**Ind. J. Pharm. Edu. Res., 2025; 59(2s):s473-s481.**
https://www.ijper.org

Original Article

# Formulation and Evaluation of Chronotherapeutic Delivery of Sacubitril Valsartan for Management of Hypertension

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## ABSTRACT

**Introduction:** Early morning surge in blood pressure is a major cause of sudden cardiac arrest. **Objectives:** Development and evaluation of chronomodulated Compression Coated Tablets (CCT) for bedtime dosing of sacubitril-valsartan for the management of cardiac arrest. **Materials and Methods:** The tablets contain fast disintegrating inner core of sacubitril-valsartan coated by compression coating technique with a hydrophilic polymer. Various ratios of HPMC K100M were used as coating polymer and investigated to achieve the expected lag time of 5 hr. The micromeritic and tableting properties of core and CCT were evaluated. Further, the drug excipient compatibility in optimized formulations was investigated. Accelerated and long-term stability studies were performed to optimize compression coated tablets. **Results:** The tableting characteristics of core and compression coated tablets were found to be within limits specified in Indian Pharmacopeia. The Core tablets (CP4) prepared using 6% crospovidone showed good similarities with marketed IR (Immediate release) tablets (*f2*-82.65). The drug release profile of compression coated tablets (H4) exhibited preprogrammed lag time of 5 hr followed by burst release of drug (98%) from core tablet. The controlled onset of drug release was due to formation of viscous gel layer by HPMC K100M at the initial stages and balanced mechanism of solvent penetration and coat erosion. Absence of significant interactions in FTIR studies reveals drug and polymer compatibility. Compression coated tablets were found to be stable after accelerated and long-term stability studies. **Conclusion:** The optimized formulation H4 formulated using 2:3 ratio of HPMC/lactose in the coating exhibited a preprogramed lag phase before the burst release of the drug from the core and achieved chronotherapeutic delivery of sacubitril-valsartan to minimize the incidence of early morning surge and cardiac arrest in hypertensive patients.

**Keywords:** Sacubitril-valsartan, HPMCK100M, lactose, Compression coating, Chronotherapeutic drug delivery, Bedtime dosing.

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**Received:** 07-07-2023;
**Revised:** 25-07-2024;
**Accepted:** 09-12-2024.

## INTRODUCTION

Cardiovascular functions are closely related to the intrinsic circadian clocks of the human body.[1,2] Chronic elevation of Blood Pressure (BP) is a major risk factor for the onset of many cardiovascular diseases, such as stroke, arrhythmia and cardiac arrest with an increased incidence in the morning.[3,4] This may be due to the early morning surge of blood pressure, with a sharp rise just before awakening and peaks around midmorning[5,6] (4:00 to 8:00 am). As the conventional drug delivery system of antihypertensives unmet the therapeutic needs when blood pressure rises abruptly, a high incidence of cardiac stroke is reported early in the morning. To overcome such conditions, bedtime dosing (approx. 10 p.m.) of anti-hypertensives using chronotherapeutic drug delivery may be appropriate which elicits rapid drug release after a preprogramed lag time, to achieve peak plasma concentration in the early hours of the morning.

Sacubitril-Valsartan (SV) was classified as a new class of drugs called Angiotensin Receptor Neprilysin Inhibitor (ARNI).[7,8] In this combination, sacubitril inhibits neprilysin thereby increasing the levels of peptides and simultaneously valsartan blocks angiotensin II type-I receptor by inhibiting the release of angiotensin II-dependent aldosterone[9] which results in improved outcomes compared with ACE inhibitors and angiotensin receptor blockers.[10-12] It was also reported as a drug with similar mortality benefit as enalapril.[13-15]

Our current investigation aims to develop chronotherapeutic delivery of SV using compression coating technology to attain maximum drug release and achieve peak plasma concentration to overcome the complications occurring due to early morning surge.

**DOI:** 10.5530/ijper.20254583

## MATERIALS AND METHODS

Sacubitril-valsartan was received from Dr. Reddy's Labs, Hyd. All other excipients were procured from SD Fine Chemicals; Hyd. Azmarda 50 mg tablets were used to compare dissolution performance.

