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Formulation, development and evaluation of pulsatile drug delivery of Rizatriptan for chronotherapy of migraine

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Abstract*— Migraine is a common neurological disorder characterized by recurrent attacks of moderate-to-severe headache, often accompanied by nausea, vomiting, photophobia and phonophobia. The onset of migraine attacks demonstrates temporal variability, with several clinical studies reporting a predominance of attacks during the early morning hours. Conventional immediate-release rizatriptan provides rapid symptomatic treatment but does not address the temporal pattern of migraine occurrence. Pulsatile drug delivery systems are designed to provide a predetermined lag time followed by rapid drug release and therefore offer a promising approach for chronotherapy. The present research proposes the formulation and evaluation of a pulsatile oral drug delivery system containing rizatriptan, designed to provide a controlled lag period followed by rapid drug release corresponding to the anticipated period of migraine attack. Rizatriptan was selected because of its established antimigraine activity and relatively short elimination half-life, making temporal control of drug availability a potentially useful formulation strategy. The proposed formulation is expected to remain substantially intact during the predetermined lag period and subsequently produce a rapid pulse of rizatriptan. Such a system could potentially synchronize drug availability with the circadian pattern of migraine and reduce the delay between drug administration and anticipated attack onset. Further in-vivo and clinical studies would be necessary to establish its therapeutic superiority over conventional rizatriptan formulations.

Keywords*— Rizatriptan, pulsatile drug delivery, chronotherapy, migraine, circadian rhythm, lag time, controlled release, chrono pharmaceutics.

I. INTRODUCTION

Migraine is a disabling neurological disorder characterized by recurrent attacks of headache that may be associated with nausea, vomiting and increased sensitivity to light and sound. The disease has a complex pathophysiology involving neuronal, vascular, inflammatory and hypothalamic mechanisms. Importantly for drug-delivery research, migraine does not necessarily occur randomly throughout the day. Several investigations have demonstrated temporal patterns in migraine attack onset, with morning hours frequently representing a period of increased risk

The circadian characteristics of migraine provide a rationale for exploring chronotherapeutic approaches. Earlier clinical observations reported an increase in migraine onset between approximately 6:00 and 8:00 AM, with peak onset between 8:00 and 10:00 AM in one study. However, migraine chronobiology is heterogeneous, and not every patient experiences attacks at the same time. Therefore, a chronotherapeutic formulation should ideally permit adjustment of the lag time according to the patient's individual attack pattern.

Conventional oral dosage forms generally release drug soon after administration. Although this is desirable for treatment of an established migraine attack, immediate release is less suitable when the therapeutic objective is to provide drug availability at a predictable future time. Pulsatile drug delivery systems address this limitation by incorporating a predetermined period during which little or no drug is released, followed by rapid drug liberation.

Chronopharmaceutical systems are designed around the concept that drug delivery should be synchronized with biological rhythms and disease activity. Such systems may use soluble or erodible coatings, swelling polymers, rupturable membranes, osmotic mechanisms, or externally triggered mechanisms.

The proposed research therefore focuses on developing a pulsatile rizatriptan delivery system

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capable of producing a predetermined lag time followed by rapid drug release.

1.1 Pulsatile systems

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after predetermined off-release periods i.e. lag time.[4] These systems are designed according to the circadian rhythm or biological clock of the body.

