydroxypropyl-β-cyclodextrin. J Drug Deliv Sci Technol.. 2020;56:101546. .

17. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217-23.

18. Patel JK, Patel NK. Validated stability-indicating RP-HPLC method for the simultaneous determination of azelnidipine and olmesartan in their combined dosage form. Scientia Pharmaceutica. 2014;82(3):541.

19. Mapara M, Thomas BS, Bhat KM. Rabbit as an animal model for experimental research.J Dent Res. 2012;9(1):111.

20. Ammann C. Stability studies needed to define the handling and transport conditions of sensitive pharmaceutical or biotechnological products. AAPS Pharm Sci Tech. 2011 ;12(4):1264-75.

21. Panda N, Reddy AV, Reddy GS, Sultana AF. Formulation design and in vitro evaluation of bilayer sustained release matrix tablets of doxofylline. Int J Pharm Pharm Sci. 2015;7(10):74-83.

22. Gaikwad SS, Avari JG. Molecular Inclusion-Novel Approach to Enhance Solubility of Olmesartan Medoxomil using Hydroxypropyl β cyclodextrin (HP β-CD). ACTA Pharmaceutica Sciencia.;59(2).