WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 15, 1182-1192. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF PULCINCAP DRUG DELIVERY OF ELETRIPTAN HYDROBROMIDE

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Article Received on
21 July 2023,

Revised on 11 August 2023,
Accepted on 31 August 2023,

DOI: 10.20959/wjpr202315-29577

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ABSTRACT

The current study aims to develop and evaluate a colon specific, pulsatile drug delivery system based on a cross-linked gelatin capsules. Pulsincap of Eletriptan Hydrobromide providing chronomodulated therapy for the better treatment of migraine. The paper demonstarte the study of compatibility between drug candidate with excipients using FTIR and conversion of soluble capsule shells into insoluble by treatment of formaldehyde and evaluate treated capsules. The present research concluded that the Eletriptan Hydrobromide was done and it was found that Eletriptan Hydrobromide shows melting point 170°C, and wavelength of 221 nm in Distilled water, characterization of FTIR peaks shows all functional group of Eletriptan Hydrobromide. FTIR data confirm that there was no chemical interaction of the drug with the other components used in the formulation Treatment of capsule with formaldehyde indicates that crosslinking of capsule occurs which results in decrease solubility of capsules so that capsules remain intact up to 14 hours by using 15% formaldehyde solution.

KEYWORDS: Pulsatile drug delivery system, Migraine, Lag time, Triptans.

INTRODUCTION

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. The diseases which are required pulsatile release like peptic ulcer, asthma, migraine, diabetes mellitus and cardiovascular diseases etc.

Pulsatile drug delivery system is time and site specific drug delivery system. Thus providing special and temporal delivery and increasing patient compliance. Pulsatile drug delivery

system is defined as the rapid and transient release of certain amount of molecules within short period immediately after a predetermined off- release period, i.e. lag time. The principle rational of the drug where a constant drug release i.e. zero order release is not desired.[3,4]

A migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe.[5] Typically, the headaches affect one half of the head, are pulsating in nature, and last from two to 72 hours.[6] Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell. The pain is generally made worse by physical activity. Up to one-third of people have an aura: typically a short period of visual disturbance that signals that the headache will soon observed. Globally, approximately 15% of people are affected by migraines. It most often starts at puberty and is worst during middle age. In some women, they become less common following menopause. Nowadays, it is one of the most common causes of disability. The word "migraine" is from the Greek hemikrania, "pain on one side of the head", from hemi "half", and kranion "skull".[7]

In case of migraine, peak symptoms occur early in the morning due to release of adrenaline in larger quantities during the early morning. Since adrenaline affects blood pressure and the regulation of dilation or contraction of the blood vessels, it plays important a role in the migraine attacks. Generally migraine patients have a complained attacks occurs in early morning between 6 to 8 am which severely impacting on their normal daily functions.[7] Triptans are primarily used in treatment of moderate to severe migraine. Triptans are considered a first-line therapy for migraine. They are fast acting, generally reducing head pain in about 2 hours Eletriptan Hydrobromide is selective serotonin receptor agonist with 4 hour half-life.[8,9] So by developing the pulsatile device i.e. Pulsincap, drug release is achieved before the patient feel the headache in morning. First pass metabolism can also be avoided and no need of frequent administration of drug due to its short biological half-life. The devices is designed to administer at night before sleeping and release of drug in occurs after 6 hours of administration, before onset of migraine attack which is chronopharmaceutical approach for the better treatment of migraine attack.[10]

Formalin treatment has been employed to modify the solubility of gelatin capsules. Exposure to formalin vapors or treatment with the aqueous formalin results in an unpredictable decrease in solubility of gelatin owing to the cross linkage of the amino group in the gelatin molecular chain with aldehyde group of formaldehyde by Schiff's base condensation.[10,11]

MATERIALS AND METHODS

Eletriptan Hydrobromide was gift sample from Ajanta Pharma Limited, Aurangabad, India. HPMC K 100M was supplied by Colorcon Asia Pvt Ltd, Mumbai. Polyox WSR 303, Polyox WSR 205, Polyox WSR 301 were obtained from Dow chemical corporation, Mumbai India. All other ingredients used were of analytical grade.