### Construction of standard curve of Sacubitril-valsartan

The primary stock solution (1000 µg/mL) of SV in 0.1 N HCl and pH 6.8 phosphate buffer was prepared separately and filtered. The above solutions were diluted to obtain a working standard (100 µg/mL) from which serial dilutions 1-20 µg/mL were prepared and spectrophotometrically analyzed at 253 nm to construct a standard curve.[16]

### Formulation of core tablets

Sacubitril-valsartan core tablets were formulated by direct compression as per the composition given in Table 1 using three different super disintegrants Croscarmellose sodium (CM1-CM4), sodium Starch Glycolate (SG1-SG4) and Crospovidone (CP1-CP4) in 3%, 4%, 5% and 6% concentrations. A multifunctional diluent Prosolv provides excellent flow characteristics to the tablet blend. Lubritab was used as a lubricant due to the incompatibility of Prosolv with a commonly used lubricant, magnesium stearate.[17] Using accurately weighed amounts of drug and excipients sieved through BSS #60 sieve, precompression blends were prepared, evaluated for flow property and compressibility tendency by determination of bulk density, tapped density,[18] angle of repose[19] and compressibility index[20] as indicated in Table 2 and then compressed to obtain Optimized Core Tablets (OCT).

### Characterization of core tablets

Core tablets are characterized by tableting characteristics like mechanical strength, uniformity of weight, content of active ingredients, wetting and disintegration time. Core tablets were evaluated for hardness and friability.[21] To determine the uniformity of weight, the average weight of 20 core tablets was taken accurately and % weight variation was calculated.[22] 20 samples were randomly selected and assayed in pH 6.8 phosphate buffer and UV absorbance was measured at 253 nm by a UV/VIS Spectrophotometer (UV 3000+, LABINDIA) to determine the amount of active ingredient per tablet.[23] Wetting time and disintegration time were determined for core tablets using pH 6.8 phosphate buffer.[24,25] The results of all the tableting characteristics were reported in Table 3.

### Dissolution performance of core tablets

Drug release performance of core tablets and commercial tablets (AZ50) in pH 6.8 buffer was evaluated as per the FDA guidance for dissolution testing of SV tablets at the temperature of medium 37±0.5°C.[26] The cumulative % drug released was calculated by spectrophotometric analysis of dissolution samples at 253 nm. The dissolution performance of all core tablet formulations was compared with commercial formulations to select the OCT formulation as shown in Figure 1.

### Mathematical modeling by the model-independent method

This approach is useful in the calculation of a difference factor (f1) and a similarity factor (f2) between experimental and marketed formulations using the following equations.

$$f_1 = \left\{\frac{\{\sum_{t=1}^{n} | \mathrm{Rt} - \mathrm{Tt} |\}}{[\sum_{t=1}^{n} \mathrm{Rt}]}\right\} x\ 100$$

$$f_2 = 50\ x\ log\left[\left\{1 + \frac{1}{n}\sum_{t=1}^{n} wt(Rt - Tt)\right\}^{-0.5} X\ 100\right]$$

### Formulation and characterization of compression coated tablets

The core tablets optimized were compression coated, using high viscosity semi synthetic polymers like HPMC K100M as coating polymer and lactose, a hydrophilic pore forming channelling agent. Initially, HPMC K100M alone (H10) was used in coating, further trials were carried out by replacing part of HPMC K100M with lactose as given in the following respective ratios, H1 (1:9), H2 (1:4), H3 (3:7), H4 (2:3), H5 (5:5). For coating of core tablets, granules were prepared and employed in etching process.[27] The Compression Coated Tablets (CCT) obtained were further evaluated for tableting characteristics as per the conditions given in core tablets and results were reported in Table 4. The thickness of CCT was measured and coating layer thickness was calculated by subtracting OCT thickness from CCT thickness.

### Dissolution performance of compression coated tablets

The dissolution of CCT was initially performed in an acidic buffer followed by the basic buffer. The dissolution study was carried out in triplicate under similar conditions as core tablets and the average values of % drug released were calculated.

## RESULTS AND DISCUSSION

### Selection of optimized core tablets

The core tablets evaluated from all batches were found to be as per the pharmacopeial specifications and showed complete drug release within 30-45 min. Wetting time was in the range of 45-57 sec and disintegration time was determined to be in the range of 108-125 sec indicating the fast-disintegrating property of tablets. Among all the formulations, CM4, SG3 and CP4 completed drug release in 30 min in comparison to AZ50 and hence mathematical modeling by model-independent approach was performed to evaluate the formulation with high similarity.

