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Development and evaluation of pulsatile drug delivery system of Telmisartan

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Abstract

The aim of the present study was the formulation of pulsatile tablets of Telmisartan by press coating technique that could release the drug time controlled manner. The core tablets and press coated pulsatile tablet of Telmisartan was prepared by direct compression technique. The core tablets were formulated using super disintegrating agent cross carmilose sodium and pulsatile tablets were by using polymer HPMC and Ethyl cellulose in various concentrations. Compatibility studies indicate that there is no interaction between the excipient and the drug. All tablets formulations were subjected to evaluation parameter. All the parameters were found within the limit. Pulsatile tablets formulation F3, F4 and F5 showed sufficient lag time of 4hr, 3hr and 4 hr respectively. The optimized formulation of F3 was consider as the best formulation with respect to drug content, hardness, lag time and *In vitro* drug release. Formulation F3 showed optimum lag time of 4 hour and release maximum drug in 8 hour. The developed formulation was found to be stable during the stability studies of 3 month indicating good stability of the tablets.

Keywords: Pulsatile Tablets; Press coated; Lag time; Telmisartan

1. Introduction

A pulsatile drug delivery system (PDDS) is a specialized drug delivery system designed to release medications with a specific delay after administration, followed by a rapid and complete release of the drug at predetermined intervals or in response to physiological stimuli. This innovative drug delivery approach aims to mimic the pulsatile nature of certain physiological processes in the body or to meet therapeutic needs that require precise timing of drug release. Pulsatile drug delivery systems are developed to address therapeutic requirements where precise control over the timing and rate of drug release is critical for achieving optimal therapeutic outcomes. Certain diseases or conditions exhibit inherent rhythmic variations in symptom severity or physiological activity, making pulsatile drug delivery an attractive approach to align drug release with this patterns.[1]

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, compel designing a delayed fast release system. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long in vivo half-lives showing an inherently prolonged duration of action, drugs with very short in vivo half-life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally, a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose.[2, 3]

Currently Chronopharmaceutics research is involve development and evaluation of drug release profile in such way therapeutic drug at right time as per biological requirement status of diseases and according to challenges of future

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drug delivery must meet. In some cases rhythms that have an effect on body in cycle is very shorter than h day which fired the neuron in millisecond. In cardian in which cycle is of twenty -four hours like waking and sleeping it contain. In the twenty-four hours clock in which illness or diseases which shows disease symptoms in pattern of day night. Some diseases does not require constant drug release, but required the pulsatile drug release in specific time in which drug release after some lag time this strategy used for development of pulsatile drug delivery system (PDDS). This system mainly includes rapid release of fixed quantity of drug moiety release after a predetermined release of drug. There are some technologies are mainly in the pulse type drug release which include micro-flora activated drug delivery, system dependent on time, system dependent on pH. These systems which are developed as per properties of drug molecule and disease physiology.[4,5]

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2. Materials and Methods

2.1. Materials

Telmisartan was obtained as gift sample from Ajanta Pharma, Mumbai. HPMC K4M Gifted by Colorcon Asia Pvt Ltd.All other chemicals are Analytical Grade.

2.2. Methods

2.2.1. Drug Excipients Compatibility Studies

Drug-excipient compatibility studies are an essential part of preformulation and formulation development processes in the pharmaceutical industry. These studies assess the compatibility of a drug substance with various excipients that are used to formulate the final dosage form. he primary purpose of drug-excipient compatibility studies is to evaluate potential interactions between the drug substance and excipients. These studies aim to identify any chemical, physical, or mechanical interactions that could affect the stability, efficacy, or safety of the final dosage form. By assessing compatibility early in the development process, formulation scientists can make informed decisions regarding excipient selection, formulation design, and process optimization. Compatibility study of drug with the excipients was determined by I.R. Spectroscopy (Shimadzu, Japan). The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of the drug and other ingredients in the formulations were compared with that of the pure drug.[8,9]

2.2.2. Preparation of Core Tablets of Telmisartan

Table 1 Formulation of Telmisartan Core Tablets

Sr. No	Ingredients	Batch		
		C1	C2	C3
1	Telmisartan (mg)	40	40	40
2	Croscarmellose Sodium (mg)	3	4.5	6
3	Magnesium stearate (mg)	1.5	1.5	1.5
4	Talc (mg)	1.5	1.5	1.5
5	Microcrystalline Cellulose (mg)	104	102.5	101
	Total Wt. (mg)	150	150	150

