RESEARCH PAPER

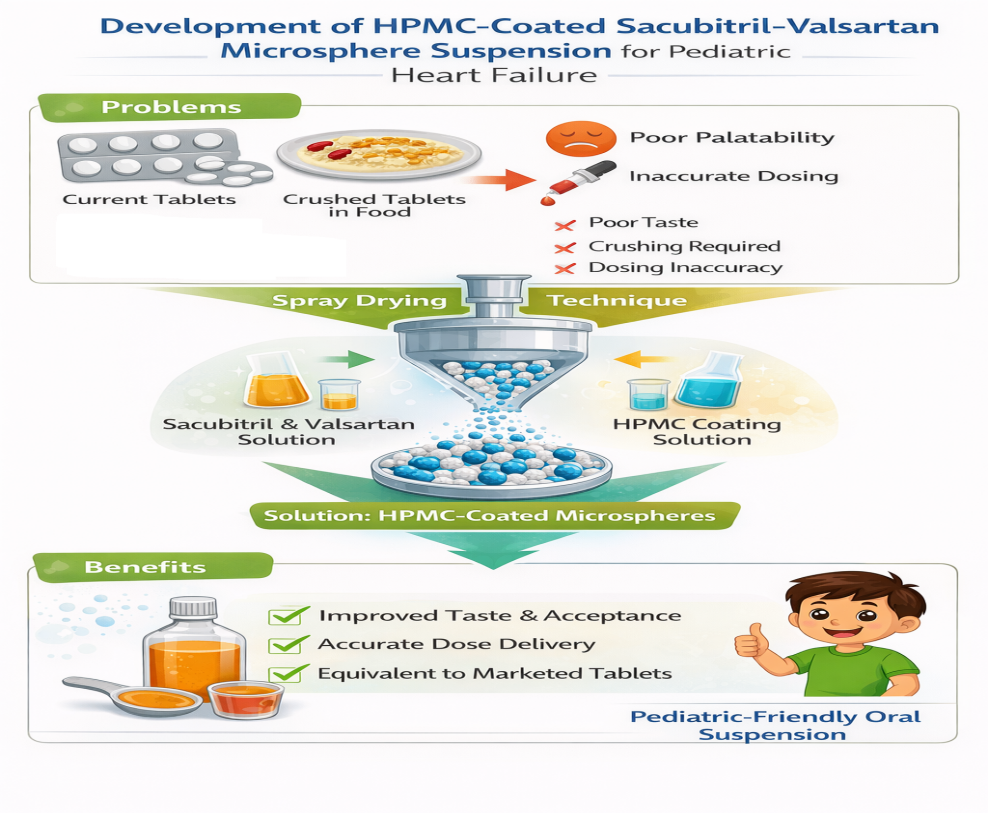
Development and Evaluation of Spray-Dried HPMC-Coated Sacubitril–Valsartan Microspheres for Oral Delivery in Pediatric Patients

Bhadri Sivaram[1], D. Ravi Sankara Reddy[2*]

[1]*Research Scholar, Department of Pharmaceutical Chemistry, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur (AP), India.*
[2]*Assistant Professor, Department of Pharmaceutical Chemistry, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur (AP), India.*

ABSTRACT
Sacubitril and valsartan are prescribed for symptomatic heart failure in pediatric patients, but currently marketed film-coated tablets require triturating and mixing with food before administration. This leads to poor acceptability and may compromise accurate dose delivery. To address this limitation, the present study plans to develop HPMC-coated sacubitril-valsartan microspheres via spray drying and to formulate them into a reconstituted oral suspension to demonstrate equivalence to the marketed products (F1 and F2) and to improve pediatric patient acceptance and accurate dose delivery.
Sacubitril, valsartan, and HPMC were dissolved in a hydroalcoholic system (water: ethanol, 80:20% v/v) at drug–polymer concentrations of 50–300 microgram per millilitre, where the solution was maintained at a temperature of 2-8 °C to minimise ethanol loss. The mixture was vortexed, then homogenised at 15,000 rpm, and subsequently spray-dried under optimised conditions. The microspheres were analysed for drug content, particle size, morphology, residual solvents, moisture content, and in vitro.
The formulations exhibited high encapsulation efficiency (50–70%) and produced spherical microspheres with a wrinkled surface. Particle size observed as D10 500 µm, D50 1120 µm, and D90 2280 µm, with a Z-average of 1300, a PDI of 0.298, and a Span of 1.58, as determined using a Malvern Zeta sizer. In vitro studies demonstrated enhanced drug release, influenced by the extent of polymer cross-linking.
100 mg of sacubitril and valsartan HPMC-coated microspheres (equivalent to 50 mg sacubitril and valsartan), Sucrose (477 mg), mannitol (339 mg), disodium edetate (8 mg), sodium metabisulfite (1 mg), HPC (7 mg), and orange flavour (70 mg) were added. To form a uniform blend, all components were mixed and sieved through a 24 mesh.
Conclusion: Spray-dried HPMC-coated microspheres showed favourable physicochemical properties and improved release behaviour, indicating their potential as a pediatric-friendly oral delivery system for sacubitril–valsartan therapy.
Keywords: Sacubitril, Valsartan, Spray drier, Microspheres, Zeta sizer, HPLC, SEM, Gas Chromatography, Karl Fischer titration, In vitro release
How to cite this article: Sivaram B, Reddy DRS., Development and Evaluation of Spray-Dried HPMC-Coated Sacubitril–Valsartan Microspheres for Oral Delivery in Pediatric Patients, Int J Drug Deliv Technol. 2026;16(6s): 193-204; DOI: 10.25258/ijddt.16.6s.25
Source of support: Nil.
Conflict of interest: None

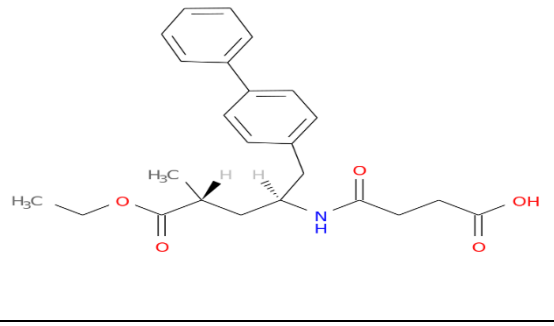
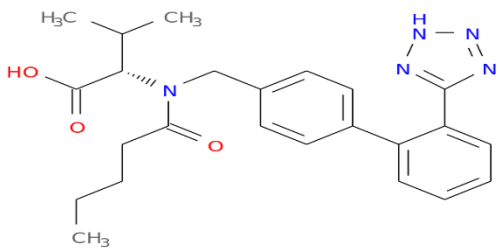
**Author for Correspondence: drsrpharma@gmail.com*



INTRODUCTION

Sacubitril and Valsartan are combination drugs usually recommended for symptomatic heart failure in children one year and older. This combination therapy enhances cardiac function when the heart cannot pump an adequate amount of blood. The cardio-renal benefits of this therapy arise from elevated concentrations of neprilysin-degraded peptides and natriuretic peptides, resulting from neprilysin inhibition by LBQ657 and from simultaneous angiotensin II inhibition by valsartan. Valsartan specifically blocks AT_1 receptors and also suppresses angiotensin II-mediated aldosterone release.[1]

Currently marketed formulations of sacubitril–valsartan are available mainly as film-coated tablets. For pediatric patients, these tablets must be triturated and mixed into food before administration, which leads to poor palatability, reduced acceptance, and a risk of inaccurate dose delivery.[2], [3]

	
Sacubitril	Valsartan

Sacubitril IUPAC Name is 4-{[(1S,3R)-1-([1,10 -Biphenyl] -4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl] amino}-4-oxobutanoic acid, and Valsartan is 3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazoyl5yl) phenyl] phenyl] methyl] amino]-butanoic acid.