Drug- Characterization

UV- Spectroscopy

Construction of calibration curve of Eletriptan Hydrobromide in Distilled Water: Preparation of standard stock solution: stock solution, 100mcg/ml, of Eletriptan Hydrobromide was prepared by dissolving 10mg of Eletriptan Hydrobromide in Distilled Water and make up to the make in 100 mcg/ml. this solution was further diluted to get various working solution. Working stock solution: For linearity study, dilutions were made for Eletriptan Hydrobromide in the concentration range 1.0 10 mcg/ml by diluting the stock solution with distilled water.[12] The calibration curve was established at 221 nm by plotting graph between absorbance and concentration. Regressions analysis of Beer's law plot done.

Fourier Transform Infrared (FTIR) Spectroscopy

The drug was subjected to FTIR studies for the purpose of characterization. Drug was mixed with potassium bromide in 1:100 proportions and spectrum was obtained in range of 400 – 4000cm-1. Potassium bromide was used as a blank while running spectrum.[12]

Drug Excipient Interaction Study

Fourier Transform Infrared (FTIR) Spectroscopy

Compatibility study- Drug excipients computability study was carried out to find out effect of temperature and humidity on drug excipients mixture, by placing drug alone and drug with individual excipients individual excipients in certain ratio of formulation in stopped vials at 40°C /75% RH for two months. Samples were physically observed and degradation was examined by FTIR spectroscopy at the end of studies.

Formulation Design

Preparation of cross linked gelatin capsule

Hard gelatin capsule of size 0 were taken. Then bodies of capsule were separated from the caps. 25ml of 5%, 10%, 15% (v/v) formaldehyde was taken into separate desiccators and pinch of potassium permanganate was added to it respectively, to generate formalin vapors.

The wire mesh containing the bodies of the capsule were then exposed to formaldehyde vapours and desiccators was tightly closed. The caps were not exposed leaving them water soluble. The reaction time was optimized by removing capsules bodies at different time intervals and dried at 50° for 30 min into room temperature to ensure completion of reaction between gelatin and formaldehyde vapours. The bodies were dried at room temperature to facilitate removal of residual formaldehyde. These capsules bodies were capped with untreated caps and stored in polythene bag.[10,13]

Test for formaldehyde treated empty capsules

Various physical test and chemical test includes visual defects, Dimension and solubility were carried out simultaneously for formaldehyde treated and untreated capsules. The length and diameter of the capsules were measured before and after formaldehyde treatment using vernier caliper.

Solubility studies of the treated capsules

The solubility tests were carried out for normal capsules and formaldehyde treated capsule for 24 hour. 10 capsules were randomly selected and subjected to solubility studies at room temperatures in buffers of pH 1.2, 7.4, and 6.8. 100 ml of buffer solution was taken in a beaker. A single capsule was placed in buffer solution and stirred for 24 hrs. The time at which the capsule dissolves or forms a soft fluffy mass was noted.

Qualitatively test for free formaldehyde

Standard formaldehyde solution was 0.002% and Sample solution was formaldehyde treated capsules bodies (25) were cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hr with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into 50 ml volumetric flask, washed with distilled water and volume was made up to 50ml with the washings.

1ml of sample solution, 9ml of water was added. 1 ml of resulting solution was taken into a test tube and mixed with 4 ml of water and 5ml of acetone reagents. The test tube was warmed in a water bath at 40°C and allowed to stand for 40 min. The solution was not more intensely colored than a reference solution prepared at the same time and in the same manner using 1 ml of standard solution in place of sample solution. The comparison should be made by examining tubes down their vertical axis.

Preparation of core physical mixture

Powder blend was prepared by mixing all the ingredients passed through 60 mesh sieve separately and collected. The ingredients were weighed, mixed and filled in capsule body.

Preparation of hydrogel plug

Hydrogel plug of three polymers Polyox WSR 205, Polyox WSR 303, HPMC K 100M, HPMC K 50 prepared by compressing the different concentration of these polymers using 6 mm punches and dies by using multiple stations CIP Tablet compression machine.

