Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 2, 2013

Research Article

FORMULATION AND EVALUATION OF PULSATILE TABLET IN CAPSULE DEVICE

ABHIJIT SONJE[1], DR. AMRISH CHANDRA[2]

[1]Bhagwant University, Ajmer, Rajasthan, India, [2]Department of Pharmaceutics, Amity University, Noida, (UP) 201302.
Email: abhi.sonje4u@gmail.com

Received: 11 Dec 2012, Revised and Accepted: 19 Jan 2013

ABSTRACT

Purpose: The aim of this study is to formulate and evaluate pulsatile tablet in capsule device of Amlodipine and Olmesartan by using Eudragit RL100 and Eudragit RS100 polymers.

Method: In this present investigation, we prepared Amlodipine immediate release blends (formulation code A1, A2 and A3) and Olmesartan coated tablet by Eudragit RL and Eudragit RS (formulation code F1, F2 and F3). Then Olmesartan coated tablets and Amlodipine immediate release blend were incorporated in hard gelatin capsule size "1" simultaneously. Finally, capsules were evaluated to obtain suitable results.

Result: Batch no. A2 of Amlodipine blends and Batch no. F2 of Olmesartan coated tablet showed best dissolution and stability result compare to batch no. A1 and A3 (Amlodipine blend) and batch no. F1 and F3 (Olmesartan coated tablets).

Conclusion: From the result it was concluded that Batch No. A2 and F2, with combination of "Tablet in a Capsule" device can be a best alternative for high blood pressure patient to avoid multiple dosing.

Keywords: Pulsatile drug delivery system, Amlodipine, Olmesartan, Tablet in Capsule device.

INTRODUCTION

Development of suitable chronotherapeutic oral dosage forms can be achieved using delayed and/or pulsatile technologies. A pulsatile release is characterized by proportioning drug concentration throughout 24-hour period (circadian rhythm) in synchrony with biological rhythm determinants of disease having right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance by avoiding side effects and drug tolerance.[2]

For this purpose, we developed tablet in capsule formulation containing two antihypertensive drugs. Two drugs, which are selected for this study, were Olmesartan and Amlodipine. The aim of this study is to reduce blood pressure and release drug at right time at right place. Amlodipine releases drug immediately from blend and Olmesartan releases from hard gelatin capsule at predetermined lag time.[1]

Amlodipine drug, which releases immediately from blend and gives pharmacological action between midnight to early morning, during which blood pressure increases. The enteric coated Olmesartan tablet release drug in the intestine after predetermined lag time of 4 hr i.e. early in the morning, when blood pressure is high and shows effective therapeutic action.[3]

The polymers, which are selected for coating purpose, are Eudragit RL and Eudragit RS. They dissolved at and above pH 6 and shows good cardiovascular activity.

MATERIAL AND METHODS

All the materials taken for this research purpose from Baxil Pharma, Haridwar. Eudragit RL and Eudragit RS were supplied by Zim laboratories, Nagpur (MH). All other chemicals used are of Analytical grade.

Drug confirmation

Amlodipine and Olmesartan both drugs are confirmed by FTIR and DSC.[4]

Preparation of Amlodipine Blend

Amlodipine blend was prepared for immediate release of drug. Diluent were selected on the basis of nature of drug. Lactose monohydrate and Avicel was used as a diluent and starch paste as a binder solvent. Accurately weighed Amlodipine (5 mg), lactose monohydrate, Avicel and starch paste were mixed together in mortar and pestle. Mixture was passed through #20 sieve followed by drying in hot air oven at 50 C for 15 min. Different formulation batches of Amlodipine blend are shown in table no. 1.[1,4]

Table 1: Composition of immediate release blend of Amlodipine

	Ingredients Formulations (Code)		
	A1	A2	A3
Amlodipine	5 mg	5mg	5mg
Avicel	150mg	160mg	170mg
Lactose Monohydrate	175mg	165mg	155mg
Starch Paste	Qs	Qs	Qs
Total wt in mg	330 mg	330 mg	330 mg