The core tablets were prepared by direct compression technique. The composition of the tablets was showed in Table 1. All the excipients were passed through sieve no.30. The required ingredients were accurately weighed and mixed

thoroughly and dry blended with talc and magnesium stearate for 5 min. The resulting blends were subjected to the micromeritic properties and compressed by using 8 mm flat face punch using multi station tablet punching machine.[10, 11]

2.3. Formulation of Press Coated Pulsatile Tablet of Telmisartan

All the ingredients were accurately weighed and passed through sieve no.70 and thoroughly mixed for 5 min. Initially half quantity of the mixture of two polymers (hydrophilic HPMC and ethyl cellulose) with different weight ratio was filled in the die of 12mm diameter and then gently compacted to make a powder bed with a flat surface. The core tablet was then carefully placed in the centre of powder bed. The die was filled with the remaining of coating mixture so that powder bed was compressed directly using 12mm flat punch to produce desired press coated tablets. Formulations of press coated tablet were shown in Table 2. The press coated tablets were further evaluated for hardness, thickness, content uniformity, friability and disintegration and dissolution time.[12-15]

Table 2 Composition of Press Coated Tablets

Sr. No	Ingredients (mg)	Batch				
		F1	F2	F3	F4	F5
1	Core Tablet	150	150	150	150	150
2	HPMC K4M	200	150	100	50	-
3	Ethyl Cellulose	-	50	100	150	200
	Total Wt. (mg)	350	350	350	350	350

2.4. Evaluation of Powder Blend (Pre-compression Parameters) [16, 17]

2.4.1. Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml.

2.4.2. Tapped Density (Dt):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for multiple times and the tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml.

2.4.3. Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h / r$$

$$\theta = \tan^{-1}(h / r)$$

Where,
θ is the angle of repose.
h is the height in cms
r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

2.4.4. % Compressibility

The Carr's compressibility index, also known as the Carr index or Carr's index, is a parameter used to assess the compressibility and flow properties of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the bulk density and tapped density of the powder and provides insights into its flowability and compaction characteristics. It indicates powder flow properties.

2.4.5. Hausner Ratio

Hausner's ratio, is a parameter used to assess the flowability of powdered or granular materials, particularly pharmaceutical powders. It is calculated based on the tapped density and bulk density of the powder and provides insights into its flow properties. The Hausner ratio is defined as the ratio of tapped density to bulk density. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25). [18,19]

2.5. Evaluation of Pulsatile Tablets

2.5.1. Weight Variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The average weight per unit is then calculated by dividing the total weight by the number of units in the sample.

2.5.2. Hardness

The hardness test is a crucial quality control measure in pharmaceutical manufacturing, particularly for solid oral dosage forms like tablets. Tablet hardness, often measured in terms of breaking force or resistance to crushing, provides an indication of the mechanical strength and robustness of the tablet. Hardness testing ensures that tablets can withstand handling, packaging, and transportation without breaking or crumbling, thereby maintaining their integrity and appearance throughout their shelf life. Hardness or tablet crushing strength ie the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

2.5.3. Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

2.6. Content Uniformity

Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered and quantity of powder equivalent to 100 mg of drug was taken and transfers it to 10 ml of phosphate buffer pH 7.4. The resulting solution was then diluted appropriately and measured using a UV-Visible spectrophotometer at 296 nm.[20]

2.6.1. Disintegration Test

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in the USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of core tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litter beaker containing 6.8 phosphate buffer solution at 37 °C ± 1 °C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.[20]

2.7. *In-Vitro* Dissolution Study

The *in-vitro* dissolution study was carried out in USP dissolution test apparatus type II (paddle) with a dissolution medium of 900 ml of phosphate buffer pH 7.4, at 50 rpm (37±0.5 °C). 5 ml aliquot was withdrawn at the specified time interval, filtered through whatman filter paper, and measured spectrophotometric ally after suitable dilution at 296 nm using UV-Visible spectrophotometer. An equal volume of fresh medium, which was pre warmed at 37 °C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. The results in the form of percent cumulative drug released was calculated.[20]

2.8. Stability study

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminium foil and was stored in stability chamber maintained at 40°C and 75% RH for the period of 3 months. The Tablet were evaluated before and after 3 months for change in appearance, Hardness, disintegration time, drug content and in -vitro drug release.[21]

3. Result and discussion

3.1. Compatibility Studies (FT-IR)

Both the polymer and pure drug's infrared spectra are examined. It has been found in this investigation that there is no chemical interaction between the polymer and Telmisartan. The major peak in the drug and polymer mixture's infrared spectra was found to remain unchanged, indicating that there was no physical interaction due to bond formation between the two substances.

