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Development, Optimization, And Characterization of Melt Sonocrystallized Agglomerates of BCS Class II Drug

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Abstract-The objective of this study was to improve the drug's solubility, dissolution rate, and processability properties. The selected BCS Class II drug, Valsartan, is widely employed in the treatment of hypertension; however, its limited solubility has posed significant challenges to its therapeutic efficacy. The melt sonocrystallization (MSC) technique was adopted, utilizing a probe ultra sonicator, with the sonication time (1, 2, and 3 minutes) and amplitude level (60%, 70%, and 80%) varied through a 3^2factorial design. Successful preparation of MSC agglomerates of Valsartan was achieved, exhibiting satisfactory yield and drug content. Evaluation of the MSC agglomerates exhibited significant enhancements in solubility and drug release compared to the pure valsartan. These improvements were attributed to the formation of porous agglomerates, resulting in improved micrometric properties. Complementary analysed through DSC and X-ray Diffraction confirmed a reduction in drug crystallinity with the increase in sonication time and amplitude. Moreover, FT-IR investigations verified the chemical stability of valsartan during the MSC process, ensuring the preservation of its chemical integrity. In conclusion, this study highlights the promising potential of melt sonocrystallization as a cost-effective approach to enhance the solubility, dissolution rate, and processability of BCS Class II drugs, exemplified by valsartan. The comprehensive insights provided herein offer valuable contributions to pharmaceutical formulation practices, potentially leading to optimized therapeutic efficacy and bioavailability of poorly water-soluble drugs.

Index Terms—Melt Sonocrystallisation Technique, Solubility, Dissolution Rate, Ultrasound, BCS

I. INTRODUCTION

The pharmaceutical industry has made significant strides in developing novel drug delivery systems to improve the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs, especially those falling under Biopharmaceutics Classification System (BCS) Class II. BCS Class II drugs are characterized by low solubility and high permeability, which present formidable challenges for effective drug delivery and formulation [1]. The physicochemical properties of drug crystals play a crucial role in the formulation process and therapeutic effectiveness of drugs. Various particle engineering techniques are employed to produce drug crystals with desired micrometric and biopharmaceutical properties. These methods focus on cost-effective standard formulations. Fine crystals are generally preferred for highly permeable and poorly soluble pharmaceuticals to enhance bioavailability [2]. However, fine crystals can pose challenges in the processability of solid oral dosage forms. Prior technologies that involve simultaneous crystallization and particle agglomeration include spherical crystallization, extrusion spheronization, melt solidification, spray drying, solution atomization, and crystallization by sonication [3]. These approaches positively contribute to improving BCS class II drugs by enhancing solubility and powder processing parameters for solid oral dosage forms [4].

Among the various approaches employed to enhance the dissolution properties of BCS Class II drugs, the concept of sonocrystallization has emerged as a promising technique [5]. Sonocrystallization, which involves the application of ultrasound energy during the crystallization process, has shown great potential in manipulating the crystal structure and particle size of drugs, leading to improved physicochemical properties. Melt Sonocrystallization (MSC), applies ultrasonic energy to a soft viscous or molten mass dispersed in a suitable medium at an appropriate temperature, with or without agitation during crystallization [6].

MSC has been used to achieve nucleation at moderate supersaturation during crystallization or terminal treatment, leading to deagglomeration and desired crystal formation. Previous studies have applied MSC to drugs such as ibuprofen, celecoxib, naproxen, and carbamazepine [7]. Valsartan, an antihypertensive drug with poor solubility, flow properties, and dissolution, has been the focus of various works aiming to enhance solubility using melt granulation and melt solidification techniques, and to improve compressibility using spherical crystallization techniques. The present study aimed to prepare and evaluate melt sonocrystallized agglomerates of Valsartan (MSC-Valsartan) to improve solubility, flow properties, and drug release [8].

II. MATERIALS AND METHODS

Valsartan was purchased from Aarti pharma, Bhandup (west) Mumbai 400078. All remaining chemicals utilized in the study were of analytical grade.

Preparation of Melt Sonocrystallized Agglomerates

The agglomerates were formulated using the melt sonocrystallization technique with amplitudes of 60%, 70%, and 80%. The sonication time was varied between 1, 2, and 3 minutes. The process involved melting (1 gram) of Valsartan in a beaker using an oil bath. The molten mass obtained was poured into a vessel containing (40 ml) deionized water, which was maintained at a constant temperature. The mixture was then sonicated at different amplitude and time levels using a probe sonicator. After solidification of the dispersed droplets, the resulting product was separated through filtration and dried at room temperature. The percentage of practical yield was determined [9].