Hydroxypropyl methylcellulose (HPMC)–coated sacubitril-valsartan microspheres were developed for oral delivery to protect against moisture, light, oxygen and acidic pH. Microspheres are spherical, small particles, typically 1-1000 µm (50 nm-2 mm) in diameter, and are suitable for oral administration, including in pediatric patients. The microspheres were developed, and the drug release was intended to be comparable to that of capsule formulations and marketed tablets.[4], [5], [6], [7], [8]

Spray drying is a scalable, energy-efficient, and highly controllable continuous manufacturing technique widely

used in pharmaceutical processing. Atomising the feed into a hot gaseous environment converts various solutions into nanosized particles, i.e., dried micron. Although spray drying has long been utilised in the food and chemical industries, its application has expanded to the pharmaceutical sector for the formulation of small-molecule drugs and, increasingly, biopharmaceuticals using carriers such as microspheres, microcapsules, and nanoparticles [9].

In this study, HPMC polymer was dissolved in a hydroalcoholic system (80:20 v/v) consisting of water and ethanol. The final drug–polymer concentration ranged from 50 to 300 mg/mL, and the solution temperature was kept at 2–8 °C to minimise ethanol evaporation. The mixture was vortexed for 30 minutes, then emulsified for 20 minutes by using a homogeniser at 15,000 rpm.

The resulting mixture was spray-dried using a spray dryer equipped with a fluid nozzle with a diameter of 0.6–1.2 mm and nozzle airflow (AF_nozzle) of 7–16 L/min. The cyclone airflow was kept up at 0.12 m³/min, while the cooling airflow (AF_cooling) continued closed. The feed solution (LF_feed) was delivered at 50–200 mL/min and atomised under an inlet airflow (AF_inlet) of 0.4–0.7 millicube per minute, with an inlet temperature of 50–80 °C (T_inlet). The final spray-dried powder was collected from the product receiver.

The crude microspheres were washed with approximately 500 mL of cold water (4 °C) three times, then centrifuged at 4000 rpm to remove the uncovered drug. The washed microspheres were freeze-dried for at least 48 hours under reduced pressure. Several spray-drying parameters were optimised to attain the desired product quality attributes.

The microspheres were characterised for surface morphology (SEM), particle size (Zetasizer), drug content (validated HPLC assay), residual solvents (headspace GC), moisture content (Karl Fischer titration), and in vitro dissolution (USP Type II)[10]. The formulations exhibited high encapsulation efficiency (50–70%) and produced uniformly spherical microspheres with wrinkled surface morphology. Particle size observed as D10 500 µm, D50 1120 µm and D90 2280 µm, Z average is 1300, PDI 0.298 and Span 1.58 by using Malvern Zeta sizer. In vitro dissolution studies demonstrated enhanced drug release, which was strongly influenced by the degree of polymer cross-linking[11], [12].

Overall, this study provides a systematic evaluation and fundamental understanding of HPMC-based microspheres loaded with sacubitril and valsartan produced by spray drying. These findings will support the development of both novel and generic microsphere formulations.

Materials and Methods

Sacubitril and valsartan sodium tablets 100 mg were purchased from a local pharmacy. Sacubitril and valsartan API gift sample provided by SK Traders, Hydroxypropyl methyl cellulose, Sucrose, mannitol, disodium edetate, sodium metabisulphite, HPC, and orange flavour were purchased from JJ Traders. Ethyl alcohol and HPLC solvents were purchased from Fisher Scientifics.

Methods

Preparation of microspheres by the spray drying technique

Using spray drying, Hydroxypropyl methylcellulose (HPMC)–coated sacubitril-valsartan microspheres were prepared. Sacubitril, valsartan, and HPMC were dissolved in a hydroalcoholic solvent system consisting of water and ethanol (80:20% v/v), with total drug–polymer concentrations ranging from 50 to 300 mg/mL. The solution was maintained at 2–8 °C to minimise ethanol evaporation. The mixture was initially vortexed and subsequently homogenised at 15,000 rpm to achieve a uniform dispersion prior to spray drying.[12], [13]

The resulting hydroalcoholic solution containing sacubitril, valsartan, and HPMC was spray-dried using a LU-228 laboratory spray dryer equipped with a bifluid nozzle (S-nozzle) with a diameter of 0.6–1.2 mm. The nozzle airflow rate (AF_nozzle) was maintained between 7 and 16 L/min. The cooling airflow (AF cooling) was turned off, and the cyclone airflow (AF cyclone) was set to 0.12 m³/min. Using an inlet airflow (AF inlet) of 0.4–0.7 m³/min, the feed solution was delivered at a flow rate (LF feed) of 50–200 mL/min and atomised. The temperature of the inlet (T_inlet) was maintained between 50 and 80 °C. The spray-dried microspheres were collected from the product receiver of the spray dryer.[12], [14]

The acquired spray-dried powders were then washed with approximately 500 mL of cold water (4 °C) and centrifuged at 4000 rpm to remove unencapsulated drug from the microsphere surface. This washing and centrifugation process was repeated seven times. The washed microspheres were then freeze-dried under decreased pressure for about 8 h to get free-flowing dry powders.

Placebo microspheres were also prepared by following the same basic formulation and processing conditions, excluding sacubitril and valsartan.

Preparation of the reconstitution dry suspension

100 mg of sacubitril and valsartan HPMC-coated microspheres (equivalent to 50 mg sacubitril and valsartan), Sucrose (477 mg), mannitol (339 mg), disodium edetate (8 mg), sodium metabisulfite (1 mg), HPC (7 mg), and orange flavour (70 mg) were added.

All components were mixed to attain a uniform blend. The final blend was passed through a 24-mesh sieve.

Figure: 01

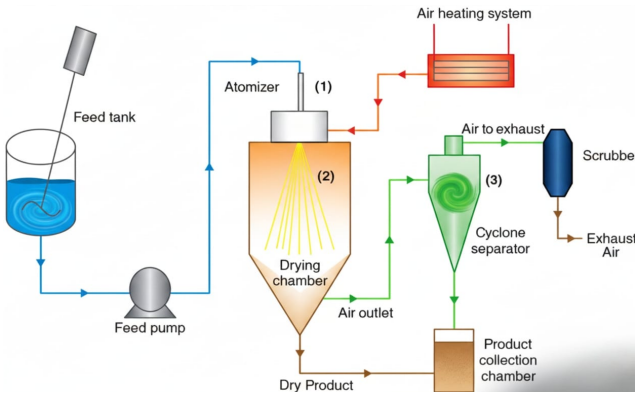


Figure: 02

Determination of content and Entrapment Efficiency

Sacubitril and valsartan loading was evaluated by executing a two-phase extraction followed by HPLC analysis. Initially, the drug-loaded HPMC microspheres (100mg) were dissolved in 100 mL of a 50:50 (v/v) dimethyl sulfoxide: methanol mixture by vortexing for 5 min. Subsequently, 2 mL of 10 mM KH_2PO_4 buffer of pH 6.2 was added, and the mixture was vortexed for an additional 5 min. Thereafter, the mixture was centrifuged at 4000 rpm for 5 min, and 1 mL of the aqueous phase was carefully collected for further analysis.