Formulation of pulsatile (modified pulsincap) drug delivery system

Formaldehyde treated hard gelatin capsules of size 0 were chosen for the formulation. The bodies and caps were separated manually**.** Formaldehyde treated capsules body was filled with and physical core blend by hand filling and slightly compressed using glass plunger. Such capsules containing the core physical blend were then plugged with different polymers like POLYOX 205, POLYOX 301, POLYOX 303 , HPMC K 100M at separated different concentration (Table 1). The water soluble caps were placed again to complete Pulsincap system.

Table 1: Preliminary batches for screening of polymers and polymer weight.

Formulation code	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
Drug	20	20	20	20	20	20	20	20	20	20	20	20
MCC	100	100	100	100	100	100	100	100	100	100	100	100
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Wt Physical mix	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5
Polyox 205	100	75	50	-	-	-	-	-	-	-	-	-
Polyox 301	-	-	-	100	75	50	-	-	-	-	-	-
Polyox 303	-	-	-	-	-	-	100	75	50	-	-	-
HPMC K 100M	-	-	-	-	-	-	-	-	-	100	75	50
Total wt. (mg)	222.5	197.5	172.5	222.5	197.5	172.5	222.5	197.5	172.5	222.5	197.5	172.5

Table 2: Preliminary batches for screening of polymer: lactose ratio.

Formulation code	L1	L2	L3	L4	L5	L6	L7	L8	L9
Wt Physical mix	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5	122.5
Polyox WSR 303	50	75	100	50	75	100	50	75	100
Lactose anhydrous	15	15	15	25	25	25	40	40	40
Total wt. (mg)	187.5	212.5	237.5	172.5	222.5	247.5	212.5	237.5	262.5

Evaluation

Evaluation of Core physical mixture

The core physical mixture was evaluated for flow properties including angle of repose, bulk and tapped density and also for Carr's index.

Evaluation of modified pulsincap device

Weight variation

10 capsules were selected randomly and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than 90% or more than 110% of the average.

In vitro release profile

Dissolution studies were carried out using USP apparatus II dissolution test apparatus. 900 ml of the phosphate buffer pH 6.8 was used. Capsules were tied to paddle with a cotton thread in each dissolution vessel to prevent floating. 10 ml of dissolution media was withdrawn at predetermined time interval and fresh dissolution media was replaced .The roatation speed was 50 rpm at 37°C± 0.5 °C. The withdrawn samples were analyzed and amount of Eletriptan Hydrobromide released was determined by UV absorption spectroscopy at 221 nm.

RESULT AND DISCUSSION

Drug Characterization

UV spectroscopy

The UV spectra of 10 ppm solution of Eletriptan Hydrobromide in Distilled Water showed an absorption at wavelength 221 nm as per BP.

Table 3: Concentration and Absorbance of Eletriptan Hydrobromide.

Sr. No.	Concentration (ppm)	Absorbance
1	2	0.18
2	4	0.38
3	6	0.56
4	8	0.77
5	10	0.97

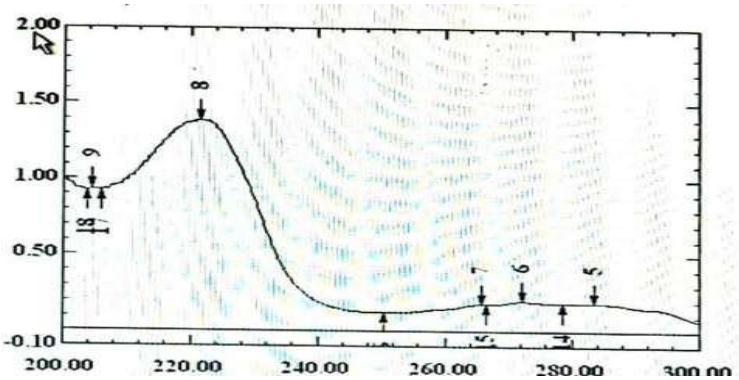


Figure 1: Spectrum of Eletriptan Hydrobromide.