Pre compression Parameters of blend of Olmesartan core tablets

Blend of Olmesartan core tablets were evaluated for various precompression parameters such as angle of repose, loose bulk density, tapped bulk density, Hausner's ratio, and compressibility index as previously reported in precompression parameter of Amlodipine blend. [4]

Preparation of core tablets

The core tablets of Olmesartan were prepared by direct compression method. For the preparation of core tablets, microcrystalline cellulose was used as a binder and croscarmellose sodium was used as superdisintegrant, Magnesium Stearate was used as a lubricant and purified talc was used as a glidant. All these ingredients were mixed together in mortar and pestle. A theoretical weight of about 160 mg powder was fed manually in to die of 27 stations Cadmach tablet compression machine and compressed using 6.4 mm flat faced punch by direct compression method. Different formulation batches of Olmesartan core tablets are shown in table no. 2 [4]

Table 2: Composition of core tablet of Olmesartan

Ingredients	Formulations (Code)		
	F1	F2	F3
Olmesartan	20mg	20mg	20mg
Avicel	100mg	110mg	120mg
CCS	20mg	15mg	10mg
PVP K30	10mg	8mg	6mg
Magnesium Stearate	3mg	3mg	3mg
Talc	7mg	4mg	1mg
Total wt in mg.	160 mg	160 mg	160 mg

Post compression Evaluation Parameters of core tablet

Prepared Olmesartan core tablets were evaluated for official and non–official post compression parameters like thickness and diameter, friability, weight variation, (USP) disintegration test, drug content uniformity. [4]

Thickness and Diameter

Thickness and diameter test permits accurate measurement and provides information on the variation between tablets. Ten core tablets were taken and the thickness and diameter was measured using a digital vernier caliper. The tablet thickness and diameter should be controlled within a 5% variation of a standard value. [4]

Friability Test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%).

Twenty tablets were initially weighed (Initial Wt) and transferred into friabilator. The Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Final Wt). The % friability was then calculated by,

$$F = \frac{\text{Initial Weight-Final Weight}}{\text{Initial Weight}} \times 100$$

% friability of tablets less than 0.5 - 1% of their weight are considered acceptable. [4]

Weight Variation Test

Twenty tablets were selected randomly from each formulation batch and weighed individually to check for weight variation. Average weight of tablets was calculated and compared with the individual tablet weight. [4]

Disintegration Test

Six core tablets were selected randomly from each batch for the disintegration test. Disintegration test was performed in simulated colonic fluid (SCF) using Electrolab Disintegration Tester (USP), and Disintegration time (DT) was measured. [4]

Drug content determination Olmesartan core tablet

The Olmesartan core tablets were tested for their drug content. Twenty tablets were finely powdered; quantity equivalent to 10 mg was accurately weighed and transferred to a 50 mL volumetric flask. Then the volume was made up with 6.8 pH phosphate buffer and shaken for 10 min to ensure complete solubility of drug. The mixture was centrifuged and the solution was filtered. Concentration of 20 mcg/mL was prepared and absorbance of resulting solution was determined using UV spectrophotometer at 265 nm. [4,10]

Selection of polymer

Anionic polymers having pH dependent solubility were selected. The polymers which Give minimum swelling in acidic buffer and maximum swelling in basic media were Selected for further study. Polymers like Eudragit RL100 and Eudragit RS100 were used for preparation of pulsatile release Olmesartan tablets. [5,6,9,16]

Preparation of Enteric coated Olmesartan tablets

5% (w/w) solutions of polymethacrylates (Eudragit RL100 and Eudragit RS100) were prepared in isopropyl alcohol: dichloromethane mixture. The ratio of Eudragit RL100: Eudragit RS100 selected was 1:2 which showed maximum solubility at 6.8 pH in normal subjects. The solution was plasticized with diethyl phthalate (5%, w/w, with respect to dry polymer), core tablets were coated by dipping method, and tablets were removed from the coating solution when the coating loads have been reached 5% (w/w). The tablets were kept in an oven for 2 h at 50^{0}C. Different formulation batches prepared of coated Tablets. [5,6,7,9]