Factorial Design

For the optimization of the formulated batches, a 3-level factorial design was employed using Design of Expert Software. This design involved evaluating two factors, amplitude (%) and sonication time (min), each at three different levels. As a result, experimental trials were conducted for all nine possible combinations [10].

III. CHARACTERIZATION

Percentage Yield

Prepared agglomerates were dried and weight was measured to determine the practical yield. The theoretical yield is based on the starting materials used. The percentage yield is then calculated [11].

Percentage Drug content

Precisely measured quantities of valsartan agglomerates were finely ground and dissolved in 100 mL of phosphate buffer at a pH of 6.8. The resulting solution underwent filtration to remove any insoluble particles. Subsequently, the filtered solution was appropriately diluted with phosphate buffer at the same pH. The concentration-adjusted solution was then subjected to spectrophotometric analysis using a Shimadzu UV Spectrophotometer (UV-1900i) at a wavelength of 250 nm [12].

Micromeritic properties

The bulk density and tapped density of both plain Valsartan and its MSC agglomerates, were measured. Carr's index and Hausner's ratio were calculated based on the bulk density and tapped density values. The angle of repose was determined using the fixed funnel method [13].

Saturation Solubility Study:

Saturation solubility studies of valsartan were conducted using five different solvents: distilled water, methanol, ethanol, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. Accurately weighed amounts of pure valsartan were introduced into separate 25 ml stoppered conical flasks, each containing 20 ml of the respective solvent. These sealed flasks were then agitated on an orbital shaker for 24 hours at a temperature of 37°C. After complete agitation, aliquots from each flask were filtered through Whatman filter paper, and the resulting filtrates were appropriately diluted and analysed using a UV Spectrophotometer at a wavelength of 250 nm. The same procedure was repeated for valsartan melt sonocrystallized agglomerates, and their absorbance values were also measured at 250 nm [14].

IR spectroscopy:

IR spectroscopy was used to characterize the prepared agglomerates of valsartan and to identify potential interactions and functional groups present in these agglomerates, in comparison to pure valsartan. The samples were dispersed in a KBr pellet and subjected to scanning using the Bruker Alpha II FTIR Spectrometer in the wavelength range of 4000 to 500 cm^{-1}[15].

X-ray Diffractometry (XRD):

X-ray diffraction patterns of both pure drug valsartan and the prepared agglomerates of valsartan were obtained using an X-ray diffractometer from Bruker Analytical Instrument Ltd., Germany. X-ray diffraction (XRD) is a technique used to analyse the crystallographic structure of materials by exposing them to X-ray radiation. When X-rays interact with the crystal lattice of a material, they undergo constructive and destructive interference, producing a diffraction pattern. This pattern is specific to the crystal structure and can be used to identify the crystalline phases present in the sample [16].

Scanning Electron Microscope (SEM):

The external morphology of both pure drug valsartan and the prepared agglomerates of valsartan was analysed using a Scanning Electron Microscope (SEM) model JEOL JSM 6360 from Japan [17].

Differential scanning calorimetry (DSC) analysis:

The thermal analysis of both pure drug valsartan and the prepared agglomerates of valsartan was conducted using a SDT Q600 V20.9 thermal analyser. For the analysis, accurately weighed samples of both the pure drug and agglomerates were placed in sealed aluminium pans. The samples were then subjected to controlled heating at a rate of 20°C per minute in the temperature range of 20°C to 300°C. During the heating process, a nitrogen flow rate of 20 ml/min was maintained to ensure an inert atmosphere [18].

In-vitro dissolution study

In-vitro dissolution studies were carried out using phosphate buffer pH 6.8 as the dissolution medium for a duration of 90 minutes. The experiments were conducted at a temperature of 37±0.5°C and a rotation speed of 50 rpm, employing a USP type II dissolution test apparatus. The volume of the dissolution medium was 900 ml. The samples were then filtered, suitably diluted, and analysed using a UV spectrophotometer at 250 nm [19].

Stability study

A stability study was performed on MSC Valsartan agglomerates, following ICH guidelines. The agglomerates were stored in a Petri dish with perforated foil at 40±0.5°C and 75±5% RH for 30 days. The evaluation was based on drug content analysis to assess the stability of the agglomerates [20].