HPLC was carried out using a mobile phase of 10 mM KH_2PO_4 buffer with pH of 6.2 and acetonitrile (70:30, v/v) at a flow rate of 1.0 mL/min. The column temperature was maintained at 30 °C, and detection was at 254 nm. A Kromasil C18 column of (150 × 4.6 mm, 5 µm) was used. A calibration curve was prepared for each run. Encapsulation efficiency was calculated by the ratio of measured drug loading to the theoretical loading, and complete extraction was confirmed by recovery studies.[15], [16], [17], [18], [19]

$$\text{Content of Drug w/w\%} = \frac{A_T}{A_S} \times \frac{W_S}{\text{Dilution}} \times \frac{\text{Dilution}}{W_t} \times P$$

Where,

A_T = Peak area of the test preparation

As = Average peak area of the standard preparation.

Ws = Weight of Standard (mg)

W_t = Weight of sample (mg)

P = Potency of standard.

Related substance analysis

Sacubitril impurities were separated from the sacubitril-valsartan microsphere matrix by using a Waters X Bridge C18 column with 250 mm x 4.6 mm x 5 µm that was operated under gradient elution mode. The mobile phase consists of 10 mM disodium hydrogen phosphate buffer and acetonitrile, delivered at a flow rate of 1.0 mL/min. Detection was carried out at 278nm using a UV detector.

Water content

By using Karl Fischer (KF) titration, the residual water content in spray-dried microsphere formulations and in drug substances (sacubitril and valsartan) was determined. Approximately 200 mg of microspheres.[20]

$$\% \text{ of water} = \frac{V \times F}{W_T} \times 100$$

V = Burette reading for test preparation (mL).

F = K.F Factor (mg/ml)

W_T= Weight of sample used in Test preparation (grams)

Surface morphology

A scanning electron microscope (Nova Nano SEM 450) equipped with an Everhart–Thornley detector was used to examine the surface morphology of the microspheres. The obtained Images were acquired at an accelerating voltage of 5 kV, with a dwell time of 3 µs, a field-free working distance of 5.8 mm, and a spot size of 3.0. The chamber pressure was maintained at 1.50×10^{-2} Pa. The micrographs were acquired at 10,000× magnification with a 10 µm scale bar.[21], [22]

Determination of particle size distribution

A Malvern Zetasizer was used to determine the particle-size distribution of the microspheres. A 5% dextrose solution was used as the dispersant. The refractive index of the material was kept at 1.50. The absorption index was 0.01, while the dispersant RI was 1.33. Before measurement, the samples were equilibrated for 60 s. Particle size parameters, including D10, D50, D90, Z-average, polydispersity index (PDI), and span, were estimated.[23], [24]

$$\text{SPAN} : \frac{(D90 - D10)}{D50}$$

Determination of residual solvent

Residual solvent determination is an essential quality-control requirement for pharmaceutical microsphere formulations prepared with organic solvents. In the present study, the residual ethanol content in drug-loaded polymeric microspheres was estimated using gas chromatography (GC). Microsphere samples were accurately weighed, dissolved in a suitable solvent, and analysed by gas chromatography with a flame ionisation detector. Separation was achieved on a DB-624 column (30 m × 0.53 mm, 3 µm film thickness). Here, hydrogen was used as the carrier gas at a flow of 40 ml/min. The temperatures of injector and detector were maintained at 250 °C and 250 °C, respectively, with a split injection mode at a split ratio 2:0. Initially, the oven temperature was programmed at 40°C then hold for 2 min, followed by an increase to 80°C at a rate of 10°C/min and further the temperature is increased to 180°C at a rate of 20°C/min (hold for 2 min). The injection volume was 1 µL.[25], [26], [27]

Determination of the in vitro release profile

To obtain concentrations equal to sacubitril (24 mg/ml) and valsartan (26 mg/ml) in a final volume of 10 ml, the sacubitril and valsartan microspheres were reconstituted in water. 1.0 g of the reconstituted sample was accurately weighed, added to 900 ml of phosphate buffer with a pH of 6.8, and the mixture was subjected to in vitro dissolution testing using a USP type II (paddle) dissolution apparatus operated at 50 rpm. Samples of 10 mL were collected at 10, 15, 20, 30, and 45 min, and the withdrawn volume was replenished with an equivalent volume of fresh dissolution

medium maintained at a similar temperature. Using a validated HPLC method, the percentage release of sacubitril and valsartan was quantified.[6], [7], [10], [28], [29], [30], [31], [32]

$$\%\ \text{Release Drug} = \frac{A_T}{A_S} \times \frac{Ws.}{\text{Dilution}} \times \frac{\text{Media Volume}}{W_T} \times P \times \frac{1}{\text{L.C}} \times \text{Wt./mL} \times \text{Factor}$$

A_T = Peak area of the test preparation
As = Average peak area in standard preparation.
Ws = Weight of Standard in mg
W_t = Weight of sample in mg
P = Potency of standard.

$f1 : \frac{\sum_{t=1}^{n}(Rt - Tt)}{\sum_{t=1}^{n} Rt} \times 100$	$f2 = 50 \times \log\left[1 + \frac{1}{n}\sum_{n=1}^{n}(Rt - Tt)^2\right]^{-0.5} X\ 100$

- f_1 = Difference factor
- f_2 = Similarity factor
- R_t = % drug dissolved of reference product at time *t*
- T_t = % drug dissolved in the test product at time *t.*
- n = Number of dissolution time points

Acceptance Limits:
f_1 = 0–15 → Profiles are **similar**
f_1 > 15 → Profiles are **dissimilar**
f_2 = 50–100 → Dissolution profiles are **similar**
f_2 < 50 → Profiles are **dissimilar**

RESULTS AND DISCUSSION

Formulation	T inlet	C Feed	AF nozzle	Ratio A/L	S nozzle	T Feed	Drug (mg)	Polymer (mg)	Ethanol (mL)	H2O (mL)
F-1	80	20	10	4	1	4	400 (1:1)	1000	20	80
F-2	*60*	20	10	4	1	4	400 (1:1)	1000	20	80
F-3	*40*	20	10	4	1	4	400 (1:1)	1000	20	80
F-4	*20*	20	10	4	1	4	400 (1:1)	1000	20	80
F-5	80	*30*	10	4	1	4	400 (1:1)	1000	20	80
F-6	80	*10*	10	4	1	4	400 (1:1)	1000	20	80
F-7	80	*5*	10	4	1	4	400 (1:1)	1000	20	80
F-8	80	20	*6*	4	1	4	400 (1:1)	1000	20	80
F-9	80	20	*12*	4	1	4	400 (1:1)	1000	20	80
F-10	80	20	*18*	4	1	4	400 (1:1)	1000	20	80
F-11	80	20	10	*1*	1	4	400 (1:1)	1000	20	80
F-12	80	20	10	*3*	1	4	400 (1:1)	1000	20	80
F-13	80	20	10	*6*	1	4	400 (1:1)	1000	20	80

F-14	80	20	10	4	*0.5*	4	400 (1:1)	1000	20	80
F-15	80	20	10	4	*1.2*	4	400 (1:1)	1000	20	80
F-16	80	20	10	4	*2*	4	400 (1:1)	1000	20	80
F-17	80	20	10	4	1	*8*	400 (1:1)	1000	20	80
F-18	80	20	10	4	1	*16*	400 (1:1)	1000	20	80
F-19	80	20	10	4	1	*24*	400 (1:1)	1000	20	80