The calculated f1 values for CM4, SG3 and CP4 were found to be 15, 13 and 3 whereas f2 values were found to be 44.68, 51.29 and 82.65 respectively. The results of the similarity factor and difference factor for the formulation CP4 and commercial formulation AZ50 indicated good similarity in the dissolution pattern of the tablets and hence, selected as optimized core tablet formulation for compression coating. Though the formulations prepared with the other 2 disintegrants completed drug release in 30 min, the drug release profiles were not similar to the drug release pattern of the commercial formulation according to similarity factor f2.

## Selection of optimized compression coated tablets

Good mechanical integrity was evidenced by the thickness, hardness and friability of coated tablets with uniformity in weight and labelled drug content as specified in Table 4. It was found that the coat thickness was 1 mm and uniform on all sides.

The cumulative % drug released and dissolution profiles of formulations H1-H5 and H10 shown in Figure 2 and the results represented in Table 5 clearly explain that in formulation H10 drug release was beyond the expected lag time of 5 hr due to high swelling and diffusion path length. In the formulations H1-H5, the drug release was retarded nearly up to the preprogramed lag time and burst release of the drug was observed after lag time due to the addition of a channelling agent. Among all the batches, formulation H4 developed using HPMC K100M and channelling agent lactose in the ratio 2:3 exhibited an initial lag phase of 5 hr followed by complete drug release (98%) in 1 hr after a lag time. During lag time, HPMC K100M undergoes swelling that slowly forms a thick firm gel but does not hydrate quickly thereby retaining the integrity of the inner core and acting as a drug release retarding polymer. This viscous gel layer controls the burst release at the initial stages followed by rupture/erosion. Later the pores were formed in the swollen matrix by channelling agent lactose due to which the drug in core material encounter the dissolution medium resulting in fast disintegration and dissolution within 1 hr after a lag time. The drug release performance of H4 was comparable with CP4 and AZ50 after the lag time as shown in Figure 3 and Table 6. Hence formulation H4 was selected as optimized CCT.

**Table 1: Composition of core tablet formulation.**

| Ing (mg/tab) | CM1 | CM2 | CM3 | CM4 | SG1 | SG2 | SG3 | SG4 | CP1 | CP2 | CP3 | CP4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SV | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| PSV | 43 | 42 | 41 | 40 | 43 | 42 | 41 | 40 | 43 | 42 | 41 | 40 |
| CMS | 3 | 4 | 5 | 6 | - | - | - | - | - | - | - | - |
| SSG | - | - | - | - | 3 | 4 | 5 | 6 | - | - | - | - |
| CPD | - | - | - | - | - | - | - | - | 3 | 4 | 5 | 6 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| LTB | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

SV: Sacubitril-valsartan; PSV: Prosolv; LTB: Lubritab; CMS: Croscar Mellose Sodium; SSG: Sodium Starch Glycolate; CPD: Crospovidone.

**Table 2: Micromeritic properties of core formulation blends.**

| Formulation code | Bulk density (g/mL) | Tapped density (g/mL) | Angle of repose (°) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| CM1 | 0.78±0.05 | 0.82±0.06 | 14±2 | 5 | 1.05 |
| CM2 | 0.76±0.11 | 0.84±0.03 | 15±1 | 7 | 1.07 |
| CM3 | 0.74±0.08 | 0.81±0.05 | 17±2 | 9 | 1.09 |
| CM4 | 0.73±0.09 | 0.79±0.12 | 16±2 | 8 | 1.08 |
| SG1 | 0.75±0.10 | 0.79±0.11 | 15±2 | 5 | 1.05 |
| SG2 | 0.66±0.14 | 0.75±0.05 | 16±1 | 7 | 1.08 |
| SG3 | 0.65±0.12 | 0.76±0.02 | 14±2 | 8 | 1.05 |
| SG4 | 0.74±0.05 | 0.83±0.04 | 16±1 | 8 | 1.07 |
| CP1 | 0.77±0.02 | 0.82±0.03 | 13±2 | 6 | 1.06 |
| CP2 | 0.73±0.06 | 0.79±0.05 | 15±1 | 8 | 1.08 |
| CP3 | 0.74±0.02 | 0.81±0.06 | 14±2 | 9 | 1.06 |
| CP4 | 0.75±0.05 | 0.83±0.04 | 16±1 | 7 | 1.07 |