1.1.1 Types of pulsatile drug delivery systems

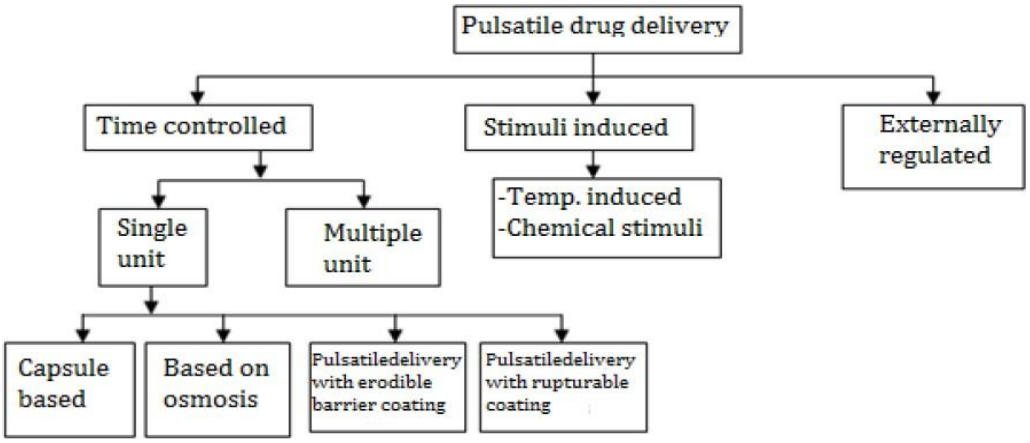

Figure 1.1 Types of pulsatile drug delivery

II. MATERIAL

List of Excipient/Chemical/Reagent Used

S. No.	Description of Item	Source of Procurement
1	Rizatriptan API	Purchased from Yarrow Pharmaceuticals, India
2	Methanol	Qualikem, Mumbai
3	Ethanol	MSG Chemicals, Mumbai
4	Chloroform	Rankem, Mumbai
5	Dimethyl sulfoxide	CDH, New Delhi
6	Octanol	CDH, New Delhi
7	HPMC K15M	Oxford Chemicals, Mumbai
8	Lactose	CDH, New Delhi
9	PVP K30	Oxford Chemicals, Mumbai
10	Magnesium stearate	Oxford Chemicals, Mumbai
11	Cross-carmellose sodium	Oxford Chemicals, Mumbai
12	Ac-di-sol	Oxford Chemicals, Mumbai
13	Lactose	Oxford Chemicals, Mumbai
14	Isopropyl Alcohol	Oxford Chemicals, Mumbai
15	Purified Talc	Oxford Chemicals, Mumbai

III. METHODS

3.1 Preformulation Studies

Preformulation studies are an aid to have the required information of the drug to make it sure that the drug is pure as well as to determine the utility of drug in the type of dosage form that is being developed. The following preformulation studies were carried out for Rizatriptan API.

3.1.1 Organoleptic properties

A small quantity of pure Rizatriptan powder was placed on a clean and dry butter paper and its color and

appearance were observed in well-lit place. The odor was determined by smelling it the powder.

3.1.2 Solubility analysis

Solubility of Rizatriptan was qualitatively determined in solvents like methanol, ethanol, dimethyl sulfoxide, and water. To observe the solubility, a small amount of Rizatriptan was shaken in test tubes that contained 1 mL of the solvent and any undissolved particles were observed.

3.1.3 Melting point

The melting point of Rizatriptan was determined by open capillary method. The pure drug was filled in a capillary tube sealed at one end and placed in the melting point apparatus to observe the temperature at which melting occurs.

3.1.4 Loss on drying

It was determined by drying the pure drug in an oven at 100°C to 105°C for 3 h. The percent loss of moisture was calculated by the difference between the initial and final weight of the drug.

3.1.5 Partition Coefficient

The partition coefficient of Rizatriptan was performed by using octanol as oil phase (10 mL) and water as aqueous phase (10 mL). Both the phases were mixed by shaking vigorously in a separating funnel and then 5 mg of drug was added. The drug was allowed to dissolve in both the phases by shaking and allowing for equilibration. Both phases were taken in a conical flask and then analyzed against their respective blank solution and the partition coefficient was calculated.

3.1.6 FTIR Spectral Study of Rizatriptan

The infrared spectrum was obtained by scanning the pure Rizatriptan from 400-4000 cm^{-1} using attenuated total reflectance type FTIR spectrophotometer. The sample was loaded on the top of the reflectance window and irradiated with the radiation of continuously changing wavelength. The spectra obtained was observed for the transmittance peaks of the functional groups present in the compound.

3.1.7 Calibration curve of Rizatriptan

The calibration curve of Rizatriptan was constructed by measuring the absorbance of using different concentrations of the drug using methanol at 310.4 nm. The stock solution was freshly prepared by dissolving 10 mg of Rizatriptan in 10 ml of methanol in a 1 ml volumetric flask and then made up the solution upto the mark using methanol for obtaining the solution of strength 1000 µg/mL (stock I). 1 ml of this solution is diluted to 10 ml with methanol to obtain a solution of strength 100 µg/mL (stock II). From this solution with draw 1, 2, 3, 4 & 5 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using methanol to get the solutions of 10, 20, 30, 40 & 50 µg/ml. The absorbance of each solution was determined at 234 nm using UV spectrophotometer.