IV. RESULTS AND DISCUSSION

Formulation of Agglomerates

In this work, 3-level factorial design was employed using Design of Expert Software for the optimization of formulated batches. An overlay plot indicated the most suitable combination of MSC Agglomerates of V9 batch, at sonication time about 3 min. and amplitude about 80% which shows 82.97% drug release and 98.88% drug content.

Percentage Yield

The agglomerates were dried and weighed to calculate the percentage yield, which varied from 89.10 ± 1.40 to 99.50 ± 0.82 w/w. The Table No. 1 presents the data for the percentage yield of all batches.

Drug content

In accordance with Table No. 1, the drug content was determined for all batches, ranging from 94% to 98%. The optimized MSC V9 batch showed a drug content of 98.88 ± 0.01%.

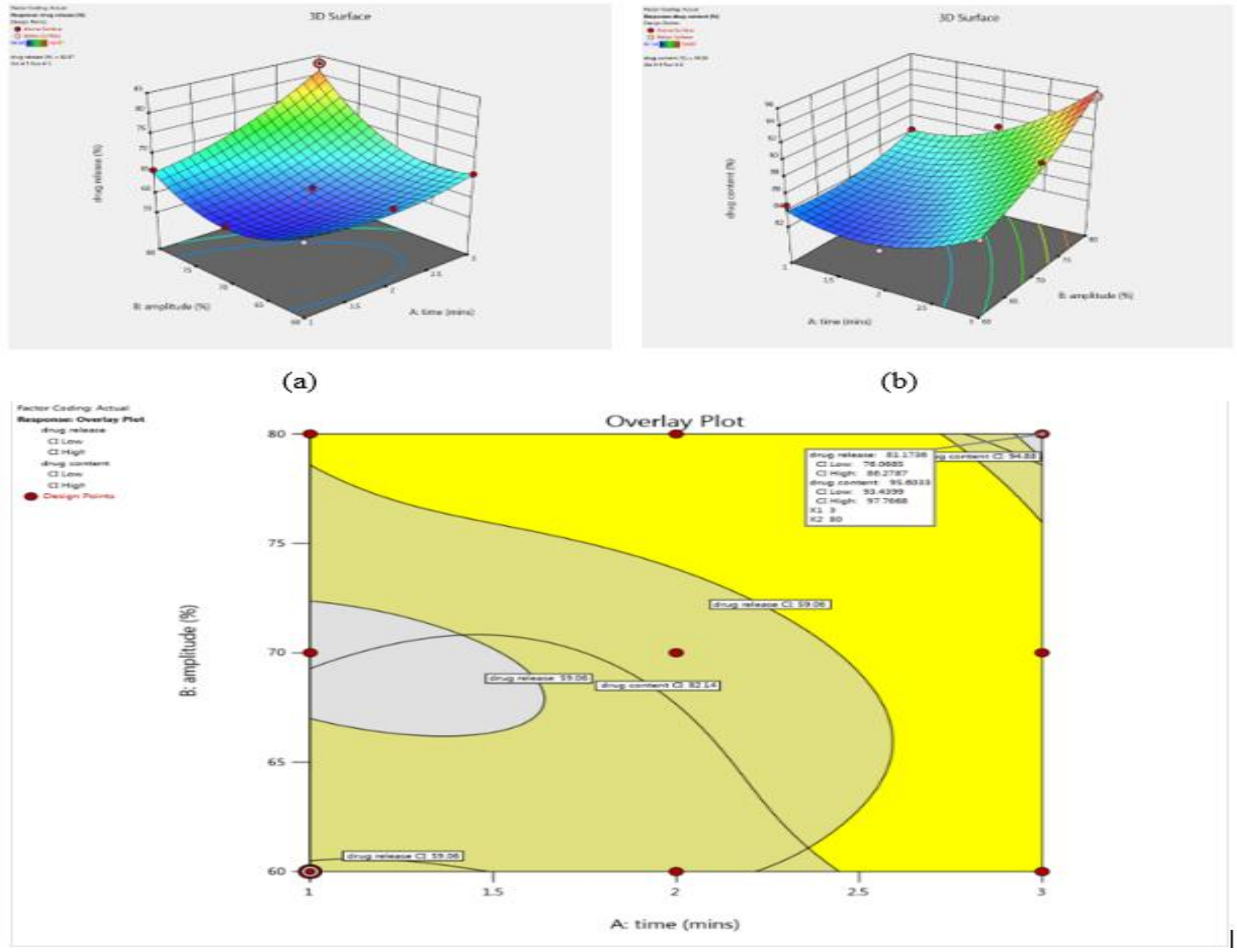


Figure No. 1: (a) 3D Graph for Drug Release, (b) 3D Graph for Drug Content, (c) Overlay Graph for Optimized Batch