## Drug-excipient interaction studies

### *Differential Scanning Calorimetry*

The physical compatibility of the drug and excipients in optimized formulation H4 was evaluated using STARe SW 9.10 software. The pure form of SV indicated a sharp endothermic peak at 135°C due to its crystalline nature and HPMC K100M showed an endothermic peak at a melting point of 100.4°C respectively as shown in Figure 4 whereas CCT formulation H4 exhibited an endothermic peak at 130.6°C. A very small fluctuation in the melting point and broadening of the endothermic peak of the drug was observed in the optimized formulation H4 may be due to very slight changes in its crystalline form during compression. Overall DSC studies reveal the absence of significant drug-excipient interaction.

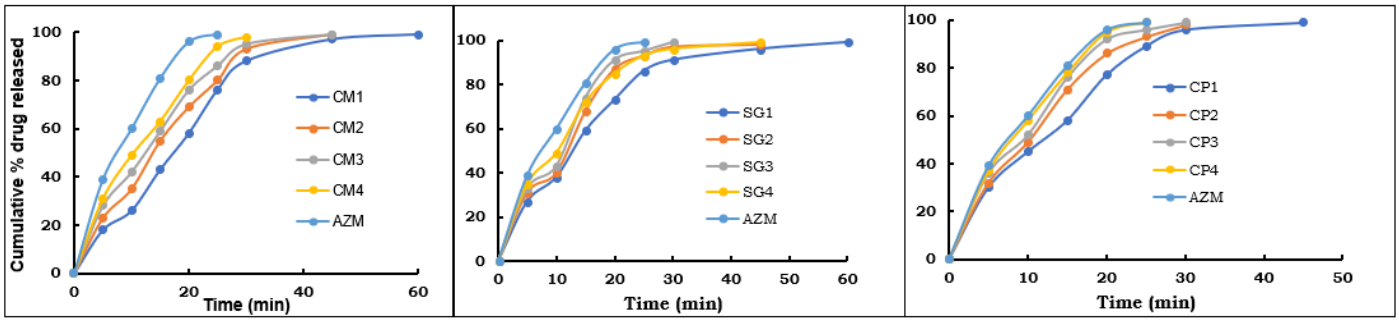


**Figure 1:** Dissolution profiles of core tablets in comparison with commercial tablet.

**Table 3: Tableting properties of core tablets.**

| Batch | Thickness (mm)[a] | Hardness[a] (kg/cm²) | Friability[b] (%) | Uniformity of weight[c] (mg) | Drug content[d] (%) |
|---|---|---|---|---|---|
| CM1 | 3.1±0.12 | 3.5±0.05 | 0.32 | 101.5±0.2 | 99.64±0.8 |
| CM2 | 3.1±0.16 | 3.2±0.02 | 0.45 | 100.2±0.4 | 99.87±0.36 |
| CM3 | 3.1±0.05 | 3.3±0.03 | 0.36 | 102.3±0.5 | 100.2±0.31 |
| CM4 | 3.2±0.13 | 3.5±0.01 | 0.42 | 99.6±0.6 | 99.61±0.42 |
| SG1 | 3.1±0.03 | 3.1±0.02 | 0.55 | 100.3±0.6 | 99.34±0.61 |
| SG2 | 3.2±0.05 | 3.2±0.03 | 0.48 | 101.4±0.3 | 100.1±0.23 |
| SG3 | 3.1±0.14 | 3.2±0.01 | 0.37 | 99.8±0.5 | 99.78±0.41 |
| SG4 | 3.1±0.15 | 3.1±0.06 | 0.43 | 100.7±0.1 | 99.65±0.13 |
| CP1 | 3.1±0.02 | 3.2±0.04 | 0.58 | 103.2±0.6 | 99.72±0.42 |
| CP2 | 3.1±0.04 | 3.2±0.02 | 0.49 | 101.6±0.2 | 99.43±0.46 |
| CP3 | 3.1±0.06 | 3.1±0.01 | 0.44 | 100.8±0.2 | 100.06±0.13 |
| CP4 | 3.1±0.07 | 3.2±0.03 | 0.38 | 102.4±0.3 | 99.68±0.41 |
| AZ50 | 3.1±0.10 | 3.1±0.04 | 0.45 | 101.2±0.4 | 99.13±0.83 |