3.2 Preparation of the hydrogel plug

The hydrogel plug was prepared by direct compression method. Accurately weighed quantity (Table 3.1) of Hydroxy propyl methyl cellulose, spray dried Lactose and polyvinyl pyrrolidone were mixed together in a mortar for 10 minutes. Magnesium stearate was added to this mixture and further blended for 5 minutes. The prepared formula blend was compressed using single punch tablet machine.

Table 3.1. Formula for preparation of hydrogel plug

S.No.	Ingredient	Role	Quantity
1	HPMC K15M	Controlling lag time	7.00 g
2	Lactose	Diluent	2.50 g
3	PVP K30	Binding Agent	0.35 g
4	Magnesium stearate	Lubricant	0.15

3.3 Preparation of Rizatriptan core tablet

Accurately weighed quantity of Rizatriptan and lactose were mixed together in a mortar. To this was added the super-disintegrants cross-carmellose sodium and ac-di-sol in required quantity as per Table 3.2 and mixed. The dry binder was added to the mixture and isopropyl alcohol if required to provide binding was added as required. Purified talc and magnesium stearate were finally added and the blend was mixed properly in a sealed polybag using tumbler action. The blends were punched into tablets by direct compression using single punch tablet press.

Table 3.2. Formula for obtaining optimum the core tablet

S. No.	Ingredient	CT1 (mg)	CT2 (mg)	CT3 (mg)	CT4 (mg)	CT5 (mg)
1	Rizatriptan	5	5	5	5	5
2	Cross-carmellose sodium	2	4	6	8	10
3	Ac-di-sol	5	5	5	5	5
4	Lactose	31	29	27	25	23
5	PVP K30	5	5	5	5	5
6	Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s
7	Magnesium stearate	1	1	1	1	1
9	Purified Talc	1	1	1	1	1
	TOTAL	50	50	50	50	50

3.4 Evaluation of core tablets

3.4.1 Hardness

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

3.4.2 Weight variation

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

3.4.3 Friability

The friability test of the formulations was performed using a Roche type friability test apparatus.. The percentage friability was then calculated by the formula

Friability % = (Initial weight – Final weight/ Final weight) X100

3.4.4 Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

3.4.5 Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 20 mg of drug was transferred in 20 mL of methanol. 10ml from this stock solution was withdrawn and diluted up to 100 mL with methanol. 0.6 mL from this stock solution was pipetted out and diluted to 10 mL. Absorbance of the resulting solution was measured at 310 nm using UV spectrophotometer and the drug content was calculated using calibration curve.

3.4.6 In vitro release profile

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated core tablets. The dissolution media used consisted of 900 mL of 0.1 N HCl and distilled water. 5 mL of samples were collected at time points and the media was replenished with the same volume of fresh media. The free rizatriptan concentration was estimated using a UV spectrophotometer at a wavelength of 234 nm.

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3.5 Preparation of cross-linked gelatin capsules

The "0" sized hard gelatin capsules about 100 in number were taken. The body of the capsules was placed on a wire mesh. 25ml of 15%v/v formaldehyde was taken into a desiccator and potassium permanganate was added to it to generate formalin vapors. The wire mesh along with the body was kept in the desiccator. The reaction was carried out for 12 hours, after which the body were removed and dried at 50ºC for 30 minutes to ensure completion of reaction between gelatin and formaldehyde vapor. They were dried at room temperature to facilitate removal of residual formaldehyde.

3.6 Preparation of pulsincap

The pulsincap was similar in appearance to a hard gelatin capsule, but the body was water insoluble. Core tablet of amiodarone was and placed into the bottom of formaldehyde treated body. The capsules were then plugged with prepared hydrogel plug and capsule cap was placed over the body.

3.7 In vitro release study of the puslincap formulation

Dissolution studies were carried out using USP dissolution test apparatus (paddle method). Capsule was tied to paddle with a cotton thread so that the capsule was immersed completely in dissolution media but not float. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used (sequential pH change method). The pH 1.2 was first used for 2 h then removed and the fresh phosphate buffer pH 7.4 was added. After 3 h the medium was removed and colonic fluid phosphate buffer pH 6.8 was added for subsequent study. 900 mL of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5°C; 10 mL of dissolution medium was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analysed at 234 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated.