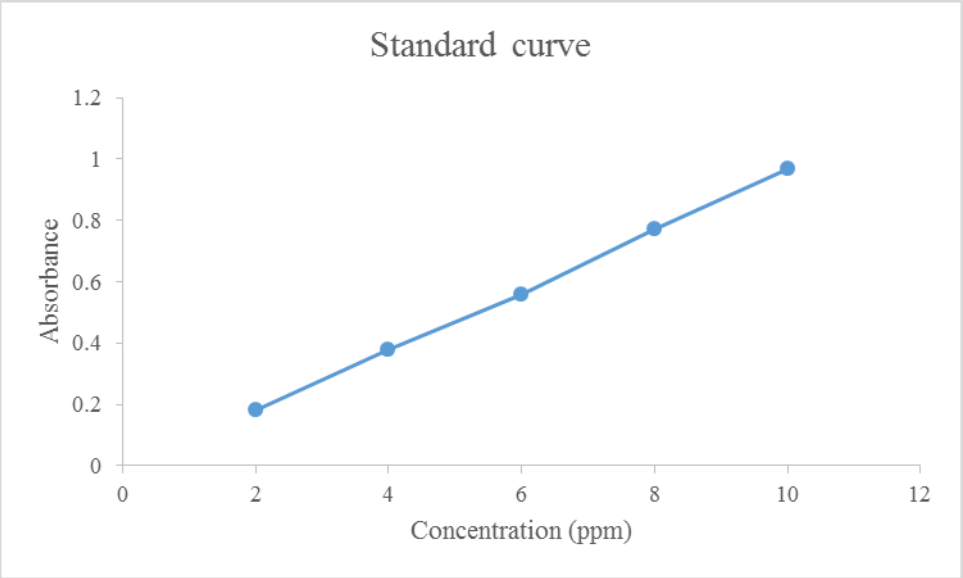
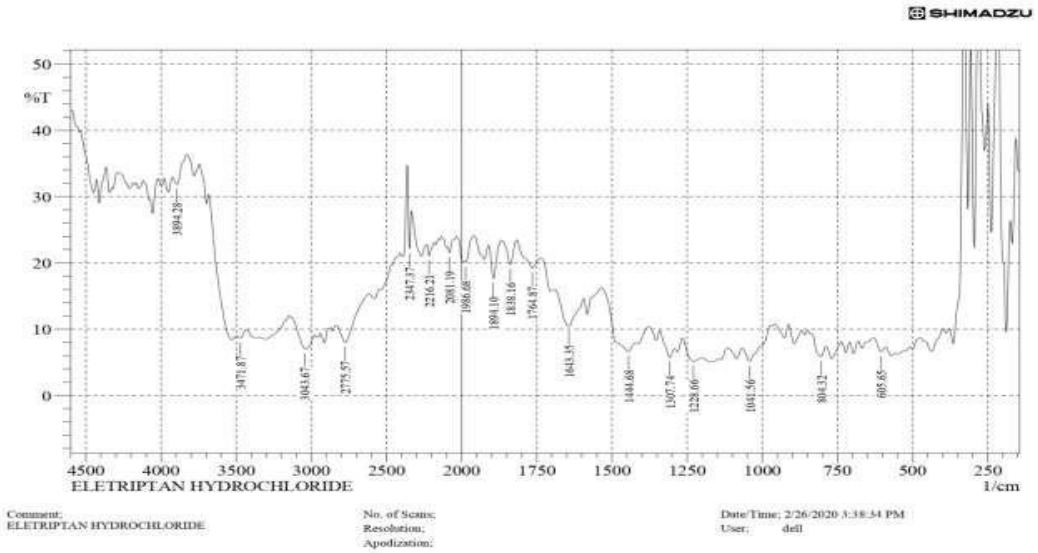


Figure 2: Standared calibration curve of Eleltriptan hydrobromide.

FTIR Spectroscopy

Characteristics peak of functional group were observed in IR spectrum of Eletriptan Hydrobromide. So, identification of Eletriptan Hydrobromide was confirmed and no impurity was detected in the IR spectrum of Eletriptan Hydrobromide. The drug shown IR peaks at 3380 cm^{-1}, 1415 cm^{-1}, 1723 cm^{-1},680 cm^{-1}.



Drug Excipient interaction study

FTIR spectroscopy

Overlay spectra of Eletriptan Hydrobromide and polymer Polyox WSR 303 showed that characteristics peaks were not shifted from their characteristics wave number. So interaction was not detected between Eletriptan Hydrobromide and Polyox WSR 303. So Eletriptan Hydrobromide was found to be compatible with Polyox WSR 303. The peaks shown at 3390 cm^{-1}, 1360 cm^{-1}, 1763 cm^{-1}, 676 cm^{-1}. Drug and Drug in combination with excipient observed same peaks with little differences.