**Table 4: Tableting properties of compression coated tablets.**

| Batch | Thickness[a] (mm) | Hardness[a] (kg/cm²) | Friability[b] (%) | Weight variation[c] (mg) | Drug content[d] (%) |
|---|---|---|---|---|---|
| H1 | 4.6±0.28 | 4.5±0.61 | 0.36 | 200±2.29 | 99.91±0.73 |
| H2 | 4.5±0.36 | 4.4±0.37 | 0.44 | 200±2.25 | 99.34±0.24 |
| H3 | 4.6±0.21 | 4.1±0.84 | 0.31 | 200±2.76 | 99.56±0.11 |
| H4 | 4.5±0.36 | 4.2±0.66 | 0.47 | 200±2.53 | 99.41±0.32 |
| H5 | 4.6±0.21 | 4.6±0.35 | 0.56 | 200±1.55 | 98.76±0.78 |
| H10 | 4.5±0.53 | 4.6±0.12 | 0.49 | 200±1.75 | 99.56±0.73 |

**Table 5:** Cumulative % drug released from CCT

| Time (hr) | H1 | H2 | H3 | H4 | H5 | H10 |
|---|---|---|---|---|---|---|
| 1 | 5.74±0.86 | 2.88±0.41 | 1.62±0.77 | 0.84±0.75 | 0.59±0.87 | 0 |
| 2 | 22.36±0.41 | 4.79±0.56 | 4.29±1.09 | 2.57±0.29 | 1.83±0.54 | 0.65±0.13 |
| 3 | 68.35±1.75 | 7.15±0.94 | 6.51±0.28 | 4.35±0.84 | 3.87±0.29 | 2.15±0.76 |
| 4 | 98.81±0.59 | 12.03±1.08 | 8.95±0.51 | 7.52±0.43 | 7.86±0.35 | 4.57±1.53 |
| 5 | | 97.65±0.43 | 84.67±0.49 | 9.08±0.75 | 8.53±0.87 | 5.61±0.89 |
| 6 | | | 99.54±0.83 | 97.95±0.67 | 11.46±0.39 | 7.23±1.25 |
| 7 | | | | 99.42±0.38 | 37.65±0.72 | 9.46±0.81 |
| 8 | | | | | 98.75±0.24 | 10.87±0.68 |
| 9 | | | | | | 13.56±1.85 |
| 16 | | | | | | 99.43±0.92 |

**Table 6:** Comparative dissolution profiles (mean±s.d., *n*=6).

| Time (hr) | H4 | CP4 | AZ50 |
|---|---|---|---|
| 0.25 | 0 | 73.13±0.54 | 76.27±0.81 |
| 0.50 | 0 | 99.52±0.86 | 99.97±0.19 |
| 1 | 0.84±0.75 | | |
| 2 | 2.57±0.29 | | |
| 3 | 4.35±0.84 | | |
| 4 | 7.52±0.43 | | |
| 5 | 9.08±0.75 | | |
| 5.25 | 71.62±0.24 | | |
| 5.50 | 90.15±0.58 | | |
| 6 | 97.95±0.67 | | |

**Table 7:** Stability studies of H4 formulation.

| Parameters | Initial | Accelerated | | Long term | |
|---|---|---|---|---|---|
| | | 3 M | 6 M | 3 M | 6 M |
| Thickness | 3.6±0.21 | 3.4±0.13 | 3.5±0.41 | 3.5±0.26 | 3.5±0.15 |
| Hardness | 5.2±0.18 | 5.1±0.32 | 5.2±0.19 | 5.2±0.42 | 5.2±0.63 |
| Uniformity in weight | 200±0.56 | 200±0.16 | 200±0.24 | 200±0.53 | 200±0.42 |
| Drug content (%) | 99.86±1.33 | 99.96±1.15 | 99.94±0.23 | 99.98±0.26 | 99.90±0.13 |

## Fourier Transformed Infrared Spectroscopy (FTIR)

Drug-excipient chemical interaction in H4 formulation was detected by FTIR and reported in Figure 5. The spectra of the pure drug sample indicated characteristic bands at 1595, 1639 and 1714 $cm^{-1}$ indicating hydrogen bonds and coordination bonds in SV and agreed with the earlier reports.[28] The optimized formulation H4 retains the characteristic bands of SV with no other additional bands indicating retention of the chemical identity of the drug and confirming the drug excipient's compatibility.