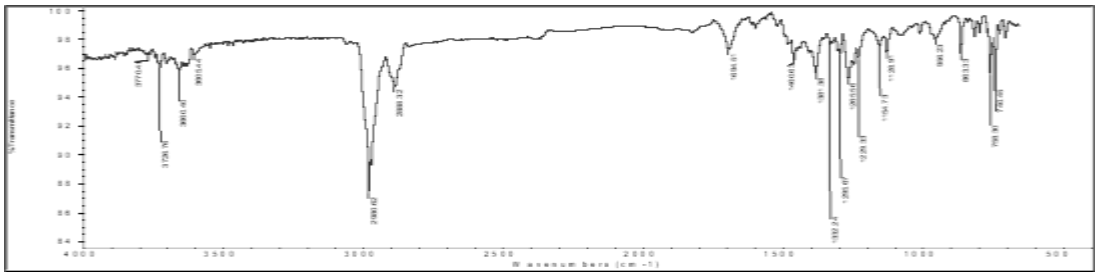

Figure 1 IR spectra of pure drug Telmisartan

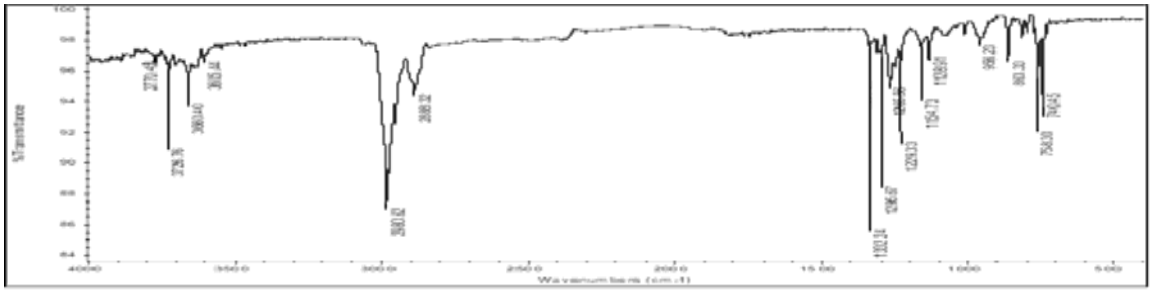

Figure 2 IR Spectra of Telmisartan Pulsatile Tablets (F3)

3.2. Evaluation of Sustained Release Tablets

3.2.1. Pre compression Parameter

The results of micromeritic properties were showed in table 2. Bulk density values obtained in the range from 0.421-0.471gm/cc for all the formulations and The tapped density values obtained in the range from 0.512- 0.552gm/cc. Angle of repose ranged between (25.32- 28.50), the compressibility index ranged between 14.15 to 15.44 and Hausner's ratio ranged between (1.19 - 1.24), confirmed good flow properties of the powder blend. Thus the powder showed better flow properties and were non aggregated.

Table 3 Micromeritics properties of powder blend of core tablets formulation

Batch	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose(Θ)
C1	0.435	0.550	14.15	1.19	25.32
C2	0.471	0.552	15.24	1.24	27.62
C3	0.421	0.512	15.44	1.21	28.50

3.3. Post Compression Parameters

3.3.1. Weight Variation:

The weight variation test for all tablets formulation (C1 to C3) was passed and found within pharmacopoeial standards. Passing the weight variation test ensures that each tablets was within a batch contains the specified amount of active pharmaceutical ingredient (API) and excipients. This ensures uniform dosing and therapeutic efficacy for patients consuming the medication.

3.3.2. Hardness

The hardness of tablets for all batch formulation (C1 to C3) was found in the range from 3 to 3.5 kg/cm2, which was found to be optimum and indicate tablets able to withstand mechanical shock.

3.3.3. Thickness

It was found from the range of 3.1 to 3.2 mm for formulation C1 to C3 is found to be optimum and indicated well distribution of pure drug. Tablet thickness directly influences the amount of active pharmaceutical ingredient (API) and excipients contained within each tablet. Consistent tablet thickness ensures uniformity of dosage across the batch, contributing to predictable and reliable therapeutic outcomes for patients.

3.3.4. Friability

The friability value of all tablets batch formulation C1 to C3 were found to be less than 1% indicating good mechanical strength of tablets. Passing the friability test ensures that tablets maintain their physical integrity and withstand mechanical stress under normal handling conditions.

