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Original Article

Design and Development of Multiparticulate Mini Tablets of Verapamil Hydrochloride for Pulsatile Drug Delivery

Bimireddy Bhavani Prasanna Kumar[1,*], Rama Rao Nadendla[2]

[1]Department of Pharmaceutics, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur, Andhra Pradesh, INDIA.
[2]Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh, INDIA.

ABSTRACT

Objectives: The objective of the research was to develop and evaluate the multiparticulate pulsatile release minitablets of verapamil hydrochloride for the treatment of hypertension at a desired time to mimic the circadian rhythms and improve the patient compliance. **Materials and Methods:** Formulation was prepared by CODAS technology. It was designed to initiate the release of verapamil after 4h lag time and reached the therapeutic levels at in the early morning hours, when the blood pressure is at its highest. The core minitablets were prepared by wet granulation process and coated with water insoluble polymer like ethylcellulose along with hydrophilic plasticizer. The formulation attributes were optimized and evaluated the *in vitro* performance. **Results:** The *in vitro* dissolution studies revealed that the coating build-up of ethylcellulose controls the initial lag time and release rate of drug product. Among the formulations (F1a) 10% w/w ethylcellulose coated minitablets showed lag time for 4 hr and controlled the release up to 24 hr. The formulation optimization studies illumined the critical attributes like fumaric acid (F2), which modified the microenvironment and improved the dissolution profile of drug product in phosphate buffer. The optimized formulation (F1a) was compared against the marketed product (CALAPTIN 120 mg SR tablets) and observed that the dissolution behaviour of the drug product followed first-order kinetics. **Conclusion:** The outcomes were presumed that the pulsatile release has been accomplished from coated minitablets with a lag time of 4hr, which is reliable with the demands of the chronotherapeutic drug delivery by efficiently control the blood pressure at early morning.

Keywords: Multiparticulates, Pulsatile release minitablets, Verapamil hydrochloride, Chronotherapeutic drug delivery, Fumaric acid, ethylcellulose.

Correspondence

Bhavani Prasanna Kumar Bimireddy
Department of Pharmaceutics, Research scholar, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur-522510, Andhra Pradesh, INDIA.
Email id: kumarbhimireddypharma@gmail.com
ORCID ID 0000-0002-9029-2187

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INTRODUCTION

Hypertension (high blood pressure) is a chronic long-term medical condition that causes cardiovascular diseases with elevated blood pressure in the arteries which majorly occur during early morning.[1] Generally, most cardiovascular dosage regimens are according to the cardiac rhythm (24 hr) pattern of blood pressure with morning rise and decline during night time. Chronotherapeutic is a pulsed release system that has been developed, which releases the drug at the desired rate and selected time to mimic the biological rhythms with enhancing therapeutic efficiency, patient compliance and reduced dosing frequency.[2] Verapamil hydrochloride (VH) is an antihypertensive drug under BCS class IV calcium channel blocker used for the treatment of high blood pressure, heart arrhythmias, and angina which prevents and relaxes the coronary artery spasm and reduction of oxygen utilization. 90% of the drug is absorbed when administered orally, bioavailability ranges from 20% to 30% due to first-pass metabolism in the portal circulation. Peak plasma concentrations are reached between 1 to 2 hr after oral administration. The mean half-life ranges from 2.8 to 7.4 hr.[3] The multiparticulate systems are generally granules, pellets and minitablets. Minitablets are small discrete subunits, containing the drug, with a diameter of 0.05 to 2 mm, which are filled into a hard gelatine capsule. After oral administration, they disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs, and reduce inter-and intra-patient variability. Minitablets have several benefits such as reliable drug release, unfluctuating clinical performance, more flexibility during the development of formulation, and maximum stability on storage.[4] In the present investigation, minitablets were developed for pulsatile release pattern, filled in hard gelatin capsules is to lag drug release for 4 hr and to reach therapeutic blood levels in the early morning hours, when the blood pressure is highest and to provide the adequate 24 hr control of blood pressure in patients.