IV. RESULTS AND DISCUSSION

4.1 Preformulation Studies

4.1.1 Organoleptic characters

The observed organoleptic characteristic of the drug sample is presented in Table 4.1.

Table 4.1Organoleptic properties of rizatriptan

S.No	Test	Observation
1	Color	White to off-white
2	Odor	Odorless
3	Appearance	Solid, crystalline

The melting point of the procured drug sample was found to be 180-182°C which was equivalent to the reported standard for rizatriptan (182-183°C) as reported at Pubchem. The LOD was found to be 0.3% and the partition coefficient was 0.649

4.1.2 Solubility profile

The results of qualitative solubility analysis are presented in Table 4.2. Solubility was qualitatively examined by observing for the presence of undissolved solid in the test solution.

Table 4.2 Solubility profile of rizatriptan

S.No	Solvent	Solubility Observed
1	Water	Slightly soluble
2	Methanol	Soluble
3	Ethanol	Soluble
4	Dimethylformamide	Soluble

4.1.3 Calibration Curve

The calibration curve of rizatriptan was prepared according to the reported procedure using methanol as the solvent. The absorbance observed is presented in Table 4.3 and the calibration curve along with the equation for straight line is presented in Figure 4.1.

Table 4.3 UV absorbance of rizatriptan in methanol

Concentration (µg/mL)	Absorbance at 234 nm
1	0.049
2	0.111
3	0.177
4	0.196
5	0.247
6	0.325
7	0.364
8	0.402
9	0.431
10	0.516

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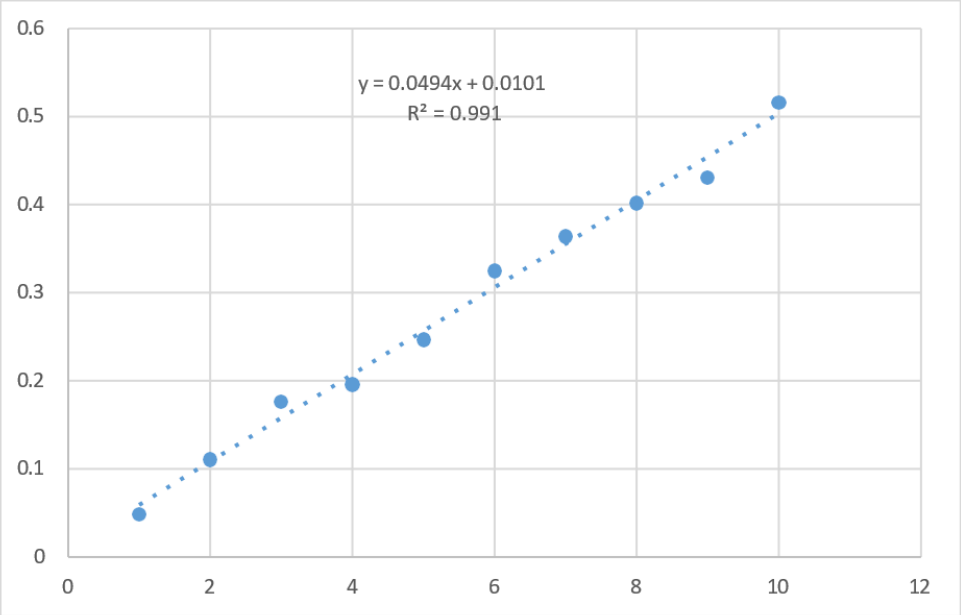

Figure 4.1 Calibration curve of rizatriptan

4.1.4 FTIR and compatibility study

The FT-IR spectrum (Figure 4.2) exhibits the major peaks of the functional groups present in rizatriptan. The functional groups which cause the occurrence of the peaks are presented in Table 4.4

Table 4.4 Major peaks occurring in the FT-IR spectra of rizatriptan

Wave Number	Functional Group
3271	N-H stretching
2925-2970	C-H stretching (alkyl)
1560	Aromatic C=C bending
1300	C-N stretching