3.3.5. Drug Content

Good uniformity of drug content was found within and among the different batches of tablet formulation. The values ranged from 95.66 to 96.72% which ware in pharmacopoeial limits.

3.4. Disintegration Time:

Disintegration time for formulation was found in the range of 30 to 45 sec and found within pharmacopoeial standards. Batch C3 showed least disintegration time of 30 sec when compared with other formulation may due to higher concentration and wicking action of disintegrating agent, croscarmellose sodium.

Table 4 Post Compression parameters of Core Tablets Formulation (C1 to C3)

Batch	Weight Variation	Hardness (Kg/cm2)	Friability (%)	Thickness (mm)	Drug Content (%)	Disintegration Time (sec)
C1	150 ± 1.4	3.5± 0.35	0.94±0.1	3.2± 0.50	95.66±0.8	45± 1.12
C2	151± 1.2	3± 0.47	0.98±0.20	3.1± 0.34	96.12±0.7	40± 1.51
C3	150± 1.2	3.5± 0.52	0.92±0.1	3.2± 0.31	96.72±0.6	30± 0.74

(SD ± Mean of n=3)

3.5. *In-Vitro* Dissolution Study

In vitro drug release study of prepared sustained release tablets of Telmisartan was determined in phosphate buffer pH 7.4 as dissolution medium. The drug release from core formulations containing C1 prepared with 2% of croscarmellose sodium showed 92.32 % at 60 min. Formulation C2 prepared with 3% of croscarmellose sodium showed 95.41 % drug release at 60 min, while formulation C3 prepared with 4% of croscarmellose sodium showed drug release of 98.61 % at the end of 60 min. All the formulation showed rapid drug release because of presence of super disintegrating agent croscarmellose sodium. Among the formulation batch C3 showed fastest drug release compare to other formulations. The results indicated that as the concentration of superdisintegrant increased the drug release was increased. Data for *In vitro* drug release of core tablets was shown in figure 3.

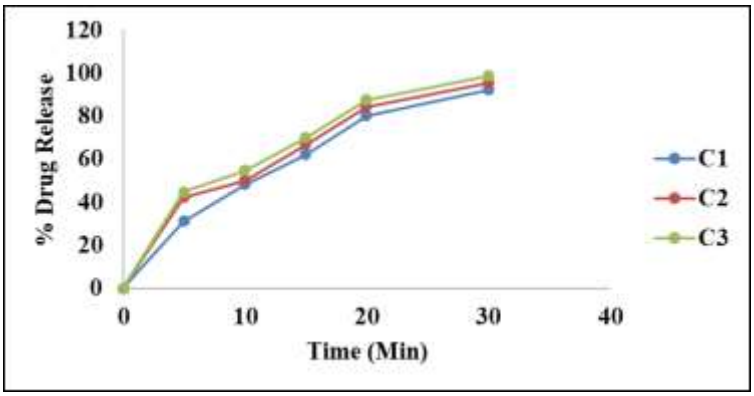

Figure 3 *In vitro* drug release profile of Telmisartan core tablets formulation

3.6. Evaluation of Press Coated Pulsatile Tablet of Telmisartan

Press coated pulsatile tablets of Telmisartan was prepared by using varying concentration of hydrophilic polymer HPMC K4M and hydrophobic polymer ethyl cellulose. The composition of formulations is shown in table 4 among the formulations of core tablets, batch C3 was considered as optimized formulation on the basis of faster disintegration and drug release and was used for press coating so as to produce pulsatile tablets. The tablets were prepared by direct compression method. The pulsatile tablets of Telmisartan were subjected to post compression analysis.

The hardness of the tablets prepared by direct compression method was determined by using Monsanto Hardness tester. The mean hardness of coated tablets was found within the range was 5.8 ± 0.32 to 6.3 ±0.36 kg/cm^2 indicating good crushing strength.

The mean thickness of coated tablets was found within the range of 4.50± 0.35 – 4.53± 0.33 mm for the pulsatile tablets. The drug content uniformity of all formulations was carried out and was found to be within the range 96.30 % to 98.42 % which found within acceptable limit.

Weight variation for all the tablets batch formulations F1 to F5 passes the test and was within pharmacopoeias limit. Friability test for all batches was less than 1% indicating good mechanical strength of tablets.