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MATERIALS AND METHODS

Materials

Verapamil hydrochloride (VH), an anti-hypertensive drug from Piramal Healthcare Limited, as a free sample used as Active Ingredient; Microcrystalline cellulose (MCC) of two grades of Avicel PH 101 and PH102, used as diluents; polyvinylpyrrolidone (PVP K30) utilized as a binder; polyethylene glycol (PEG400) utilized as a plasticizer; ethylcellulose (EC100cps), used as controlled release polymer; magnesium stearate, used as a lubricant; fumaric acid, used as pH modifier and isopropyl alcohol, used as granulating liquid were purchased from S.D. Fine Chem. Pvt. Ltd., Chennai. All the inactive ingredients used in the research were pharmaceutical grade. HPLC grade dichloromethane was purchased from Sigma Chemical Industries, Hyderabad.

Methods

Formulation studies

Preparation of verapamil HCl minitablets: The core minitablets were fabricated by the wet granulation process. The weighed quantity of VH, MCC (Avicel PH 101) were granulated with 5% w/w fumaric acid solution and followed by 20% w/w PVP K30 in isopropyl alcohol which is dried at 40°C in an oven and mixed with MCC (Avicel PH102) which was sifted via #30 and lubricated with #60 sifted magnesium stearate. The resulting granules were compressed into minitablets with a 2 mm multi-tip punch (Figure 1). The composition of verapamil HCl minitablets (VHMTs) is as shown in (Table 1).

Coating of verapamil HCl minitablets: The core minitablets were coated with the ethyl cellulose (strength of 2% w/w) prepared in the ratio of 60:40% w/w of isopropyl alcohol, dichloromethane, and 5% w/w PEG400. The resulting coating solution was sprayed onto the minitablets with 0.01 g/mL of spray rate with rotating speed 30RPM at 30 to 40°C inlet temperature and continued the coating until the weight build-up achieved up to 5%, 10%, 15%w/w (Figure 2) and the coated minitablets (Around 28 minitablets) were filled in size "1" gelatine capsules is equivalent to core tablet weight (Figure 3).

Figure 1: Compressed 2 mm minitablets.

Figure 2: EC coated minitablets 10% w/w.

Analytical methods for Verapamil HCl minitablets

Method for assay

The mobile phase was prepared by a combination of pH 3.0 triethylamine phosphate buffer, acetonitrile, and methanol in the ratio of 60:24:16% v/v and filtered with vacuum through a 0.45 µm membrane filter and degassed in a sonicator for about 5 min.[5]

Table 1: Composition of Verapamil HCl minitablets.

Ingredients	F1	F1a	F1b	F2	F 3	F4	F5	F6	F7
Intra-granular									
Verapamil HCl	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00
MCC (Avicel PH 101)	106.87	106.87	106.87	109.67	109.67	104.87	107.16	106.60	106.87
Fumaric acid	2.80	2.80	2.80	0.00	2.80	2.80	2.80	2.80	2.80
PVP K30	9.13	9.13	9.13	9.13	6.33	11.93	9.13	9.13	9.13
Extra-granular									
MCC (Avicel PH 102)	39.20	39.20	39.20	39.20	39.20	39.20	39.20	39.20	39.20
Magnesium Stearate	2.00	2.00	2.00	2.00	2.00	2.00	1.71	2.27	2.00
Coating composition									
Ethylcellulose	14.00	28.00	42.00	28.00	28.00	28.00	28.00	28.00	28.00
Polyethylene glycol(PEG 400)	0.70	1.40	2.10	1.40	1.40	1.40	1.40	1.40	0.84
Total	294.70	309.40	324.10	309.40	309.40	309.40	309.40	309.40	308.84

Figure 3: EC Coated minitablets filled in capsule size"1".

Table 2: Chromatographic Parameters for assay and dissolution method development of verapamil HCl minitablets.

Chromatographic Parameters	Assay	Dissolution studies
Stationary phase	Inertsil ODS 3V 150 × 4.6 mm, 5µm	Inertsil ODS 3V 150 × 4.6 mm, 5µm
Mobile phase	60:24:16% v/v combination of pH 3.0 triethylamine phosphate buffer, acetonitrile, and methanol	60:40v/v mixture of pH 3.0 triethylamine phosphate buffer, acetonitrile
Diluent	20:80 % v/v methanol: water	Dissolution Medium
Flow rate	1.3 mL/min	1.3 mL/min
Detection wavelength	216nm	278nm
Column temperature	30°C	30°C
Sample temperature	25°C	25°C
Injection volume and run time	20 µL, 15min	10 µL, 6min

The chromatographic parameters for assay method development of VH minitablets are tabulated in (Table 2).