Micromeritic properties

The flow properties of MSC agglomerates were assessed using various parameters such as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. The bulk density and tapped density results indicated good flow characteristics, with Carr's index ranging from 9.36±0.02 to 15.92±0.18. Hausner's ratio ranged from 1.103±0.02 to 1.189±0.01, indicating good flowability. In contrast, the drug itself exhibited less desirable flow properties, as evident from its higher Carr's index of 34.44±0.02 and Hausner's ratio of 1.525±0.01, likely due to the irregular shape of its crystals. The angle of repose for the pure drug was measured at 36.53°, while for MSC Valsartan agglomerates, it ranged from 19.12° to 26.28°, indicating good to excellent flowability.

Table No. 1: Micromeritic properties, Percentage Yield and Drug content

Batch Code	Bulk Density gm/ml	Tapped Density gm/ml	Hausner's Ratio	Carr's Index (%)	Angle of Repose (θ)	% Yield	% Drug content
Pure drug	0.453±0.03	0.691±0.02	1.525±0.01	34.44±0.02	36.53°±0.02	-----	----
V1	0.492±0.02	0.567±0.02	1.152±0.02	13.23±0.17	22.17°±0.02	89.10 ±1.40	94.65 ± 0.02
V2	0.623±0.01	0.741±0.01	1.189±0.01	15.92±0.18	20.56°±0.01	97.80 ±0.80	94.14 ± 0.23
V3	0.476±0.02	0.544±0.02	1.143±0.02	12.50±0.04	21.14°±0.01	98.70 ±0.53	96.62 ±0.1
V4	0.529±0.02	0.598±0.01	1.130±0.02	11.54±0.87	25.86°±0.02	96.90 ±0.36	97.21 ± 0.05
V5	0.584±0.01	0.668±0.02	1.144±0.01	12.57±0.71	23.65°±0.01	98.80 ±0.08	96.47 ± 0.14
V6	0.492±0.03	0.552±0.01	1.122±0.02	10.87±0.73	26.28°±0.02	99.10 ±1.81	95.93 ± 0.08
V7	0.625±0.03	0.725±0.01	1.124±0.01	11.03±0.62	22.78°±0.01	97.90 ±0.77	96.27 ± 0.03
V8	0.588±0.02	0.658±0.02	1.119±0.02	10.64±0.16	21.39°±0.02	93.80 ±0.94	95.96 ± 0.06
V9	0.523±0.02	0.577±0.01	1.103±0.02	9.36±0.02	19.12°±0.01	99.50 ±0.82	98.88 ± 0.01

Saturation Solubility

The findings from the solubility studies revealed that the pure form of Valsartan has notably lower solubility compared to the agglomerates of V9 batch obtained through the Melt Sonocrystallization process. Evidently, the solubility of MSC agglomerates showed a substantial improvement, with an observable increase in the sonication time and amplitude.

Table No. 2: Saturation Solubility

Sr. No.	Solvents	Solubility (mg/ml)	
		Pure valsartan	MSC V9 Batch
1	Water	0.024.1±0.02	4.31±0.07
2	PBS at pH 6.8	6.6±0.012	9.2±0.9
3	PBS at pH 7.4	5.2±0.05	7.2±0.04
4	Methanol	8.4±0.07	9.6±0.07
5	Ethanol	8.7±0.01	9.1±0.06

IR spectroscopy:

The spectrum of valsartan displayed characteristic peaks at 848.44 cm^{-1}, due to C–H aromatic bond, at 1205.71 cm^{-1}, due to C–N bonding, at 1516.77 cm^{-1}, due to C=C aromatic bond, at 1727.22 cm^{-1}, due to carboxylic acid, at 2879.23 cm^{-1}, due to presence of C-H aliphatic bond, at 1599.15 cm^{-1}, due to amine group.