## Stability studies

Samples of optimized formulation were kept in hermetically sealed bottles stored at 30°C/70% RH for the long term and 40±2°C/75±5% RH for accelerated testing conditions in humidity chambers as per ICH guidelines for zone IV.[29,30] After every 3 and 6 Months (M), the samples were withdrawn from storage to evaluate the physicochemical characteristics and dissolution profile and compared using the similarity factor (*f2*).

**Table 8:** Dissolution profile of H4 tablets.

| Time (hr) | Cumulative % drug released | | | | |
|---|---|---|---|---|---|
| | Before storage | Accelerated | | Long term | |
| | | 3 M | 6 M | 3 M | 6 M |
| 1 | 0.84±0.75 | 0.79±0.35 | 0.86±0.52 | 0.81±0.65 | 0.78±0.97 |
| 2 | 2.57±0.29 | 2.63±0.31 | 2.42±0.85 | 2.69±0.23 | 2.51±0.17 |
| 3 | 4.35±0.84 | 4.46±0.75 | 4.11±0.57 | 4.51±0.24 | 4.33±0.77 |
| 4 | 7.52±0.43 | 7.68±0.41 | 7.39±0.47 | 7.74±0.13 | 7.12±0.44 |
| 5 | 9.31±0.75 | 9.74±0.84 | 9.17±0.16 | 9.46±0.46 | 9.75±0.49 |
| 6 | 97.95±0.67 | 97.13±0.42 | 97.20±0.46 | 97.75±0.56 | 97.48±0.97 |
| 7 | 99.42±0.38 | 98.73±0.47 | 98.59±0.66 | 98.74±0.51 | 98.26±0.84 |
| $f_1$ | | 7 | 6 | 9 | 3 |
| $f_2$ | | 64 | 76 | 80 | 73 |