Method for dissolution

The mobile phase was prepared by a combination of pH 3.0 triethylamine phosphate buffer, acetonitrile in the ratio of 60:40% v/v, and filtered with vacuum through a 0.45 µm membrane filter and degassed in a sonicator for about 5 min. The chromatographic parameters for dissolution method development of VH minitablets are tabulated in (Table 2).

Evaluation studies

Precompression studies

The rheological characteristics of lubricated blend was assessed like the angle of repose, bulk density (BD), tapped density (TD), Carr's index (CI), and Hausner's ratio (HR). All the tests were executed in triplicated (n=3) excluding for CI and HR and the results are expressed as (Mean ± SD). CI and HR were computed from the mean values of BD and TD.

Post-compression studies

The post-compression characteristics of compressed minitablets were evaluated like thickness (mm), crushing force (kg/cm^2), friability, and mass variation. For the assay, minitablets weighed corresponding to 120 mg of VH and transferred into 100 mL of water: methanol and ultrasonicated for 15 min. All tests are carried out in triplicate (n=3) and the results are expressed as (Mean ± SD).[6]

In vitro dissolution studies

In vitro drug release studies were performed using USP apparatus II (Paddle), 50 rpm at 37 ± 0.5°C for 24 hr. Accurately weighed minitablets equivalent to label claim was taken into a capsule fitted in sinker size "0" and transferred into the dissolution vessel with 900 mL of pH 6.8 (PBS) and collected sample at time intervals as 1, 2, 4, 6, 8, 10, 12, 18, 24 hr. The collected samples were determined for the % drug dissolved by HPLC at 278 nm. The dissolution profile optimized were compared against the marketed product (CALAPTIN 120 mg SR tablets) and also performed multimedia dissolution profile in pH 1.2 HCl (HBS), pH 4.5 acetate buffer solution (ABS) with the same procedure. The percent drug release was calculated by the formula.[7,8]

In vitro release kinetic studies of optimized formulation

The drug release data obtained after *in vitro* dissolution studies were fitted into various order kinetics: Zero-order (Cum. % drug release vs. time), First order (Log cum. % drug undissolved vs. time), Higuchi's (Cum. % drug release vs. √time), and Korsmeyer-Peppas (Log cum. % drug released vs. Log time) to comprehend the kinetics and mechanism of drug release from minitablets.[9,10]

Optimization studies

The formulation attributes like the concentration of fumaric acid, magnesium stearate, and concentration of coating build-up on minitablets were studied by one factor at a time method and evaluated by measuring the critical quality attributes like dissolution profile of drug product in pH 6.8 phosphate buffer. The justification for the selection of formulation attributes is as below.

Fumaric acid is an organic acid that acts as a pH modifier, changes the microenvironment around the drug substance in the product, and improves the solubility of the drug substance. Hence, the concentration of fumaric acid was selected as a critical formulation attribute and studied the effect in formulation (F1a) with and without (F2) fumaric acid.

Polyvinyl pyrrolidine (PVP K30) is a binder, which imparts the cohesive properties between the blend particles and improves the rheological properties of dried granules, and also improves

the hardness of minitablets. The change in concentration of PVP K30 impacts the rheological properties of dried granules and the release profile of drug product. Hence different concentration levels like 2.26% w/w (F3), 3.26% w/w (F1a) and 4.26% w/w (F4) were studied.

Magnesium stearate is a hydrophobic lubricant, which prevents the granules from sticking to the die cavity. The change in concentration imparts the hydrophobic nature around the active substance and impacts the dissolution profile of the final product. Hence, different concentrations like 0.61% w/w (F5), 0.71% w/w (F1a), and 0.81% w/w (F6) were studied.

Ethylcellulose is a hydrophobic controlled release polymer. The change in its concentration modifies the dissolution profile of the drug product. Hence the different percentage coatings build-up with 5% w/w (F1), 10% w/w (F1a), and 15% w/w (F1b) were studied.

PEG 400 is used as a water-soluble plasticizer. The change in concentration of plasticizer impacts on the coating film nature and dissolution profile of the drug product. Hence different concentration like 5% w/w (F1b), 3% w/w (F7) and without (F8) PEG400 was studied.