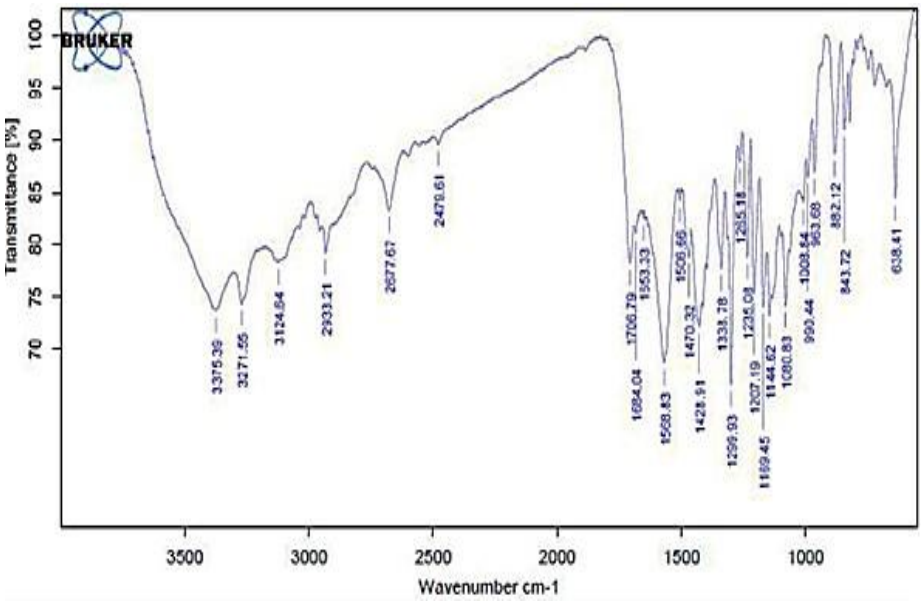

Figure 4.2 FT-IR spectra of rizatriptan

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4.2 Evaluation of core tablet

Table 4.5. Post compression parameters of core tablets

Formulation Code	Hardness (Kg/cm^2)	Thickness (mm)	Average Weight variation (%)	Friability (%)	Drug content (%)
CT1	2.9	2.56	6.4	0.69	95.60
CT2	3.1	2.53	6.1	0.64	94.90
CT3	2.9	2.57	5.7	0.59	97.40
CT4	2.8	2.54	4.9	0.57	96.80
CT5	3.2	2.51	4.4	0.48	97.10