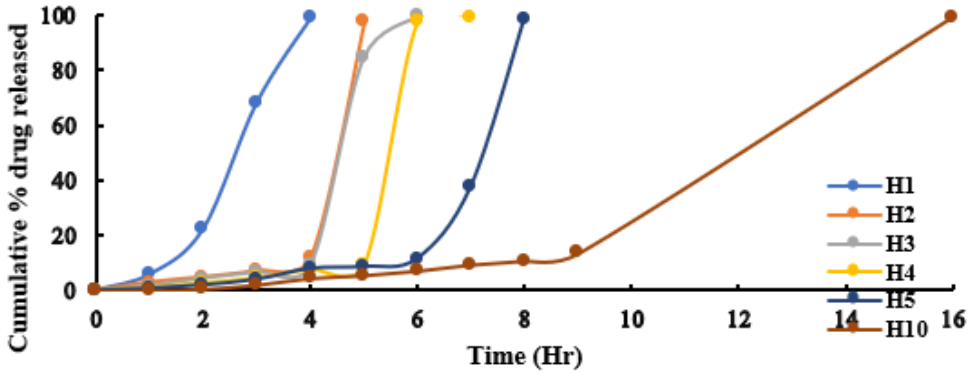


**Figure 2:** Dissolution profiles of CCT formulations.

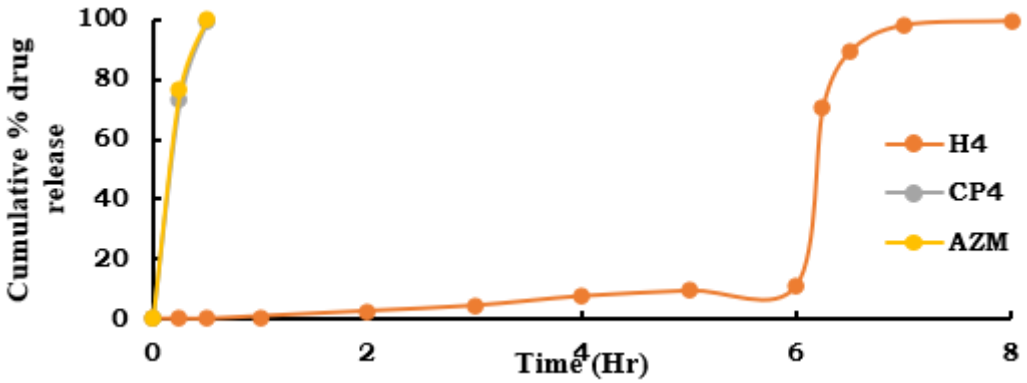


**Figure 3:** Comparative dissolution profiles of optimized compression coated tablets and core tablets.

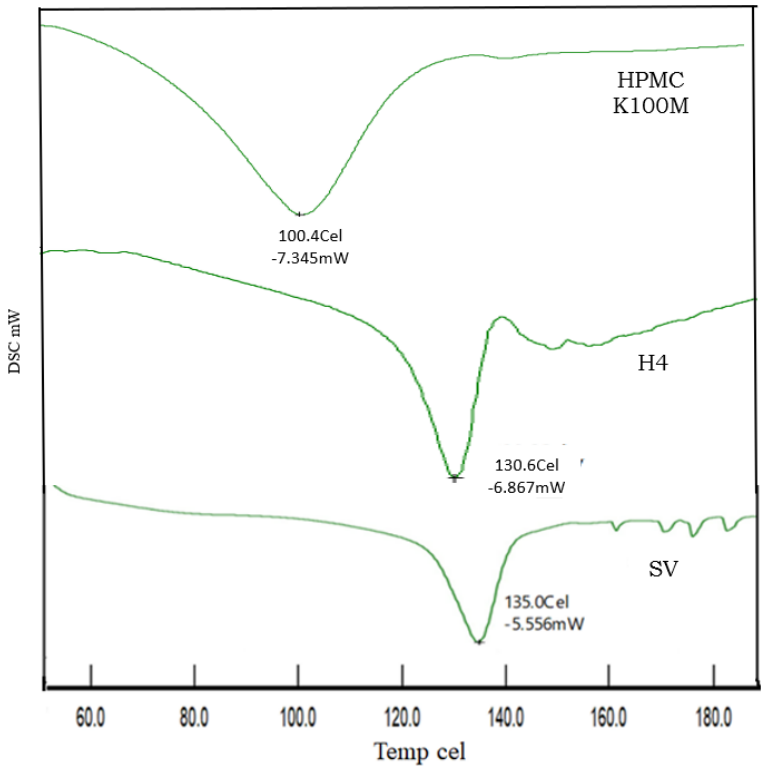


**Figure 4:** DSC thermogram of HPMC K100M, H4 formulation and pure SV.

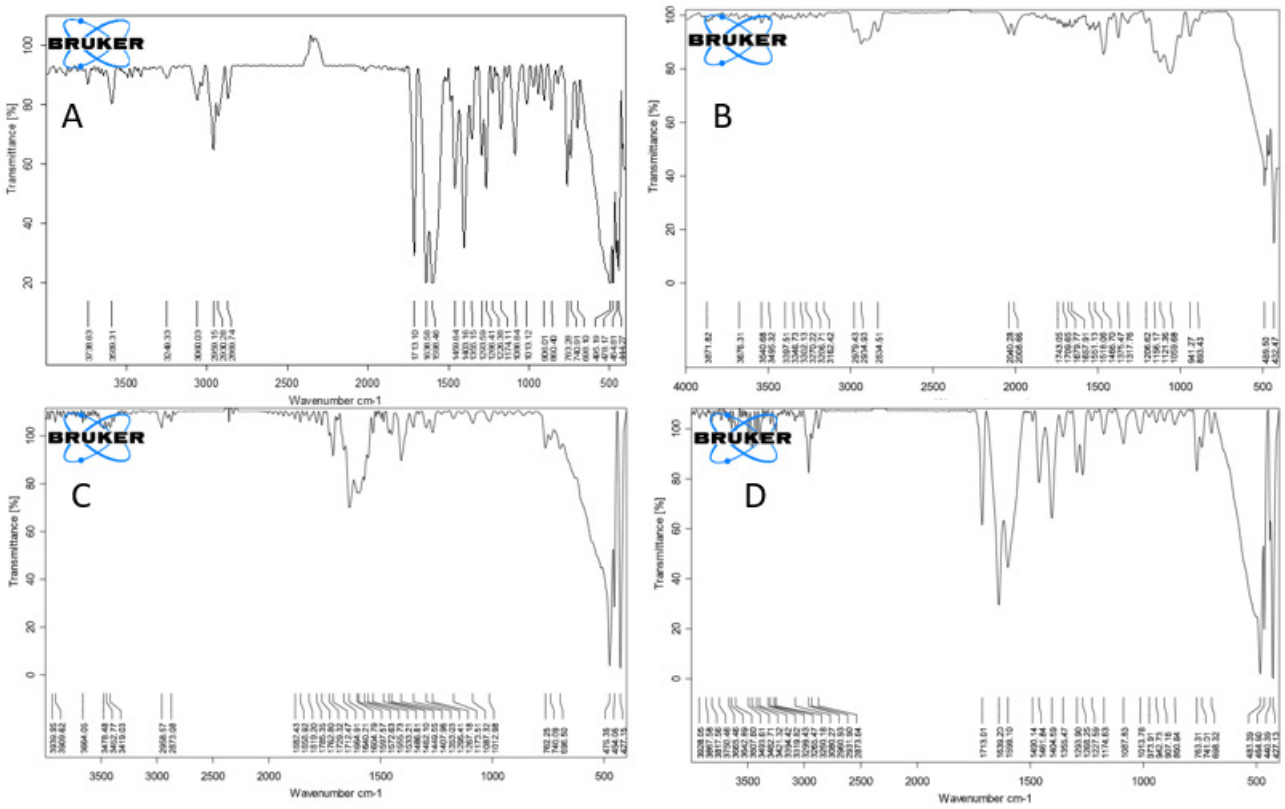


**Figure 5:** FTIR spectra (A) Pure drug (B) HPMC K100M (C) SV+HPMCK100M admixture (D) H4.

### Results of stability studies

The unaltered tableting properties of optimized CCT formulation H4 during storage in long term and accelerated stability conditions represented in Table 7 indicated that the formulation was stable. The cumulative percent drug release of H4 after Accelerated Stability (AS6M) and Long term Stability for 6 months (LS6M) were compared with fresh samples as shown in Figure 2 and the results were given in Table 8. Further Similarity factor (f2) was calculated for (AS6M), (LS6M) and found to be 84 and 91 respectively indicating no significant change in dissolution performance of drug product observed after storage.

## CONCLUSION

The development of chronotherapeutic drug delivery of sacubitril-valsartan of 24/26 mg strength by compression coating technique using semi synthetic polymer HPMC K100M has been reported for the 1st time in this investigation. The optimized formulation H4 developed from HPMC K100M and lactose in the ratio 2:3 achieved 5 hr lag time with maximum drug release within 1 hr after lag time to attain the