Formulation	Content		Water Content	Residual Solvent	Dissolution					PSD			
	Sacubitril	Valsartan			10 Min	15 Min	20 Min	30 Min	45 Min	D10	D50	D90	SPAN
F-1	58	63	0.56	156	18	34	61	78	98	654	1120	2280	1.45
F-2	48	54	3.2	6341	8	14	28	41	48	321	1532	3546	2.11
F-3	46	52	2.1	4201	13	29	58	69	89	673	1267	2875	1.74
F-4	53	60	0.61	345	16	39	64	76	94	586	1057	1864	1.21
F-5	56	67	0.21	237	23	46	69	86	99	872	1326	5421	3.43
F-6	39	43	2.4	4132	17	28	35	62	78	865	1635	3986	1.91
F-7	28	35	4.8	5876	21	28	28	71	86	912	1854	3601	1.45
F-8	53	56	0.45	145	28	34	41	58	67	254	1723	3921	2.13
F-9	59	59	1.76	3801	26	42	58	67	79	762	1494	3167	1.61
F-10	56	49	3.9	5109	19	37	43	67	94	823	1660	2409	0.96
F-11	64	61	1.2	2312	29	43	57	69	81	367	987	3467	3.14
F-12	32	47	0.96	3054	17	34	63	78	96	438	1061	2231	1.69
F-13	24	38	0.85	2739	9	17	36	72	99	665	1283	1965	1.01
F-14	61	67	0.45	562	12	28	54	78	94	498	1263	3241	2.17
F-15	65	61	0.21	825	16	37	57	71	99	761	1492	4109	2.24
F-16	71	64	0.32	289	10	26	54	76	89	843	1507	2347	1.00
F-17	51	56	0.76	1760	15	39	68	81	100	728	1209	3671	2.43
F-18	44	49	0.92	1295	24	35	48	77	98	156	942	1782	1.73
F-19	38	51	0.81	1848	3	16	23	46	54	469	1835	2643	1.18