Table 5 Evaluation of Press Coated Pulsatile Tablets (F1 to F5)

Batch	Weight Variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)	Lag Time (Hr)
F1	351 ± 0.23	6 ± 0.42	0.62±0.34	4.51± 0.52	97.61±0.23	0
F2	353± 0.41	5.8 ± 0.32	0.51±0.30	4.53± 0.33	98.12±0.67	1
F3	351± 0.57	6 ± 0.57	0.46±0.27	4.50± 0.35	98.42±0.19	4
F4	349±0.22	6.2 ±0.21	0.52±0.25	4.52±47	97.36±0.26	3
F5	352±0.25	6.3 ±0.36	0.54±0.38	4.51±64	96.30±0.30	4

(SD ± Mean of n=3)

The lag time of the press coated tablets was measured by determining the time for which there is no release of drug, batch F1 prepared with HPMC K4M alone showed 0 hours of lag time which may due to hydrophilic nature of polymer. Batch F2, F3, F4 and F5 showed 1 hour, 4 hour, 3 hour and 4 hour of lag time respectively. Batch F3 and F5 showed highest lag time of 4 hours. Evaluation data of core coated tablets are shown in table 4.

3.7. *In vitro* Drug release of Press Coated Pulsatile Tablets

Tablets were subjected to dissolution in 6.8 pH phosphate buffer. The dissolution study of these formulations was performed in order to understand the effect of different polymers and their increasing concentrations. The formulation was optimized on the basis of desired value of lag time and dissolution profile. Batch F1, formulated with HPMC alone showed 0 hour of lag time and 92.7 % drug release at the end of 8 hour. Batch F2, F3 and F4 prepared with varying amount of HPMC and EC showed 90.26%, 96.60% and 86.825 drug release at the end of 8 hour respectively. Batch F5 prepared with polymer EC showed lag time of 4 hours and 41.32 % of drug release in 8 hour, high lag time and low drug release may due to hydrophobic nature of EC polymer. Among the formulations batch F3 gives sufficient lag time and optimum drug release and hence considered as optimum formulation. The % cumulative drug release versus time data for all formulations batch is shown in table 8.6 and graphs has been projected in figure 4.

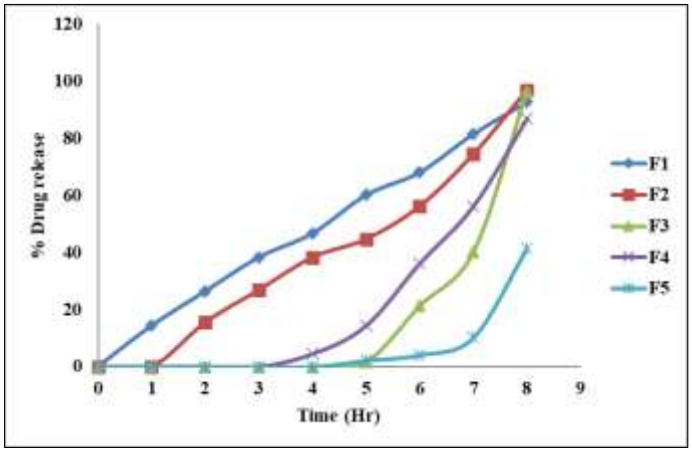

Figure 4 Comparative dissolution profile of batch F1 to F5

3.8. Stability studies

Telmisartan pulsatile tablets formulation showing optimum lag time and drug release, was selected for stability studies. According to ICH guidelines, optimized formulations F3 were stored at 40^0C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated for appearance, Hardness, drug content and *In vitro* release. At the end of 3 months no significant difference was observed in hardness, drug content and *In vitro* drug release. From the stability study it was concluded that press coated pulsatile tablets formulation F3 was found to be stable.

Table 6 Stability data of optimized formulation F3

Formulation Code	Parameter	Before storage (0 month)	After storage (3 month)
F3	Hardness (kg/cm2)	6	5.8
	Drug content	98.42	97.36
	% drug release	97.6	96.10
	Lag Time (Hr)	4	4

4. Conclusion

From the present study following conclusion were observed the pulsatile tablets of Telmisartan can be prepared by direct compression technique by using HPMC and ethyl cellulose as a polymer. All the prepared formulations were showed satisfactory results. IR- spectroscopic studies indicate no drug- excipient interaction in formulation.

Formulation F3 was consider as the ideal formulation which gives lag time of 4hr and exhibited 96.6% drug release in 8 hrs. Future detailed investigation is required to established in vivo efficiency of pulsatile tablet of Telmisartan and the long term stability study need to be confirm the stability of pulsatile tablet of Telmisartan.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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