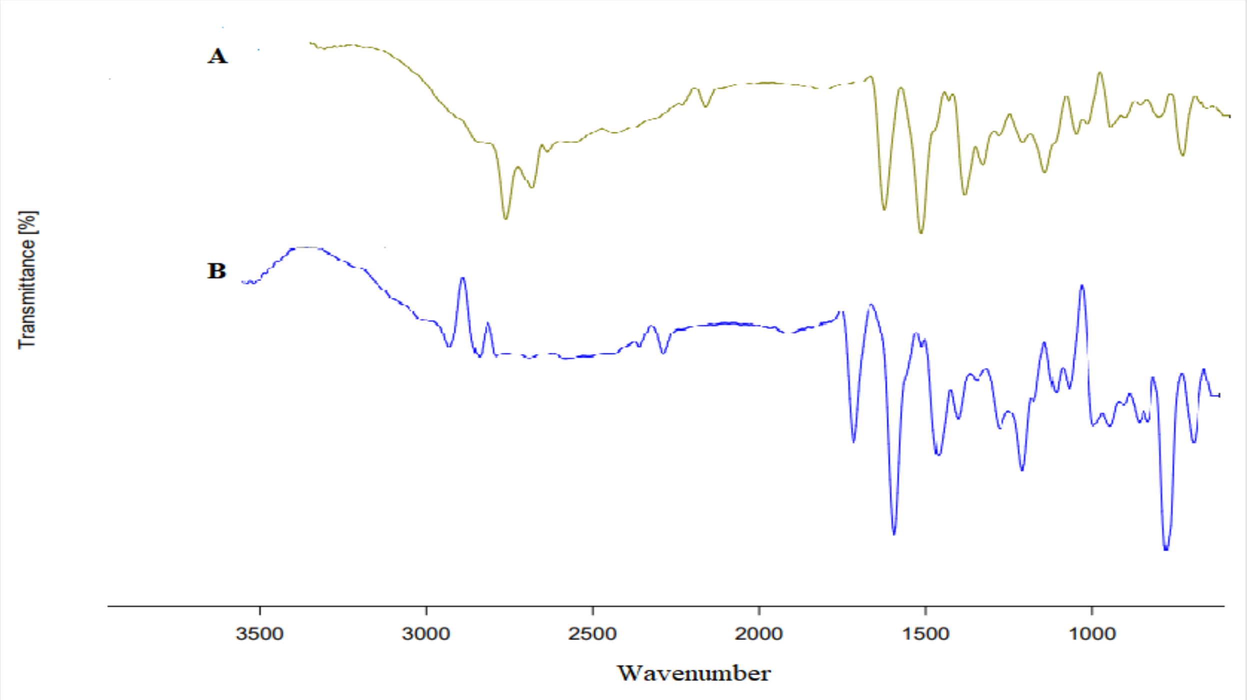


Figure No. 2: FTIR spectra of (A) MSC agglomerates of V9 batch; (B) Valsartan

The spectrum of MSC valsartan V9 batch displayed characteristic peaks at 834.88 cm^{-1}, due to C–H aromatic bond, at 1204.35 cm^{-1}, due to C–N bonding, at 1516.99 cm^{-1}, due to C=C aromatic bond, at 1727.85 cm^{-1}, due to carboxylic acid, at 2877.83 cm^{-1}, due to presence of C-H aliphatic bond, at 1608.85 cm^{-1}, due to amine group. In Comparison with the FTIR spectrum of pure drug valsartan, it was observed that there is a slight change in wavenumbers and peaks of MSC agglomerates of valsartan (V9 batch). The change is may be due to stretching and bending of drug as well as the procedure followed during formulation of melt sonocrystals.

In the optimised formula of MSC agglomerates, the drug spectra peaks are almost intact, showing that the general symmetry of the molecule is not greatly altered and demonstrating that there is no interaction between the formulation of the agglomerates and the pure drug. This finding strongly shows that the drug has not changed significantly in terms of its characteristics or even its formulation, and is still there in its usual form.

X-ray Diffractometry (XRD)

The XRD of the pure drug valsartan revealed strong peaks at specific angles (7.23°, 10.86°, 15.93°, 16.44°, 20.71°), indicating its crystalline nature. On the other hand, the MSC agglomerates of Valsartan exhibited less intense peaks of 2θ, (7.23°, 10.86°, 15.93°, 16.44°, 20.71°) suggesting partial amorphization or decrease in crystallinity or changes in crystal size and structure. These results imply that increased time and amplitude led to decreased crystallinity, possibly due to efficient sonication with water.