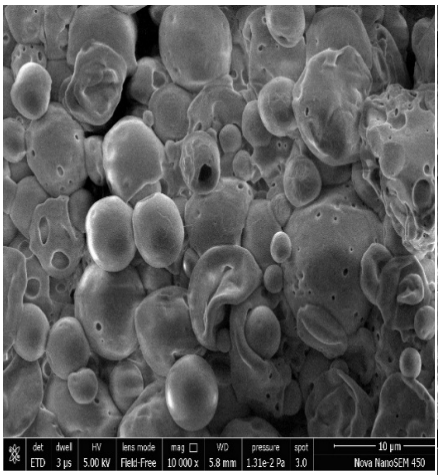


Figure 03

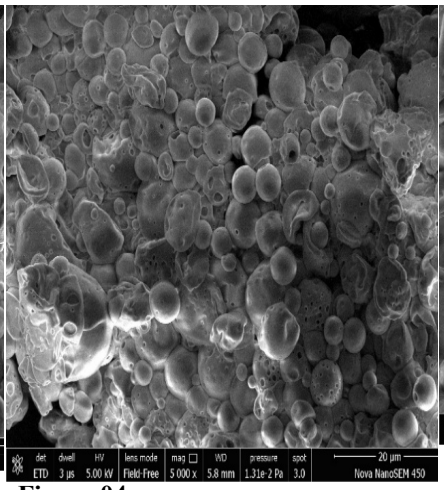


Figure 04

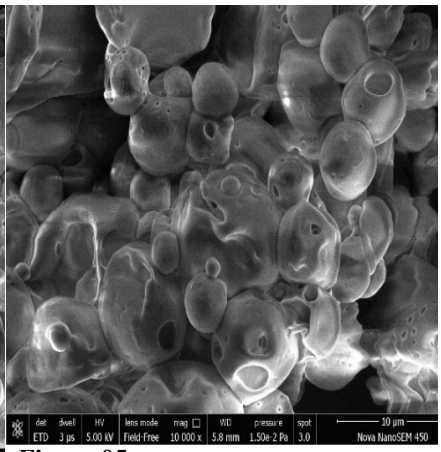


Figure 05

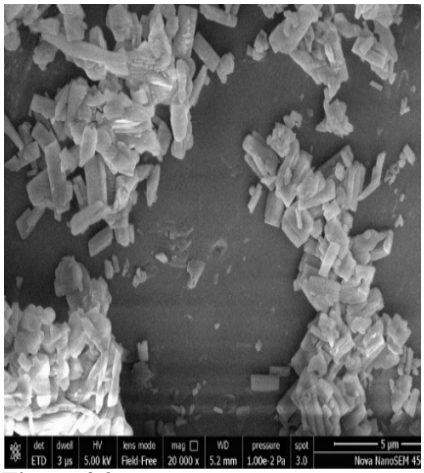


Figure 06

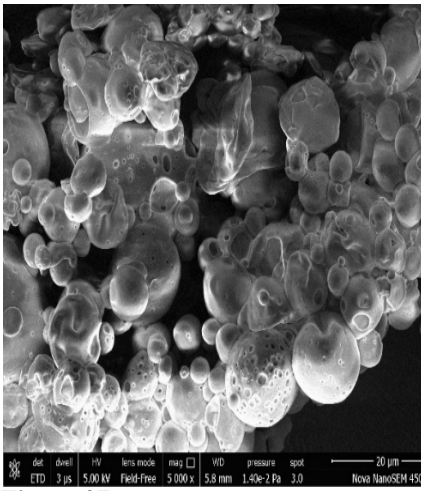


Figure 07

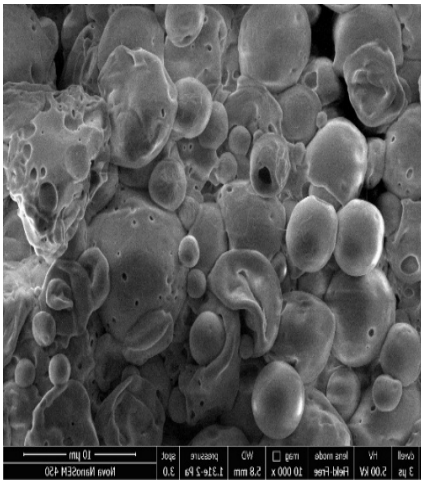


Figure 08

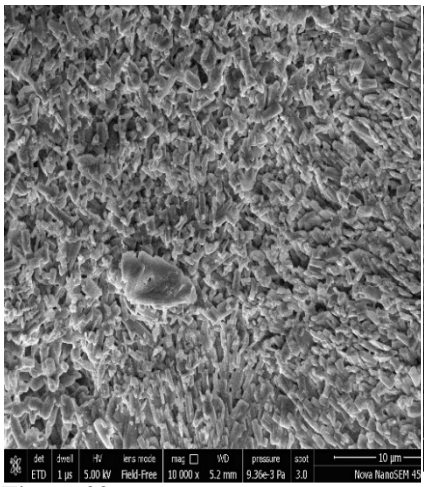


Figure 09

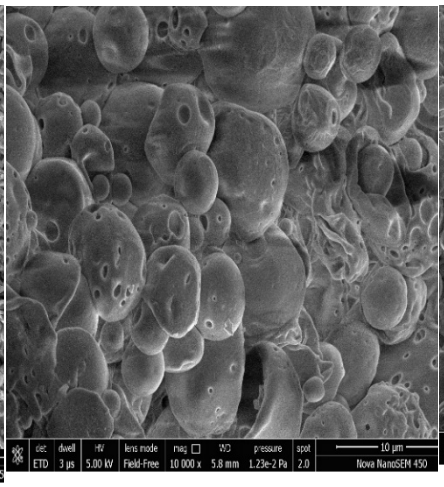


Figure 10

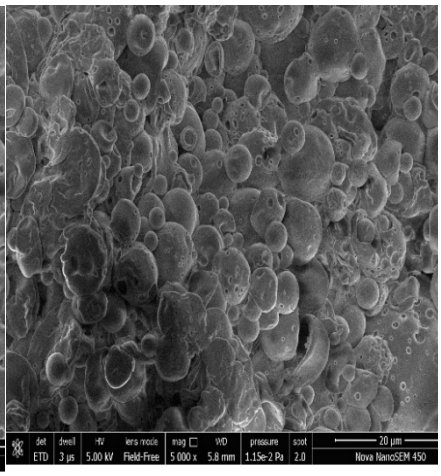


Figure 11

Particle Size Distribution

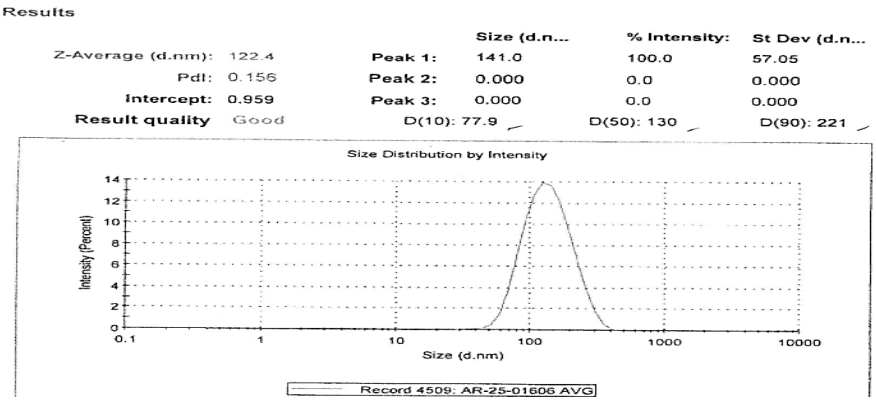
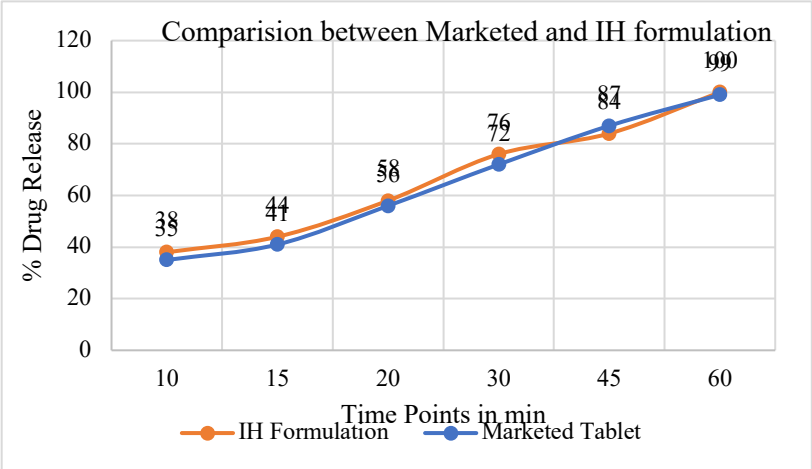
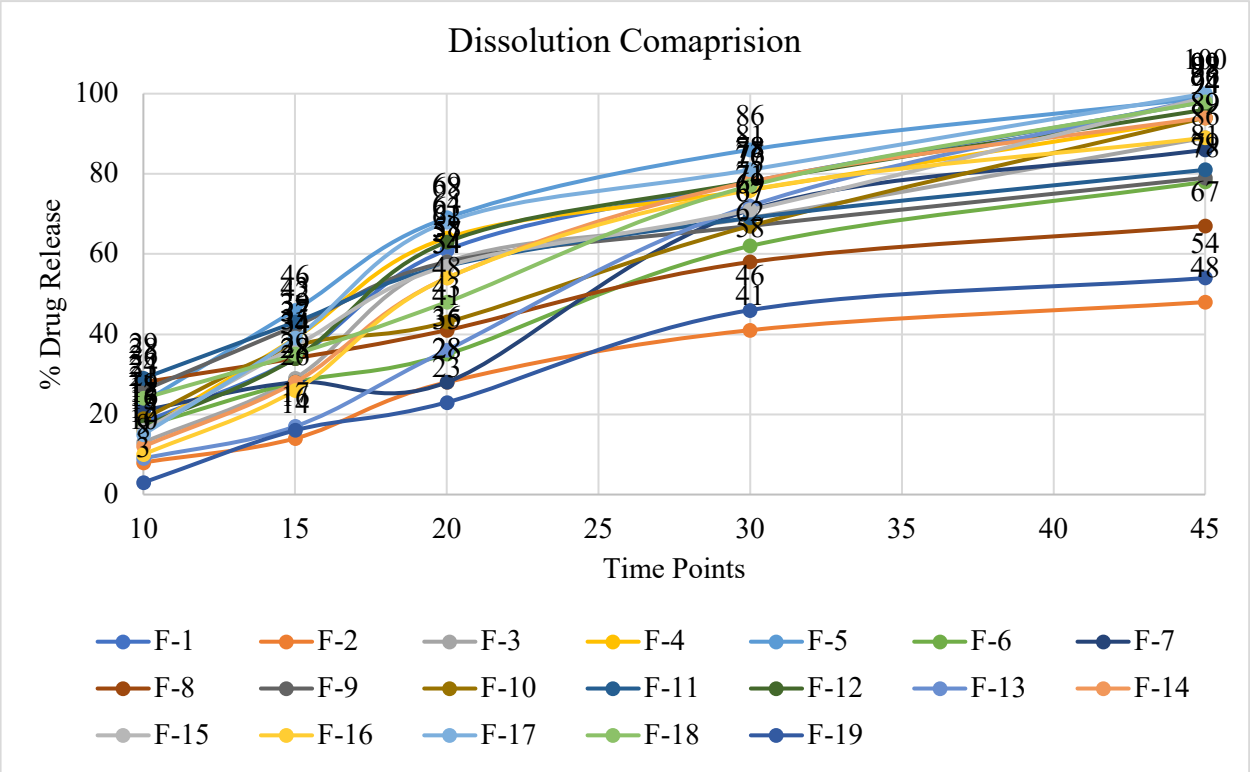
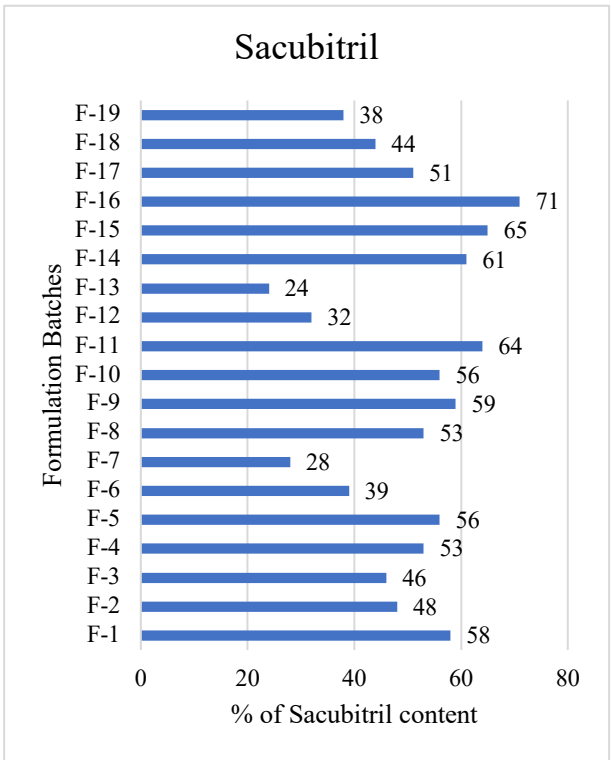