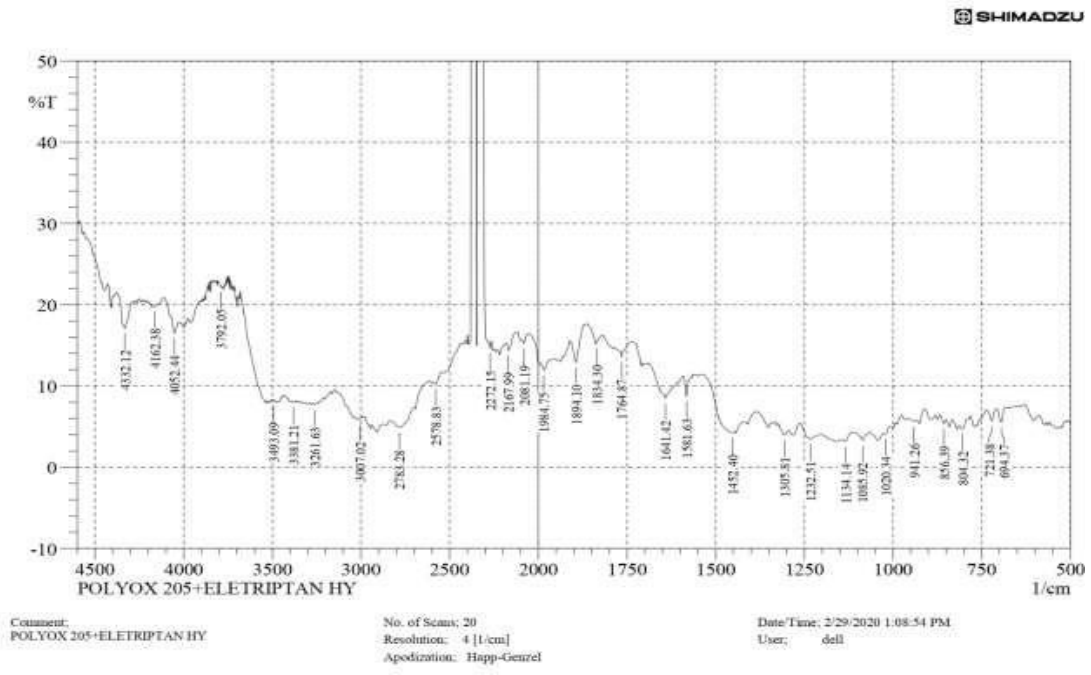


Figure 14: IR spectrum of Eletriptan Hydrobromide and all excipients.

Evaluation of core physical mixture

It was found that angle of repose was in the range of 31-35°. This shown that the core mixture for the rheological properties which had good flow properties. The Hausner's ratio was found to be within 1.09-1.12. The carr's index was observed in the rangfe of 11.35 ± 0.30% to 12.19 ± 0.25%. All the formulation shown good flow property with good compressibility. The drug content was found to be in the range of 95±0.69 to 98.23±0.58%. Results observed that in all the formulation the drug content was uniform.

Evaluation of hydrogel plug

The prepared hydrogel plugs were evaluated by thickness, hardness and lag time. It was found that 80 mg plug showed 3.5 hrs lag time and 100 mg plug showed 6.5 hrs lag time. Therefore 100 mg plug was optimized.

Evaluation of modified pulsincap

Weight variation

The filled capsules pass the weight variation test as their weights are within the specified limits.

In-vitro release studies

In-vitro drug release profiles of formulation were found to have very good sustaining efficacy. During the dissolution studies, it was observed that, the enteric core of the Polyox WSR 303 was intact for 2 hours in pH 1.2, but dissolved in intestinal pH, leaving the soluble cap of capsule, which also dissolved in pH 7.4 phosphate buffer and then the exposed polymer plug which absorbed the surrounding fluid, swelled and released the drug through the swollen matrix. After complete wetting of the plug, it formed a soft mass, which was then easily ejected out of the capsule body; releasing the granules into simulated colonic fluid (pH 6.8 phosphate buffer). With all the formulations, there was no drug release in pH 1.2.