Stability studies of the optimized formulation: The final optimized formula (F1a) of minitablets were filled in gelatine capsule Size "1" and packed in an HDPE bottle and placed at temperature 40±2°C up to 3 months. The stability samples of 1st month and 3rd month, capsules were subjected to assay and *in vitro* dissolution studies in pH 6.8 phosphate buffer (PBS).

RESULTS AND DISCUSSION

Precompression studies

The change in the concentrations of formulation attributes has no impact on the rheological properties of lubricated blend results shown in (Table 3). The flow properties of all the executed batches were shows free flow and good compressibility index, it indicates that lubricated blend of all batches are suitable for compression.[11]

Table 3: Results of pre-compression studies on core Verapamil HCl minitablets.

F. Code	Angle of Repose* (°)	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Carr's index (%)	Hausner's ratio
F1 and F7	24.93±0.73	0.55±0.02	0.64±0.02	14.06	1.16
F2	23.52±0.35	0.53±0.02	0.61±0.02	13.11	1.15
F3	25.12±0.42	0.53±0.01	0.63±0.02	14.29	1.17
F4	23.61±0.28	0.56±0.02	0.66±0.02	15.15	1.18
F5	24.20±0.31	0.56±0.03	0.62±0.01	16.13	1.19
F6	23.15±0.53	0.56±0.02	0.64±0.02	17.19	1.21

*All the tests except were performed in triplicate (n=3) and the values are expressed as (Mean ± SD). CI and HR were computed from the mean values of bulk density and tapped density.

Table 4: Results of post-compressed studies on core Verapamil HCl minitablets*.

F.Code	% mass. variation (%)	Thickness (mm)	Crushing force (kg/cm²)	%Friability (%)	% Assay (%)
F1 and F7	279.3±1.25	2.65 ±0.03	1.05±0.05	0.16	99.38±0.26
F2	276.9±1.41	2.63 ±0.04	1.03±0.06	0.18	98.96±0.32
F3	278.4±1.10	2.62 ±0.06	1.06±0.04	0.14	99.36±0.28
F4	278.5±1.32	2.60 ±0.03	1.13±0.05	0.10	97.96±0.46
F5	277.2±1.23	2.62 ±0.05	1.04±0.03	0.19	98.60±0.41
F6	279.2±1.34	2.63 ±0.03	1.01±0.07	0.26	98.47±0.48

*For % Mass. Variation test (n=20), % Friability test (n=1), and remaining tests were performed in triplicate (n=3) and the results were expressed as (Mean ± SD).

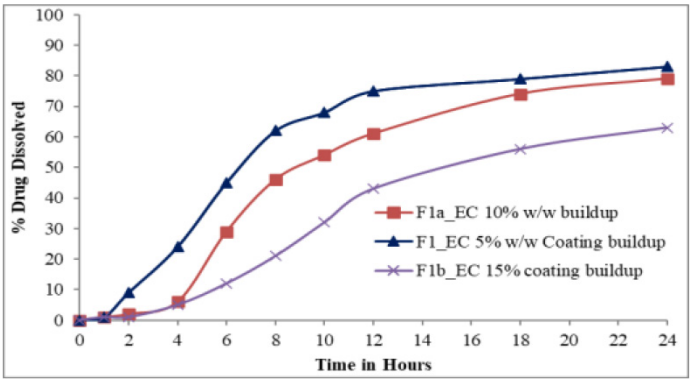

Figure 4: Comparative *in vitro* dissolution profiles of different levels of coating build-up of EC 100 cps in pH 6.8 PBS.

Post-compression studies

The proposed changes in formulation attributes has no impact on the compression properties of core minitablets, which were included crushing force, friability, thickness, and mass variation, and the results shown in (Table 4). The crushing force of formulation F4 was shown high force 1.13±0.05 kg/cm², it could be due to the high concentration of binder (PVP K30 11.93 mg/unit) when compared against the other formulation optimization batches. However, all the results were found satisfactory and met the limit criteria according to pharmacopeia specifications.