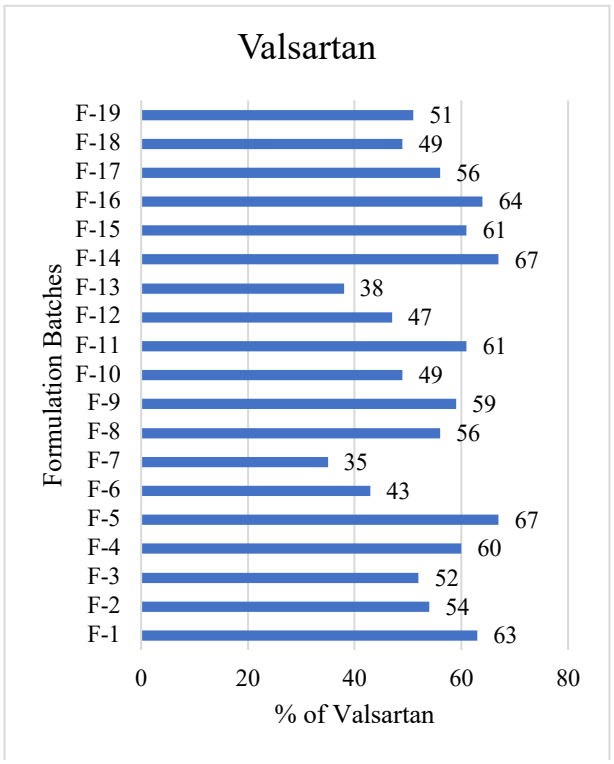
Figure: 09
Comparison between Marketed and IH Formulation

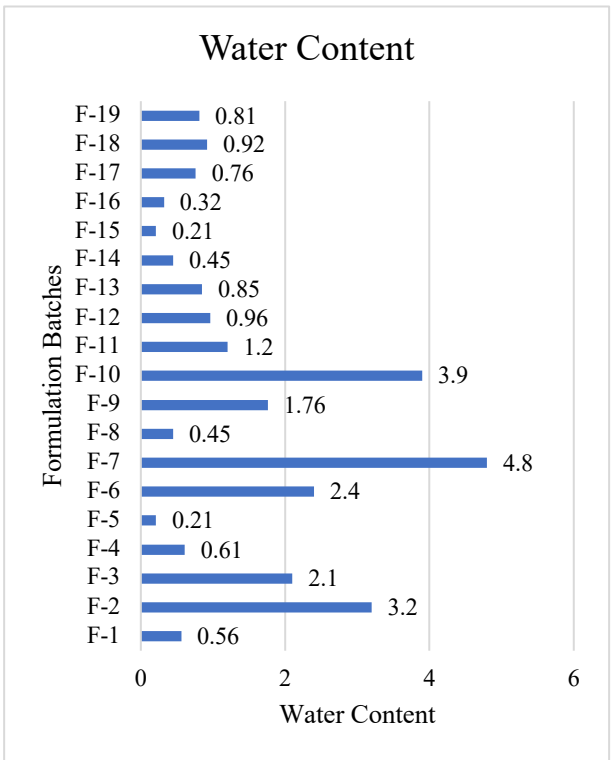


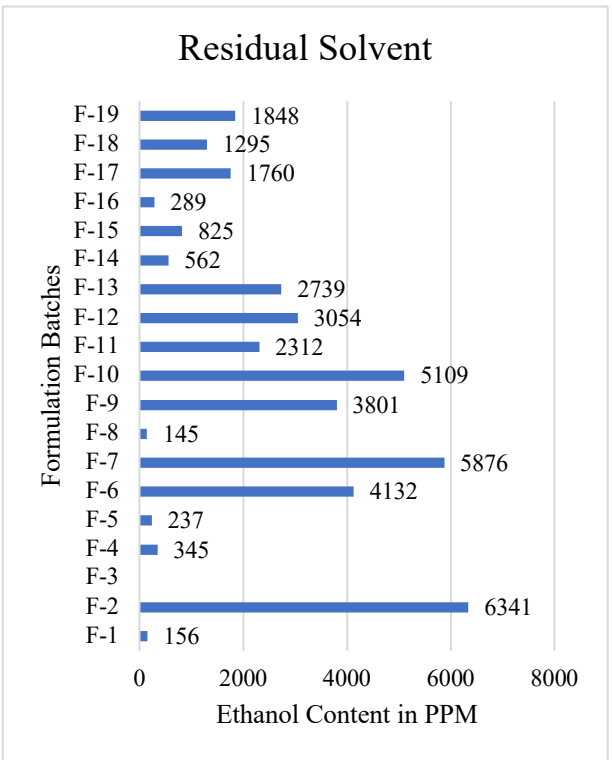


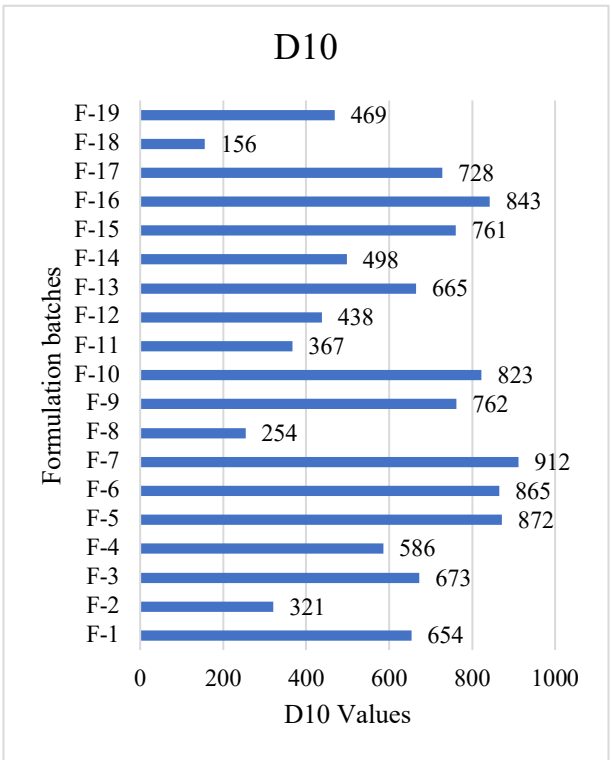
Author for Correspondence: drsrpharma@gmail.com

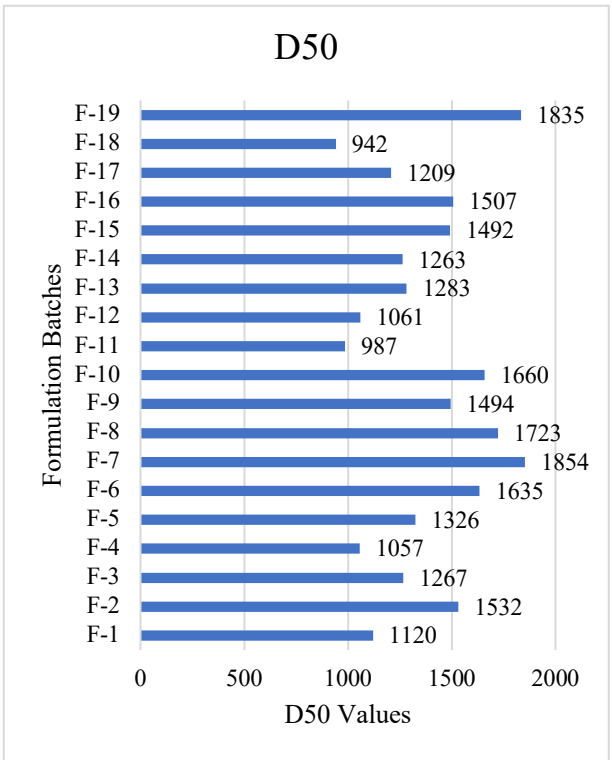

Sacubitril
Formulation Batches
F-19 38
F-18 44
F-17 51
F-16 71
F-15 65
F-14 61
F-13 24
F-12 32
F-11 64
F-10 56
F-9 59
F-8 53
F-7 28
F-6 39
F-5 56
F-4 53
F-3 46
F-2 48
F-1 58
0 20 40 60 80
% of Sacubitril content