Preparation of tablet in capsule formulation

The first step in the formulation of tablet in capsule approach was to select the appropriate capsule size that can accommodate coated tablet and immediate release blend. For the purpose, size "1" capsule was selected according to specifications given by USP. According to USP, capsule size "1" can accommodate total weight of 500 mg. This capsule size can accommodate optimized batch of coated Olmesartan tablet weighing 160 mg and optimized batch of immediate release Amlodipine blend weighing 330 mg. finally capsule was seal with the help of capsule hand filling machine. [7,11,12,13,14,15]

In vitro drug release study

In vitro release study of Amlodipine blend

Prepared blend of Amlodipine was kept in hard gelatin capsule and dissolution studies were performed using a USP XXIII dissolution apparatus I (basket type) in 900 mL medium at 37±0.5 C at a rotation speed of 50 rpm. In vitro release study was carried out in acidic media at pH 1.2 for 2 h. Five milliliters sample was withdrawn at specific intervals and replaced with a fresh dissolution medium. These samples were filtered using a 0.45 µm membrane filter. The concentration of samples was analyzed using UV spectrophotometer at λ max 350 nm. [1,10,17]

In vitro release study of coated Olmesartan tablets

In vitro drug release studies were performed using USP XXIII dissolution apparatus II paddle type in 900 mL medium at 37.0±0.5 C, at a rotation speed of 50 rpm. Dissolution media selected was 0.1 N Hcl (pH 1.2) and phosphate buffer of pH 6.8. Dissolution test was performed for 2 h in 0.1 N Hcl (pH 1.2) and for 6 h in phosphate buffer (pH 6.8) respectively. Five milliliters sample was withdrawn at specific intervals and replaced with a fresh dissolution medium. These samples were filtered using a 0.45 µm membrane filter. The concentration of samples was analyzed using UV spectrophotometer at 265 nm. [10,17]

In vitro release study of tablet in capsule formulation

In vitro drug release studies were carried out in a USP XXIII dissolution apparatus I

Basket type (TDT-08L plus, Electrolab, Mumbai, India)) in 900 mL medium at 37±0.5 C at a rotation speed of 50 rpm. The capsule was placed in the basket. Hard gelatin capsule (500mg) containing optimized batches of Amlodipine blend and coated Olmesartan tablet were transferred to the dissolution medium. For simulating conditions of the GI tract, dissolution tests were carried out in media with pH 1.2 and pH 6.8 (phosphate buffers). The study was performed for 2 h for acidic stage (pH1.2) and for 6 h in the 6.8 pH phosphate buffer. 5 mL sample was withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45µm and analyzed using UV spectrophotometer using multicomponent method for first 2 h at λ max 350 nm respectively. After 2 h dissolution sample were analyze by UV spectrophotometer at λ max 265 nm. [7,11,12,13,14,15]

RESULT & DISCUSSION

Drug Confirmation

Form FTIR and DSC results, it is revealed that both the drugs are identified.

Flow Properties

Angle of repose and Compressibility index of Amlodipine Blend and Olmesartan core tablets blend was calculated. The compressibility index of Olmesartan blend was good, which shows suitability for direct compression. Angle of repose of both blends showing good flowing property. Results are shown in table 3.

Physicochemical properties of Olmesartan Tablet

Average weight, Hardness, Diameter and Friability of Olmesartan tablet was determined. Results are shown in table 4. All the batches of tablets show results according to official limits.