CONCLUSION

The objective of the present study was to develop a pulsatile drug delivery system synchronized with circadian rhythms of body for effective chronotherapy for migraine. Patient suffering from migraine experience marked head-ach in between 6 to 8 AM. The PDDS with predetermined lag time is supposed to synchronize peak plasma blood levels of drug with the peak pain in early morning hours. The work was initiated with through literature survey on pulsatile drug delivery, pathogenesis of migraine and treatments available

for migraine. Most of the treatments available do not consider the circadian rhythm in pathogenesis of disease. The devices was designed to administer at night before sleeping and release of drug in occurs after 6 hours of administration , before onset of migraine attack which is chronopharmaceutical approach for the better treatment of migraine attack. The adverse effects can be minimized if the therapy is synchronized with peak time of symptoms. This can be achieved by chronotherapy.

In summary, the present research concluded that the Eletriptan Hydrobromide was done and it was found that Eletriptan Hydrobromide shows melting point 170°C, and wavelength of 221 nm in Distilled water, characterization of FTIR peaks shows all functional group of Eletriptan Hydrobromide. FTIR data confirm that there was no chemical interaction of the drug with the other components used in the formulation. Calibration curve of Eletriptan Hydrobromide was performed on Distilled Water which can be used for drug quantification in dissolution analysis. Treatment of capsule with formaldehyde indicates that crosslinking of capsule occurs which results in decrease solubility of capsules so that capsules remain intact up to 14 hours by using 15% formaldehyde solution. Evaluation of core mixture for the rheological properties which shows good flow properties.

REFERENCES

1. Khalifa AZ, Zyad H, Mohammed H, Ihsan K, Alrawi L, Abdullah M, et al. Recent advances in remotely controlled pulsatile drug delivery systems. Journal of Advanced Pharmaceutical Technology and Research, 2022.
2. Sawant R, Parkar S, Kegade P, Gade A. Colon Targeted Drug Delivery: A Review on Novel Approaches. Asian J Res Pharm Sci, 2020.
3. Gangadhar B, Sree BSB, Swamy P, Devi MA. PULSATILE DRUG DELIVERY SYSTEM: A REVIEW. Int J Res Ayurveda Pharm, 2022.
4. Jain D, Raturi R, Jain V, Bansal P, Singh R. Recent technologies in pulsatile drug delivery systems. Biomatter, 2011.
5. Olla D, Sawyer J, Sommer N, Moore JB. Migraine Treatment. Clinics in Plastic Surgery, 2020.
6. De Tommaso M, Delussi M. Circadian rhythms of migraine attacks in episodic and chronic patients: A cross sectional study in a headache center population. BMC Neurol, 2018.
7. Van Oosterhout WPJ, van Someren EJW, Schoonman GG, Louter MA, Lammers GJ,

Ferrari MD, et al. Chronotypes and circadian timing in migraine. Cephalalgia, 2018.

8. Madasu SB, Vekariya NA, Hari Kiran MNVD, Gupta B, Islam A, Douglas PS, et al. Synthesis of compounds related to the anti-migraine drug eletriptan hydrobromide. Beilstein J Org Chem, 2012.
9. Spandana B, Shashidher B, Dinesh S, Nagaraj B. Eletriptan hydrobromide orodispersible tablets: Design, development and in vitro characterization. Res J Pharm Technol. 2020;
10. Jagdale SC, Phule PS, Chavan GJ. Formulation and evaluation of modified pulsincap drug delivery system of rizatriptan benzoate. Int J Pharm Pharm Sci., 2014.
11. Hiral CD, Rakshit SN, Prajapati A P, Patel MM. Formulation and Evaluation of Modified Pulsincap as Pulsatile Drug Delivery System for Treatment of Rheumatoid Arthritis. Int J Pharm Sci Nanotechnol., 2016.
12. Sukanaya M, Sai Kishore V. Design and development of chronopharmaceutical drug delivery of simvastatin. J Chem Pharm Res., 2012.
13. Ramadevi S, Tamkeen J, Rahman A, Prasanthi D. Pulsatile Delivery of Methylphenidate Hydrochloride Pulsincap by Box-Behnken Design. J Pharm Res Int., 2022.