In vitro dissolution studies

The *in vitro* release profiles of optimization batches F1 to F7 illuminate the release mechanism of VHMTs. The release of VH from minitablets coated with ethylcellulose is mainly driven by diffusion through the aqueous pores of hydrophilic plasticizer (PEG 400) on the polymer membrane.[12,13]

The coating build-up of polymer controls the initial lag rate, formulation F1a with 10% EC100cps coating showed slow lag for 4 hr as it acted as a barrier and controlled drug release up to 24 hr when compared with other formulations F1 and F1b (with 5% and 15% w/w respectively) is shown in (Figure 4).[14] The

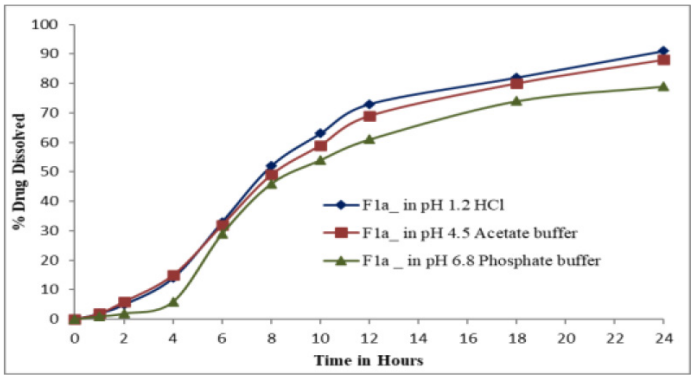

Figure 5: Comparative *in vitro* dissolution profiles of optimized (F1a) in pH 1.2HCl, pH 4.5 ABS and pH 6.8 PBS.

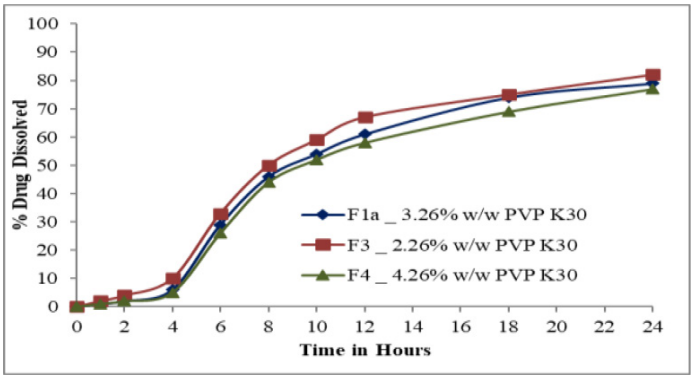

Figure 8: Comparative *in vitro* dissolution profiles of different levels of povidone K30 in pH 6.8 Phosphate buffer.

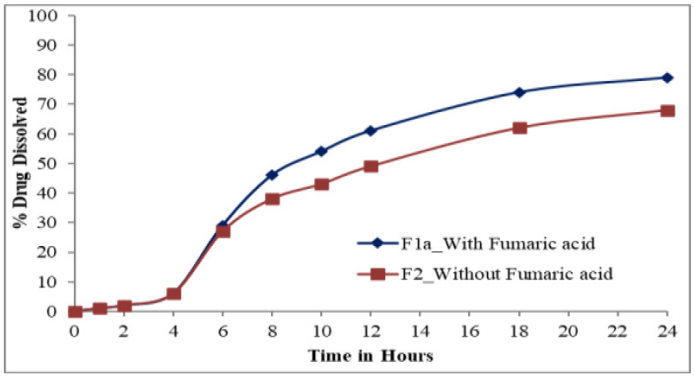

Figure 6: Comparative *in vitro* dissolution profiles of different concentration of fumaric acid in pH 6.8 Phosphate buffer.

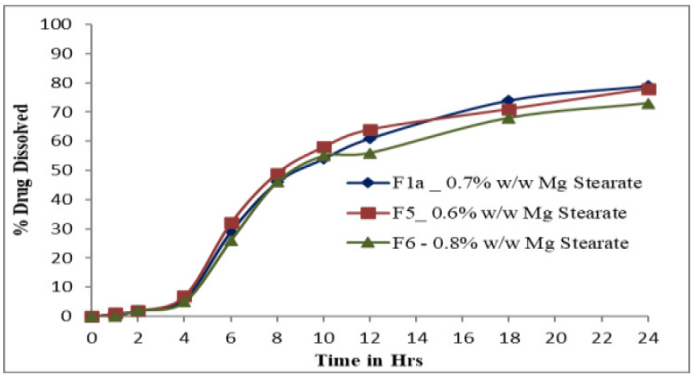

Figure 9: Comparative *in vitro* dissolution profiles of different concentration of magnesium stearate in pH 6.8 PBS.