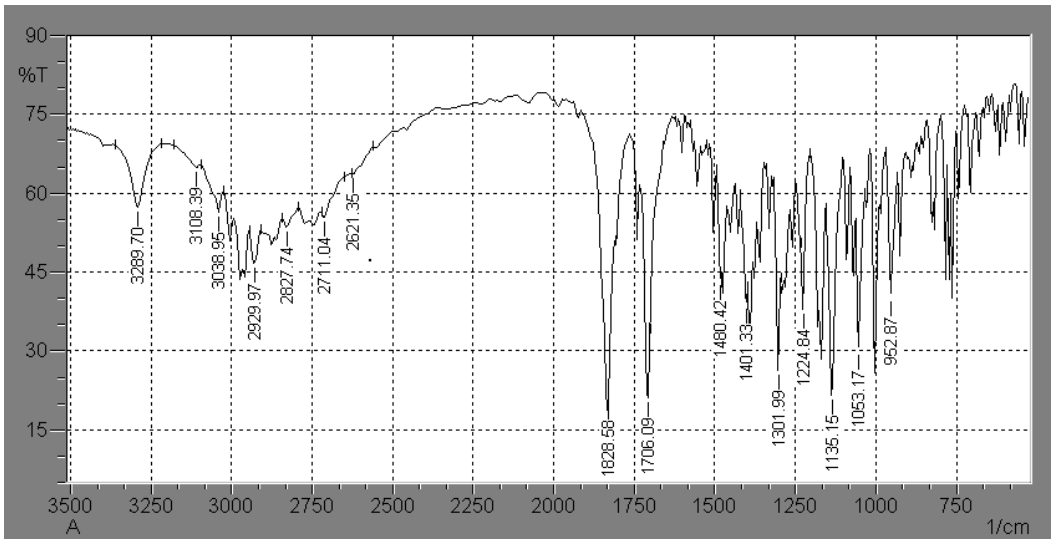

Fig. 1: FTIR Spectra of Olmesartan

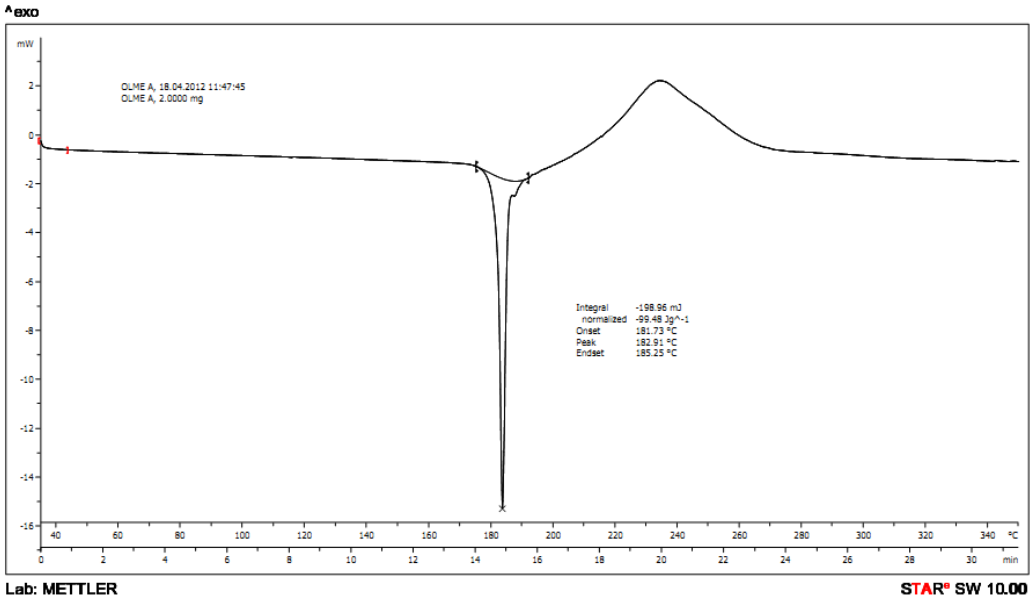

Fig. 2: DSC Spectra of Olmesartan

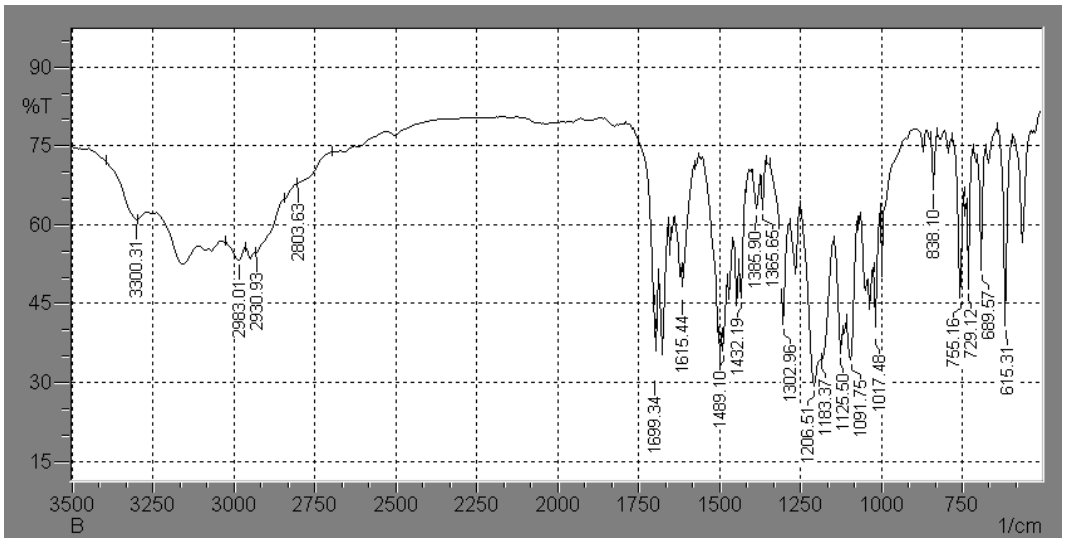

Fig. 3: FTIR Spectra of Amlodipine

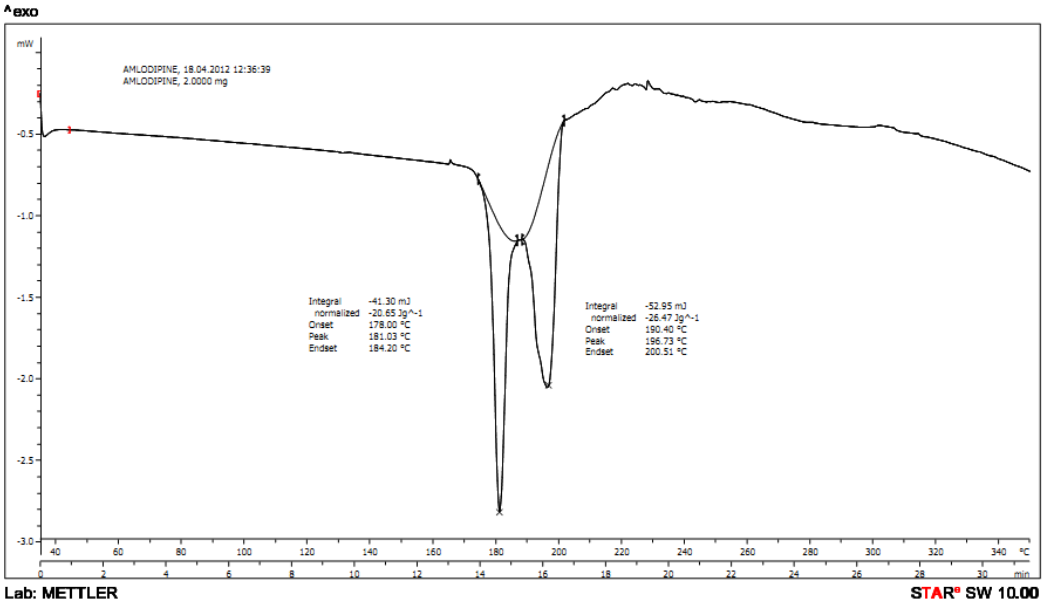

Fig. 4: DSC Spectra of Amlodipine

In Vitro release of Amlodipine blend

Dissolution profile of Amlodipine is shown in figure. After capsule was ruptured, Amlodipine releases drug immediately. About 65% drug was released in 30 min and completely dissolution achieved in 120 min. From A1, A2, and A3 batches, A2 shows better result and selected for further study.