It is known that transforming from a crystalline state to a partial amorphous state can enhance drug's solubility and dissolution rate. Remarkably, the XRD pattern of the MSC agglomerates resembled that of the original drug crystals.

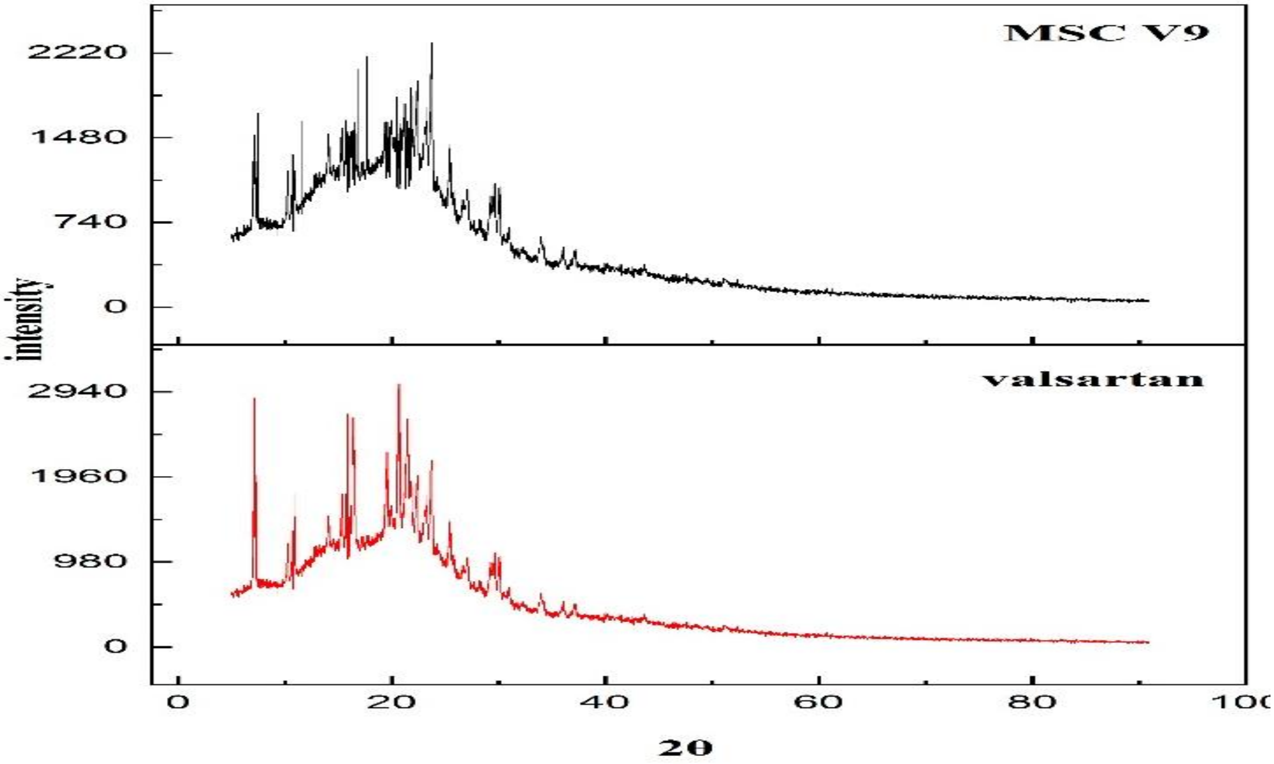


Figure No. 3: XRD of Valsartan and MSC agglomerates of V9 batch Differential scanning calorimetry (DSC) analysis