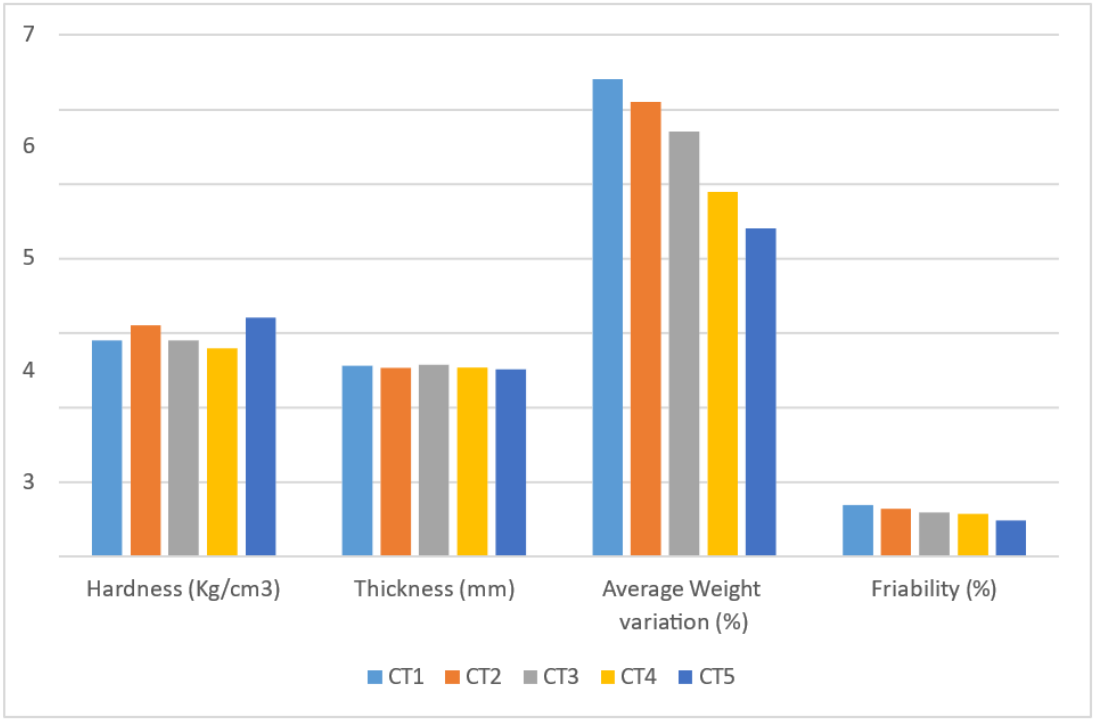

Figure 4.3. Post compression parameters of core tablets

The release of rizatriptan from the core tablets was studied and it was found that 100% rizatriptan was released in 90 min from the core (Table 4.6).

Table 4.6. Cumulative release data of rizatriptan from core tablets

Time (minutes)	% Cumulative Release				
	CT1	CT2	CT3	CT4	CT5
0	0.00	0.00	0.00	0.00	0.00
15	9.30	11.40	13.70	14.90	15.20
30	24.90	25.10	26.30	28.60	29.50
45	41.30	46.50	48.70	49.20	51.40
60	66.40	69.60	74.40	74.80	75.20
75	79.10	87.30	91.60	92.40	94.60
90	96.3	98.9	100.1	102.1	102.1

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4.3 Evaluation of pulsincap

The release of rizatriptan in various pH conditions according to the transit of the pulsincap was studied for a duration of 24h. It was found that in the acidic conditions of the stomach, about 60% of amiodarone was released in 2h whereas at pH 7.4 none was released in 3h. At pH 6.8 (colon), about 41% of the remaining drug was released in 19h of study (Table 4.7).

Table 4.7 Dissolution of pulsincap

pH of dissolution medium	Time (min)	% Release
1.2	10	11.1
	20	17.3
	30	20.2
	40	31.2
	50	39.4
	60	49
	90	54.5
	120	59.2
7.4	180	0
	240	0
	300	0
6.8	360	5.4
	420	7
	720	19.1
	1200	29.5
	1260	33.2
	1320	35.4
	1380	40.4
	1440	42.3