Table 3: Flow properties (Angle of Repose and Compressibility Index) of all batches of Amlodipine and Olmesartan (A1-A3 and F1-F3)

Batch	Angle of Repose	Compressibility Index
A1	31.26	13.21
A2	29.86	12.96
A3	30.95	14.32
F1	30.74	12.84
F2	28.61	11.89
F3	29.42	11.91

Table 4: Physicochemical properties of all batches of Olmesartan tablet (F1-F3)

Batch	F1	F2	F3
Average Weight	164.8 MG	166.5 MG	162.3 MG
Hardness	4-5 KG/CM2	4-5KG/CM2	4-5KG/CM2
Diameter	3.32	3.33	3.32
Friability	0.58%	0.62%	0.81%
D.T.	5-6 MIN	5-6 MIN	5-6 MIN

In Vitro release of enteric coated of Olmesartan tablet

Eudragit RL and Eudragit RS are soluble at pH 6-7. These polymers do not release the drug in pH 1.2. But in pH 6.8 (phosphate buffer) drugs get rapidly released, due to solubility of polymers in phosphate buffer. Eudragit RL and Eudragit RS are taken as 1:2 ratios. These polymers releases drug in intestine and shows pulsatile drug release.

In Vitro release of Tablet in Capsule Device

Optimized batch of Amlodipine blend (B) and Eudragit coating of Olmesartan tablet (F2) was selected. Hard gelatin capsule get ruptured in acidic media. After rupturing of hard gelatin capsule, Amlodipine get released from blend and more than 65% drug released within 30 min. and completely dissolved in 2 hrs. in1.2 pH. Olmesartan get released up to 15% in 1.2 pH. After that tablet was placed in 6.8 buffer and remaining amount of Olmesartan released after predetermined lag time.

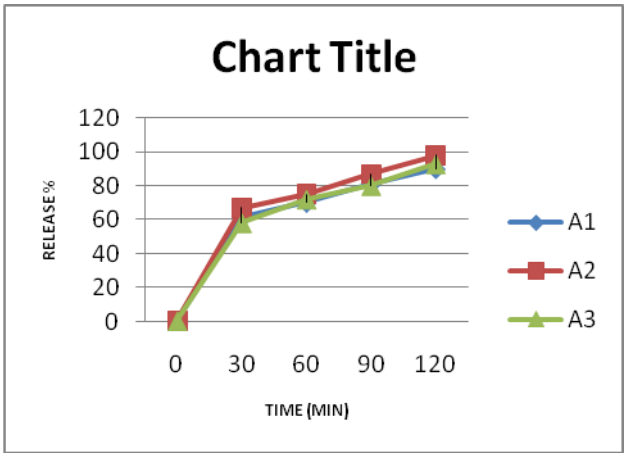

Fig. 5: In vitro release of Amlodipine Blend (A1-A3)

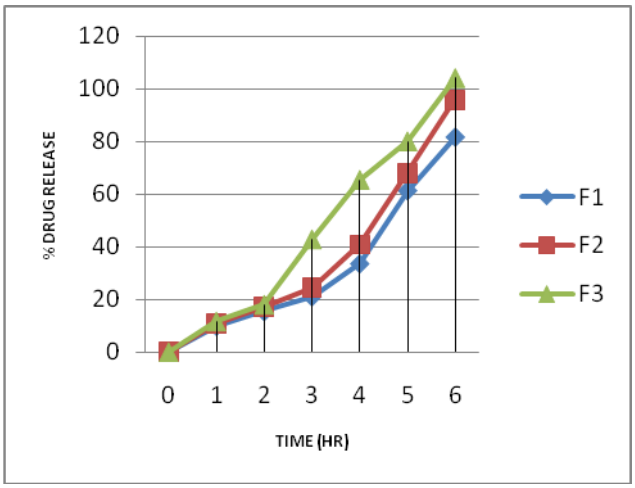

Fig. 6: In vitro release of enteric coated of Olmesartan tablet (F1-F3)

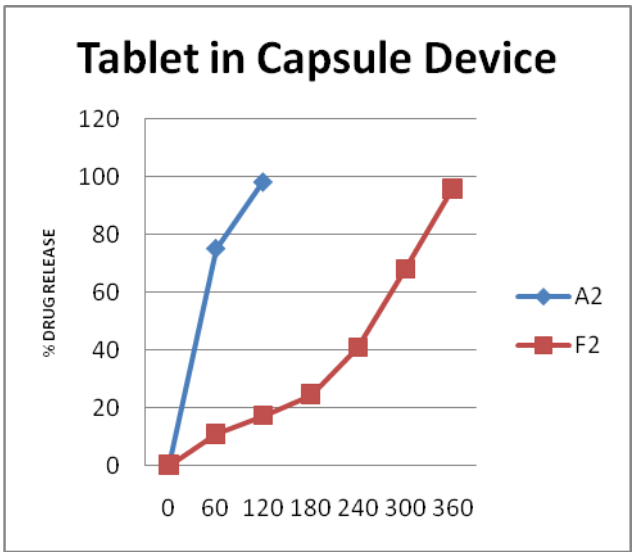

Fig. 7: In vitro release of Tablet in Capsule Device (A2-Amlodipine and F2-Olmesartan)