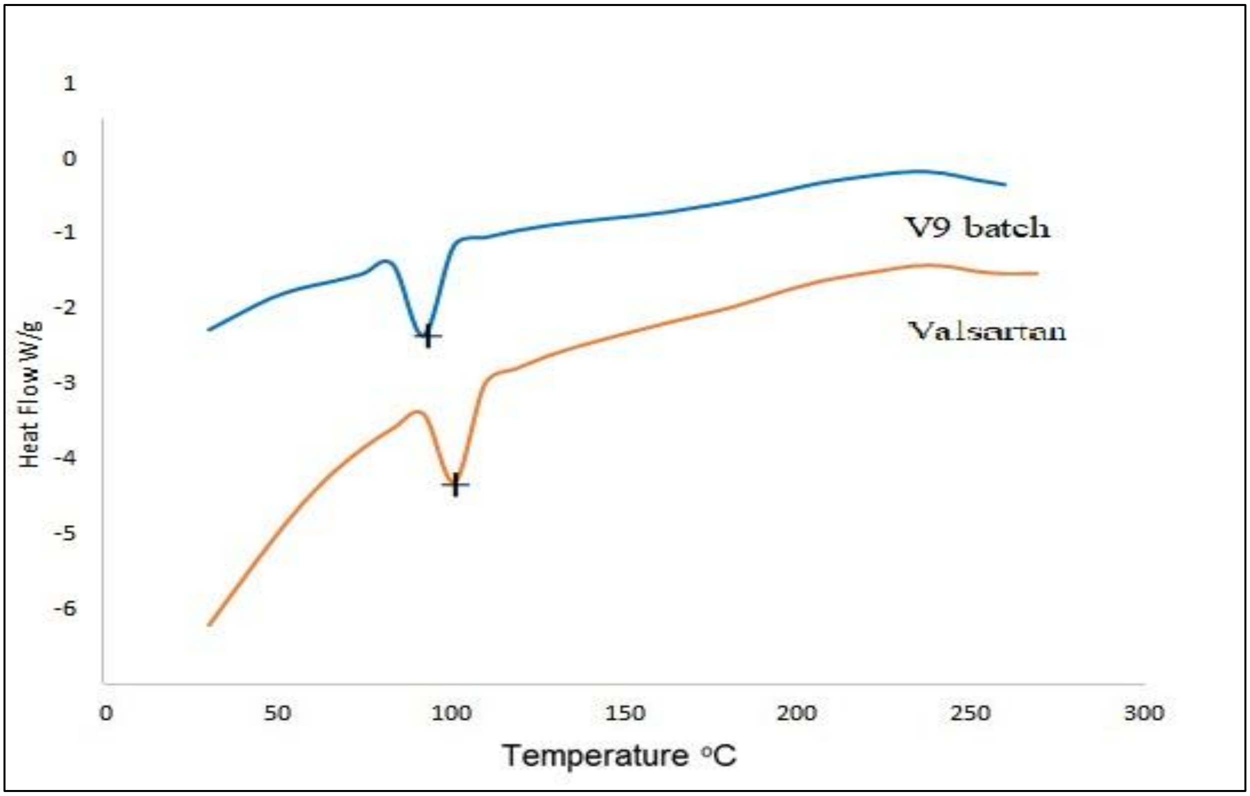
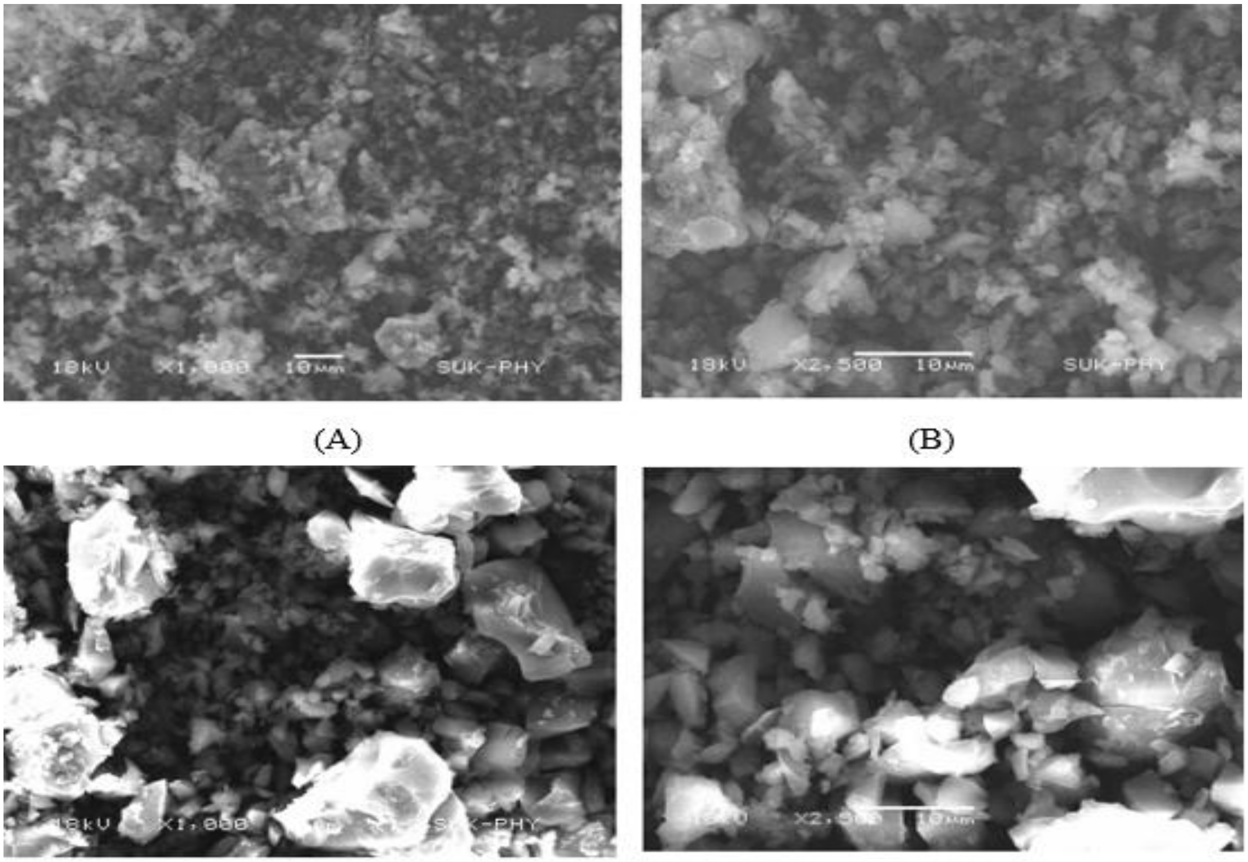