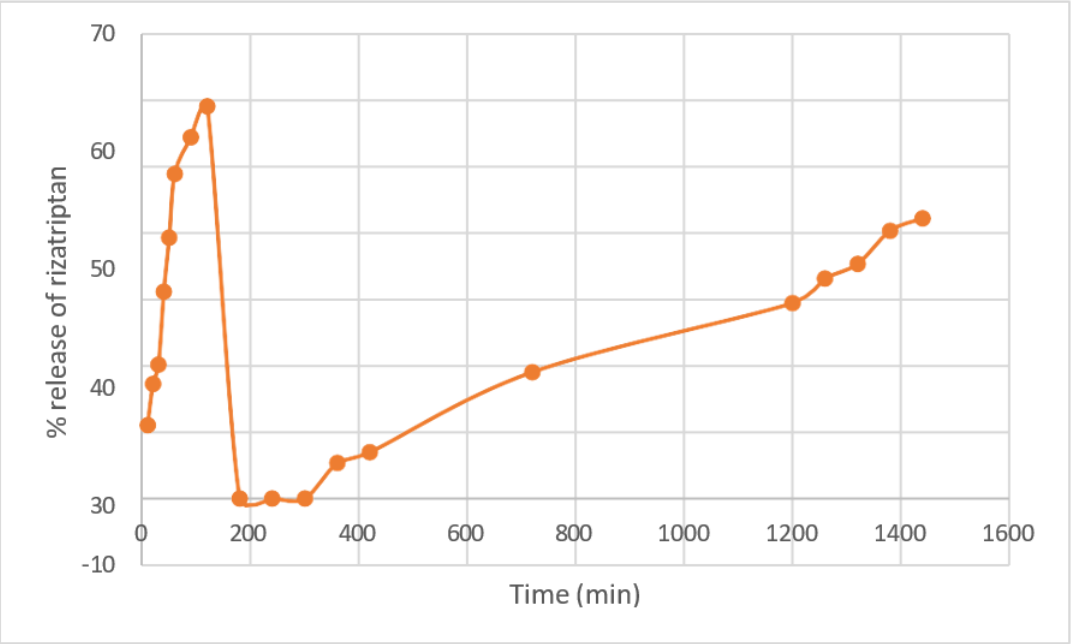

Figure 4.4. Release plot of amiodarone from pulsincap

The drug shows significant solubility and release in acidic conditions, suggesting it is readily available in gastric fluid. The release is fast initially, then slows down as it approaches equilibrium. In the neutral medium (pH 7.4) no release observed up to 300 min. This indicates strong pH-dependent solubility, with negligible release in intestinal fluid at pH 7.4. At pH 6.8, initially a very slow release is seen (5.4% at 360 min, 19.1% at 720 min) which gradually increases to 42.3% at 1440 min. The drug releases slowly and continuously in pH 6.8, showing sustained release behavior. This suggests partial solubility in intestinal fluid, but much slower compared to acidic conditions.

Rapid gastric release at pH 1.2 mimics an immediate pulse for drugs that need fast action in the stomach. The absence of release in pH 7.4 and minimal release in early hours at pH 6.8 suggests the system is designed to hold the drug until a certain time or location. The delayed, gradual release in pH 6.8 mimics a secondary pulse in the intestine, though here it is more sustained than abrupt.

V. SUMMARY AND CONCLUSION

5.1 Summary

The present study was undertaken to develop and evaluate a pulsatile drug delivery system of rizatriptan for the chronotherapy of migraine. Preformulation studies confirmed the suitability of rizatriptan, which exhibited a melting point of 180–182°C, good solubility in methanol, ethanol and dimethylformamide, and a λmax of 234 nm. FTIR studies indicated compatibility between the drug and selected excipients.

A hydrogel plug was prepared by direct compression using HPMC K15M, spray-dried lactose and PVP K30. The optimized plug showed satisfactory physical characteristics, including 4.521 ± 0.026 mm thickness, 0.24% friability, and approximately 65% swelling after 12 h. Rizatriptan core tablets were formulated using cross-carmellose sodium and Ac-Di-Sol as superdisintegrants. The prepared tablets exhibited satisfactory flow properties, hardness, thickness, weight variation, friability and drug content (94.90–97.40%), with complete drug release within 90 min.

The pulsatile system was assembled using formaldehyde-treated crosslinked gelatin capsules containing the core tablet and hydrogel plug. In-vitro release studies demonstrated pH-dependent and time-controlled drug release, with approximately 60% drug release in 2 h under acidic conditions, no release at pH 7.4 for 3 h, and approximately 42% of the remaining drug released at pH 6.8 over 19 h. Overall, the developed pulsatile delivery system demonstrated potential for controlled, delayed and site/time-specific release of rizatriptan, making it a promising approach for migraine chronotherapy.

5.2 Conclusion

The present investigation successfully formulated and evaluated a pulsatile drug delivery system (pulsincap) of Rizatriptan for chronotherapy of migraine. Preformulation studies confirmed the purity and suitability of Rizatriptan for dosage form development. The drug exhibited appropriate organoleptic properties, solubility in common solvents, a melting point consistent with reported standards, and a reliable calibration curve. FTIR analysis validated the presence of functional groups without incompatibility issues. Hydrogel plugs prepared with HPMC K15M, lactose, and PVP K30 showed excellent physicochemical properties, including uniform weight, low friability, and sustained swelling capacity across different pH conditions, ensuring their integrity for controlled lag time. Core tablets demonstrated good flow properties (angle of repose <30°, Carr's Index <15%), acceptable hardness (<4 kg/cm²), low friability (<1%), uniform thickness, and consistent drug content (94.9–97.4%). In vitro release studies confirmed complete drug release within 90 minutes, validating rapid availability of Rizatriptan from the core. Cross-linked gelatin capsules treated with formaldehyde provided insoluble capsule bodies, enabling delayed release. The pulsincap system exhibited pH-dependent release behavior: rapid release in acidic medium (pH 1.2), negligible release at pH 7.4, and sustained release at colonic pH 6.8 over 24 hours.

Thus, the study demonstrates that pulsatile delivery of Rizatriptan using hydrogel plug and cross-linked gelatin capsule technology is a promising approach for chronotherapy of migraine, and may serve as a model for time-specific drug delivery systems in other chronotherapeutic applications.

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