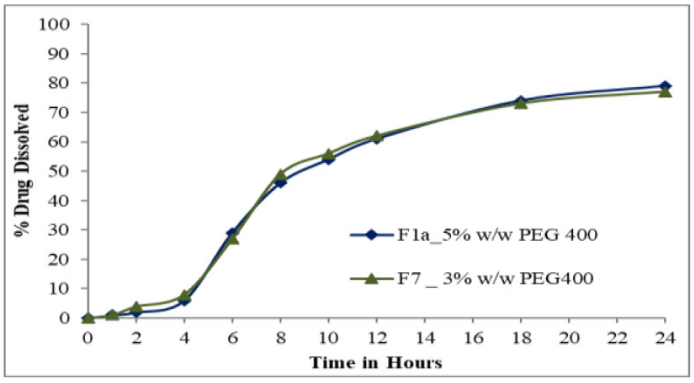

Figure 7: Comparative *in vitro* dissolution profiles of different concentrations of PEG400 in pH 6.8 phosphate buffer

in vitro multimedia dissolution profiles of optimized formulation (F1a) in pH 1.2 HCl, pH 4.5 ABS, and pH 6.8 PBS are shown in (Figure 5) revealing that the EC 100cps coating membrane controls the release of drug substances regardless of the pH condition of physiological dissolution media.[15]

Even though the variation in % of drug release at end point was observed in pH 6.8 PBS (at 24 hr 80%) when compared against the pH 1.2 HCl (at 24 hr 93%) and pH 4.5 ABS (at 24 hr 88%), it is due to the weak basic nature of VH. To minimize the pH-dependent solubility of VH incorporated the pH modifier like fumaric acid in the formulation which helps to maintain the microenvironment around the drug substance in acid nature and by improve the dissolution profile of the drug product in pH 6.8 PBS.[16] It was supported by the *in vitro* dissolution profiles of VHMT formulation with (F1a) and without fumaric acid (F2) with 10%w/w coating of EC shown in (Figure 6).

In coating composition, the levels of plasticizer PEG400 (F1a with 5% w/w and F7 with 3% w/w) shown as a minute impact on the *in vitro* performance of the drug product is shown in (Figure 7), which is due to a slight change in the concentration of PEG400.[17] Other formulation attributes like PVP K30 with different concentrations exhibited an impact on dissolution profile as shown in (Figure 8).[18] Though, the dissolution profile of low (F3 with 2.2% w/w) and high (F4 with 4.2% w/w) concentration depicted a similarity factor of F2 < 50 when compared with the optimized formula (F1a). The different levels of magnesium stearate showed less impact on the dissolution profile of the drug product (Figure 9).

Comparative *in vitro* dissolution profile of optimized formulation (F1a) vs marketed formulation (CALAPTIN 120 SR Tablets) in pH 6.8 PBS is shown in (Figure 10) reveals that the marketed

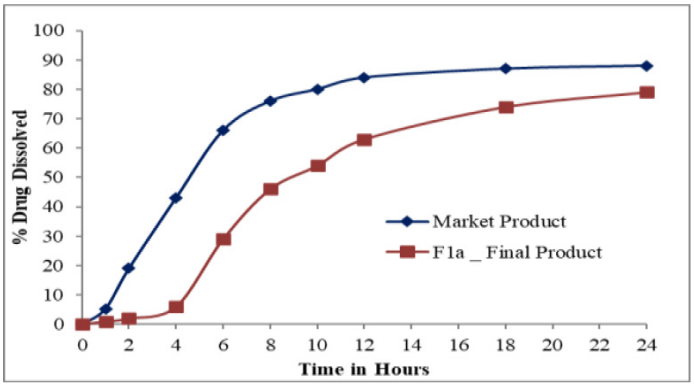

Figure 10: Comparative *in vitro* dissolution profiles of optimized formulation (F1a) Vs marketed formulation (CALAPTIN 120 SR Tablets) in pH 6.8 PBS.

Table 5: *In vitro* dissolution kinetic data of the optimized formulation (F1a).