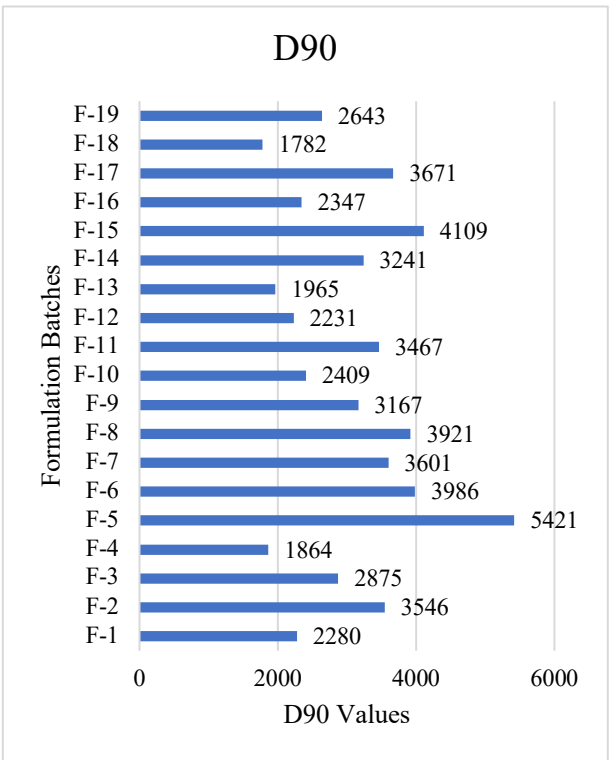

Valsartan
Formulation Batches
F-19 51
F-18 49
F-17 56
F-16 64
F-15 61
F-14 67
F-13 38
F-12 47
F-11 61
F-10 49
F-9 59
F-8 56
F-7 35
F-6 43
F-5 67
F-4 60
F-3 52
F-2 54
F-1 63
0 20 40 60 80
% of Valsartan

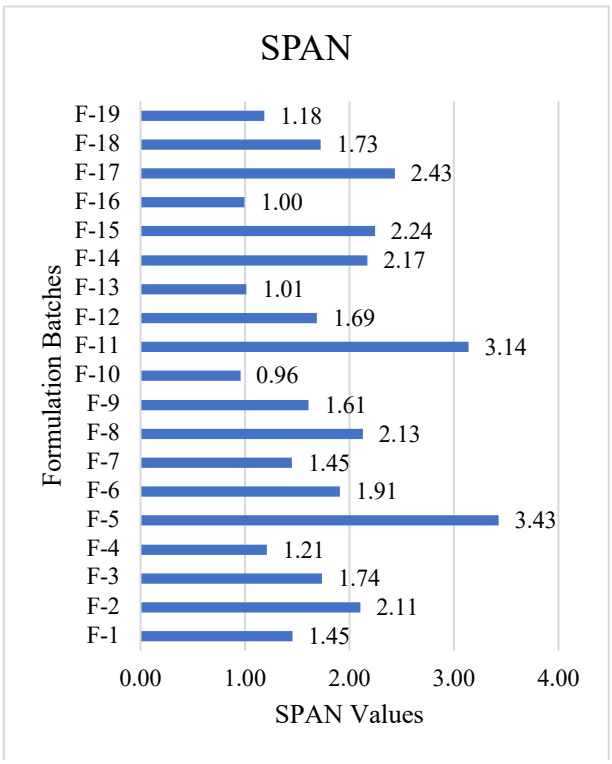

Water Content
Formulation Batches
F-19 0.81
F-18 0.92
F-17 0.76
F-16 0.32
F-15 0.21
F-14 0.45
F-13 0.85
F-12 0.96
F-11 1.2
F-10 3.9
F-9 1.76
F-8 0.45
F-7 4.8
F-6 2.4
F-5 0.21
F-4 0.61
F-3 2.1
F-2 3.2
F-1 0.56
0 2 4 6
Water Content


Residual Solvent
Formulation Batches
F-19 1848
F-18 1295
F-17 1760
F-16 289
F-15 825
F-14 562
F-13 2739
F-12 3054
F-11 2312
F-10 5109
F-9 3801
F-8 145
F-7 5876
F-6 4132
F-5 237
F-4 345
F-3
F-2 6341
F-1 156
0 2000 4000 6000 8000
Ethanol Content in PPM









Conclusion

HPMC-coated sacubitril and valsartan microspheres were developed using a spray-drying technique. The spray-drying process parameters were systematically verified and optimised by preparing trial batches at high and low levels of critical process variables that significantly influence microsphere quality. Key parameters such as inlet temperature, feed concentration, atomization airflow, nozzle size, and feed temperature were identified as critical, as they directly affect particle characteristics, drug loading, release behaviour, and residual solvent levels, including ethanol and moisture content.

The optimised spray-drying conditions produced the microspheres with desirable surface morphology, narrow particle size distribution, and satisfactory drug loading, along with negligible residual ethanol and moisture. While some trial batches exhibited either slower or faster drug release profiles, selected optimised formulations

demonstrated dissolution behaviour compared with the marketed product, as confirmed by difference (f_1) and similarity (f_2) factor analysis.

Finally, the optimised HPMC-coated sacubitril and valsartan microspheres were blended with a reconstitution oral suspension excipient in a 1:9 ratio to enhance palatability, improve pediatric patient acceptance, and ensure accurate dose delivery