required $C_{max}$ when the symptoms aggravated and helpful in the prevention of the sudden heart failure in patients with morning surge. Hence, the formulation was further studied for its *in vivo* behaviour to evidence it as a more effective and potential approach than other conventional treatments.

## ACKNOWLEDGEMENT

The authors are grateful to Prof. K. V. Ramana Murthy for his constant support and guidance and to Dr. Reddy's Labs Ltd., for providing SV.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**CCT:** Compression Coated Tablets; **IR:** Immediate release; **BP:** Blood Pressure; **SV:** Sacubitril-Valsartan; **ARNI:** Angiotensin Receptor Neprilysin Inhibitor; **OCT:** Optimized Core Tablets; **AS6M:** Accelerated Stability for 6 months; **LS6M:** Long term stability for 6 months.

## SUMMARY

This study developed a novel chronotherapeutic system for sacubitril-valsartan (24/26 mg) using HPMC K100M, that achieves a 5-hr lag time followed by rapid release to target morning surge in hypertensive patients. This system can be beneficial in reducing the rehospitalization and mortality rate in cardiac arrest. Further research regarding pharmacokinetics is needed to confirm the findings and address the potential for conventional treatments.

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**Cite this article:** Aleti R, Nijhawan M, Sailaja G. Formulation and Evaluation of Chronotherapeutic Delivery of Sacubitril Valsartan for Management of Hypertension. Indian J of Pharmaceutical Education and Research. 2025;59(2s):s473-s481.