F. Code	Zero-order	First-order	Higuchi	Korsmeyer -Peppas	
F1a	r^2-value				*n*-value
	0.953	0.973	0.963	0.960	0.830

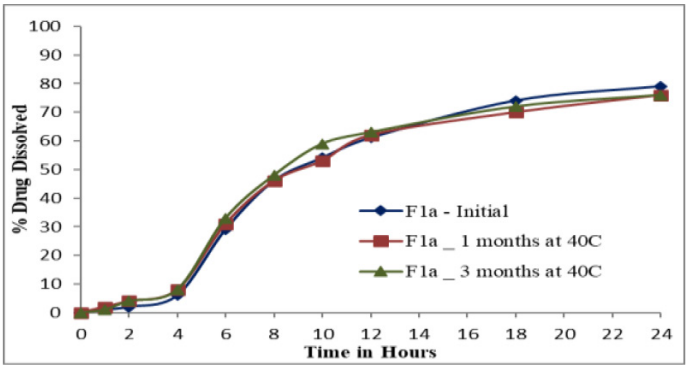

Figure 11: *In vitro* dissolution profile of stability studies of optimized formulation (F1a) at 40±2°C of 1 and 3 months in pH 6.8 PBS.

product sustained the release profile up to 8 hr only whereas F1a prolonged the drug release up to 24 hr and with a lag up to 4 hr.

The *in vitro* release kinetics of pulsatile VHMTs was studied by zero-order, first-order, Higuchi model, and Korsmeyer-Peppas model. The outcomes explained that the *in vitro* release profile of the VHMTs will follow the first-order kinetic and non-Fickian mechanism shown in (Table 5).

Stability studies of optimized formulation: The stability studies were performed on the formulation (F1a) at a temperature of 40±2°C up to 3 months for analyzed the *in vitro* release performance of the drug product. All the results showed similarity factor F2 of more than 50 when compared against the initial results (Figure 11). And the assay results of the stability samples were found as 98.92% (1 month) and 99.26% (3 months) respectively.

CONCLUSION

It is concluded from the current study of formulation and development of a novel multiparticulate pulsatile drug delivery system of VH for the treatment of hypertension was successfully done. Based on the results the developed optimized formulation (F1a) released the drug with a lag time of 4 hr after administration at bed time and reaching the blood therapeutic levels in the early morning hours, when the blood pressure was high. Consequently, this dosage form regiment provided the adequate 24 hr control of blood pressure in patients and followed the concepts of chrono pharmaceutics, for effectively controlling hypertension at their peak biological time, thereby providing relief to the patient.[19-23]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BCS: Biological classification system; **CODAS:** Chronotherapeutic oral drug absorption system; **EC:** Ethylcellulose; **GI Tract:** Gastrointestinal Tract; **HDPE Bottle:** High density polyethylene Bottle; **h:** Hours; **SR Tablets:** Sustained release tablets; **PEG 400:** Polyethylene glycol 400; **PVP K30:** Polyvinylpyrrolidone -K30; **RPM:** Rotations per minute; **VH:** Verapamil Hydrochloride; **VHMT:** Verapamil Hydrochloride minitablets.

SUMMARY

In the current study it can be concluded that the *in vitro* dissolution profile of verapamil hydrochloride minitablets were controlled by hydrophobic polymer coating with hydrophilic plasticizer, as the coating build-up increased the lag time build-up was increase and delayed the release rate respectively. Among the formulations F1 (5%), F1a (10%), and F1b (15%); the F1a with 10% w/w of Ethylcelluose 100 cps coating build-up delayed the release up to 4 hr by acting as a barrier and controlled the release up to 24 hr. Optimization studies was assess the formulation attributes like increase in the conc. PVP K30 (binder), magnesium stearate (lubricant) have decreased the% drug release and the levels of fumaric acid modified improved the dissolution in alkaline condition by modified the microenvironment around the drug substance. The optimized formulation (F1a) compared against the marketed product and achieved pulsatile release in all physiological buffers (pH 1.2 HBS, pH 4.5 ABS, and

pH 6.8 PBS,) and showed first-order kinetics, non-Fickian mechanism. The optimized formulation (F1a) results showed that when the dose is taken at bedtime, the VH was released with a lag time of 4 hr, reaching therapeutic blood levels in the early morning hours which met all the provisions of CODAS technology fruitfully.

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