REFERENCE

1. M. E. Katz, W. H. Frishman, and W. S. Aronow, "Sacubitril-Valsartan (LCZ696) in the Treatment of Systemic Hypertension: An Updated Review of Neprilysin Inhibition Combined with Angiotensin II Receptor Blockade," Cardiol. Rev., vol. 33, no. 5, pp. 437–440, 2025, doi: 10.1097/CRD.0000000000000648.
2. Copyright © 2000-2026 Drugs.com. All rights reserved., "Sacubitril and Valsartan: Package Insert / Prescribing Info," Drugs.com.
3. https://www.ema.europa.eu/en/about-us/about-website/legal-notice, "Entresto," An Official website of european union.
4. S. Chaurasia and B. Mishra, "Synthetic polymers as biomaterials for the treatment of colon diseases," in Advanced Drug Delivery Systems for Colonic Disorders, Elsevier, 2024, pp. 95–130.
5. A. Rai, R. K. Malviya, D. Patidar, K. Sharma, and V. Raj, "Formulation development and evaluation of gastroretentive delivery system (microspheres) using natural polymer.," Journal of Drug Delivery & Therapeutics, vol. 9, no. 4, 2019.
6. N. Venkateswaramurthy, R. Sambathkumar, and P. Perumal, "Design and evaluation of controlled release mucoadhesive microspheres of amoxicillin for anti Helicobacter pylori therapy," Asian Journal of Pharmaceutics (AJP), vol. 5, no. 4, 2011.
7. M. C. S. Subha, "Biodegradable interpenetrating polymer network hydrogel membranes for controlled release of anticancer drug," Asian Journal of Pharmaceutics (AJP), pp. 129–136, 2015.
8. S. Singh et al., "A Review on Microspheres and Its Role in Different Drug Delivery System as a Novel Approach," International Journal of Pharmaceutical Sciences, vol. 2, no. 6, pp. 1112–1126, 2024.
9. S. Indira, S. D. Ans, M. D. Amuthan, V. Gowsik, and V. Mahalekshmi, "MICROSPHERES: AN OVERVIEW ON, METHODS OF PREPARATION, CHARACTERIZATION AND PHARMACEUTICAL APPLICATIONS," 2023.
10. P. K. Gaur, S. Mishra, and M. Bajpai, "Formulation and evaluation of controlled-release of telmisartan microspheres: In vitro/in vivo study," J. Food Drug Anal., vol. 22, no. 4, pp. 542–548, 2014.
11. K. Bhalala, D. Jadeja, and K. Dudhat, "Microspheres: Preparation Methods, Advances, Applications, and Challenges in Drug Delivery," Biomedical Materials & Devices, vol. 4, no. 1, pp. 221–260, 2026, doi: 10.1007/s44174-025-00281-w.
12. S. Thakur, R. Kour, S. Kaur, and S. K. Jain, "Spray-Dried Microspheres of Carboplatin: Technology to Develop Longer-Acting Injectable with Improved Physio-Chemical Stability, Toxicity, and Therapeutics," AAPS PharmSciTech, vol. 23, no. 5, p. 128, 2022, doi: 10.1208/s12249-022-02281-1.
13. Y. Ma, K. J. Thurecht, and A. G. A. Coombes, "Development of enteric-coated, biphasic chitosan/HPMC microcapsules for colon-targeted delivery of anticancer drug-loaded nanoparticles," Int. J. Pharm., vol. 607, p. 121026, 2021, doi: https://doi.org/10.1016/j.ijpharm.2021.121026.
14. S. Bahri, N. Zerrouk, M.-A. Lassoued, N. Tsapis, J.-C. Chaumeil, and S. Sfar, "Préparation des microsphères de citrulline à ciblage colique par la technique de spray drying," Ann. Pharm. Fr., vol. 72, no. 2, pp. 132–140, 2014, doi: https://doi.org/10.1016/j.pharma.2013.12.002.
15. B. Sivaram and T. Shyam, "Stability-indicating RP-HPLC method development and validation for determination of sacubitril impurities in sacubitril and valsartan microsphere dosage form," NeuroQuantology, vol. 20, no. 9, p. 4969, 2022.
16. L. R. Snyder, J. J. Kirkland, and J. L. Glajch, Practical HPLC Method Development, vol. 64, no. 13. John Wiley & Sons, 1992. doi: 10.1021/ac00037a722.
17. T. H. Kumar, T. Banu, B. Ravindar, S. H. Rasheed, and N. Gajji, "Quantification of sacubitril and valsartan in tablet formulation by RP-HPLC method," Int J, vol. 1, pp. 10–16, 2021.
18. B. A. Moussa, H. M. A. Hashem, M. A. Mahrouse, and S. T. Mahmoud, "Experimental design approach in HPLC method development: application for the simultaneous determination of sacubitril and valsartan in presence of their impurities and investigation of degradation kinetics," Chromatographia, vol. 81, no. 1, pp. 139–156, 2018.
19. C. Vijaykumar, Y. R. Kumar, P. Aparna, and P. S. P. Rao, "Development and validation of a stability-indicating, single HPLC method for sacubitril–valsartan and their stereoisomers and identification of forced degradation products using LC–MS/MS," Biomedical Chromatography, vol. 37, no. 2, p. e5550, 2023.
20. J. Kay, R. Thomas, J. Gruenhagen, and C. J. Venkatramani, "Simultaneous quantitation of water and residual solvents in pharmaceuticals by rapid

headspace gas chromatography with thermal conductivity detection (GC-TCD)," J. Pharm. Biomed. Anal., vol. 194, p. 113796, 2021, doi: https://doi.org/10.1016/j.jpba.2020.113796.

21. H. Yoshizawa, S. Nishino, K. Shiomori, S. Natsugoe, T. Aiko, and Y. Kitamura, "Surface morphology control of polylactide microspheres enclosing irinotecan hydrochloride," Int. J. Pharm., vol. 296, no. 1, pp. 112–116, 2005, doi: https://doi.org/10.1016/j.ijpharm.2005.02.010.
22. X. Huang, J. Gao, W. Li, H. Xue, R. K. Y. Li, and Y.-W. Mai, "Preparation of poly(ε-caprolactone) microspheres and fibers with controllable surface morphology," Mater. Des., vol. 117, pp. 298–304, 2017, doi: https://doi.org/10.1016/j.matdes.2016.12.096.
23. P. Tian, X. Zhao, W. Liu, and J. Zhang, "Preparation and application of cross-linked PVA microspheres with narrow particle size distribution by suspension polymerization using uniform porous tube," React. Funct. Polym., vol. 171, p. 105153, 2022, doi: https://doi.org/10.1016/j.reactfunctpolym.2021.105153.
24. H. Yu, C. Zhou, L. Wang, C. Yang, S. Li, and W. Wang, "Enhancing optical performance of LED light diffusing plates through particle size and distribution control of organosilicone microspheres," Opt. Mater. (Amst)., vol. 151, p. 115317, 2024, doi: https://doi.org/10.1016/j.optmat.2024.115317.
25. O. Adetunji, S. Kaur, N. Wheeler, V. Nam, H. Shi, and P. Nam, "Monitoring residual solvents in pharmaceutical products using a portable pre-concentration GC-PID," J. Pharm. Biomed. Anal., vol. 249, p. 116327, 2024, doi: https://doi.org/10.1016/j.jpba.2024.116327.
26. J. Tian and A. Rustum, "Development and validation of a fast static headspace GC method for determination of residual solvents in permethrin," J. Pharm. Biomed. Anal., vol. 128, pp. 408–415, 2016, doi: https://doi.org/10.1016/j.jpba.2016.06.020.
27. M. S K et al., "Development of a green GC-FID method for residual solvent analysis in paliperidone nanocrystal formulations: Validation and greenness assessment," Talanta Open, vol. 12, p. 100520, 2025, doi: https://doi.org/10.1016/j.talo.2025.100520.
28. B. Jadach, A. Froelich, A. Tatarek, and T. Osmałek, "An overview of the methods used to increase the dissolution rate of meloxicam for oral administration," J. Drug Deliv. Sci. Technol., vol. 97, p. 105836, 2024, doi: https://doi.org/10.1016/j.jddst.2024.105836.
29. J. B. Eriksen, Z. Azimi, J. Milsmann, A. Bauer-Brandl, and M. Brandl, "Impact of prandial state on luminal and permeation-behavior of fosamprenavir oral suspension studied by in vitro tools: Solubility-, bioconversion- and permeation- studies in biomimetic media," J. Drug Deliv. Sci. Technol., vol. 90, p. 105170, 2023, doi: https://doi.org/10.1016/j.jddst.2023.105170.
30. S. S. Gaikwad, J. O. Morales, N. B. Lande, J. Catalán-Figueroa, U. D. Laddha, and S. J. Kshirsagar, "Exploring paediatric oral suspension development: Challenges, requirements, and formulation advancements," Int. J. Pharm., vol. 657, p. 124169, 2024, doi: https://doi.org/10.1016/j.ijpharm.2024.124169.
31. M. C. S. Subha, "Biodegradable interpenetrating polymer network hydrogel membranes for controlled release of anticancer drug," Asian Journal of Pharmaceutics (AJP), pp. 129–136, 2015.
32. R. Tao et al., "Recent advances in the design of controlled-and sustained-release micro/nanocarriers of pesticide," Environ. Sci. Nano, vol. 10, no. 2, pp. 351–371, 2023.