CONCLUSION

From the result of A2 and F2, it can be concluded that the use of two antihypertensive drugs with a combination in "Tablet in a Capsule" device can be a best alternative for high blood pressure patient. Amlodipine lowers the blood pressure at night by releasing drug while Olmesartan lowers the blood pressure at early morning. So formulation industry should take into consideration about such combined formulation to avoid multiple dosing for hypertensive patients.

ACKNOWLEDGEMENT

Special acknowledgement to Dr. Amrish Chandra and Arun Yadav for their continue support for this research work.

REFERENCES

1. Anal AK. Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds. Recent Patents on Drug Delivery and Formulation. 2007; 1: 73-79.
2. Sonje A. S., Yadav A. R. Chronotherapeutic: Revolutionizing from aged to novel pulsatile drug release, JPRCP; 2012; 2(1): 97-104.
3. Stehlin I. A Time to Heal: Chronotherapy Tunes In to Body's Rhythms. FDA Consumer magazine. April 1997, 21-23.
4. Banker G.S., Anderson N.R., In: The Theory and Practice of Industrial Pharmacy, Lachman L, Liberman H.A., Kanig J.L., 3rd edition, Vanghese publishing house, 293-345.
5. Arora S, Ali j, Ahuja A, Baboota S, Qureshi J. Pulsatile drug delivery system: an approach to controlled drug delivery. Indian J. Pharm. Sci. 2006; 68 (3): 295-300.
6. Krogel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm Res. 1998; 15(3):474-481.
7. Ying-Huan, L., Zhu, J., Modulation of combined-release behaviors from a novel tablets-in-capsule system. Journal of controlled release, 2004: 95, 381– 389.
8. Maroni A., Zema L., Cerea M., Sangalli M., Oral pulsatile drug delivery systems, Expert opinion drug delivery, 2005, (2), 855-871.
9. Pozzi F., Furlani P., Gazzaniga A., Davis, S., The Time Clock system: A new oral dosage form for fast and complete release of drug after predetermined lag time, Journal of controlled release, 1995 (31), 99-108.
10. Costa, P., Sousa Lobo, J. M., Modelling and comparison of dissolution profiles. European Journal Pharmaceutical Science, 2001 (13) 123-133.
11. Siegel, R.A., Pitt, C.G., A strategy for oscillatory drug release general scheme and simplified theory, Journal of controlled release, 1995 (46), 59-73.
12. Saslawski, O.,Weigarten, C., Benoit, J.P., Magnetically responsive microspheres for the pulsed delivery of insulin. Life Sciences, 1988 (42), 1521.
13. Rogel I., Bodmeiera R., Pulsatile drug release from an Insoluble Capsule Body Controlled by an Erodible Plug, pharmaceutical research 1998, 15:3.
14. Qui M., Wang P., Wu D., A Novel pH- and Time-Dependent System for Colonic Drug Delivery, Drug Development and Industrial Pharmacy, 2003 (29), 661–667.
15. Zou H, Jiang X., Design and gamma-scintigraphic evaluation of a floating and pulsatile drug delivery system based on an impermeable cylinder. Chem. Pharm. Bull. 2007; 55:580–585.
16. Pradeep K. S., Pratibha D., Parthibarajan R. P and Rubina R. C., Novel colon specific drug delivery system: A review, International Journal of Pharmacy and Pharmaceutical Sciences, 2012, 4 (1), 22-28.
17. Shaji J. and Shinde A., Design and in vitro characterization of floating pulsatile microspheres of Aceclofenac for Rheumatoid Arthritis.