Figure No. 4: DSC analysis of Valsartan and MSC agglomerates of V9 batch

The DSC analysis of Valsartan and formulation batch V9 agglomerates, prepared using the melt sonocrystallization technique, was presented in figures 9.17 and 9.18. Valsartan exhibited a single sharp endothermic peak at 103°C (-4.929 W/g), as observed in the DSC thermogram of the samples. In contrast, batch V9 agglomerates displayed an endothermic peak at 101°C. The agglomerates in the MSC form of the drug showed a slightly broader endothermic peak, coinciding with a decrease in heat flow (-3.213 W/g). The alteration in the endothermic peak and heat flow can be attributed to the amplitude and sonication time utilized during the preparation process, as well as the presence of a distinct crystal structure in the agglomerates. These results suggest that the drug material remained unaffected by hydration during the particle crystallization in the aqueous medium.

Scanning Electron Microscopy:

Scanning electron microscopy (SEM) was employed to examine the morphological features of both the drug and the formulated agglomerates. The SEM images of valsartan and batch V9 agglomerates were presented in fig. no. The findings from all MSC agglomerate batches consistently revealed the formation of agglomerates with rough surfaces, cracks, and irregular shapes, resulting in a diverse range of particle sizes and size enlargement, in contrast to the pure drug valsartan.



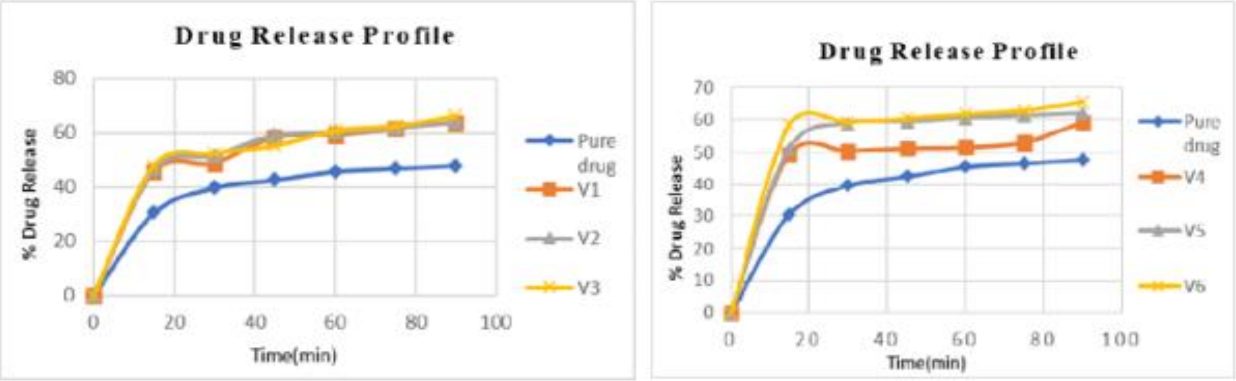
(A) (B)

(C) (D)

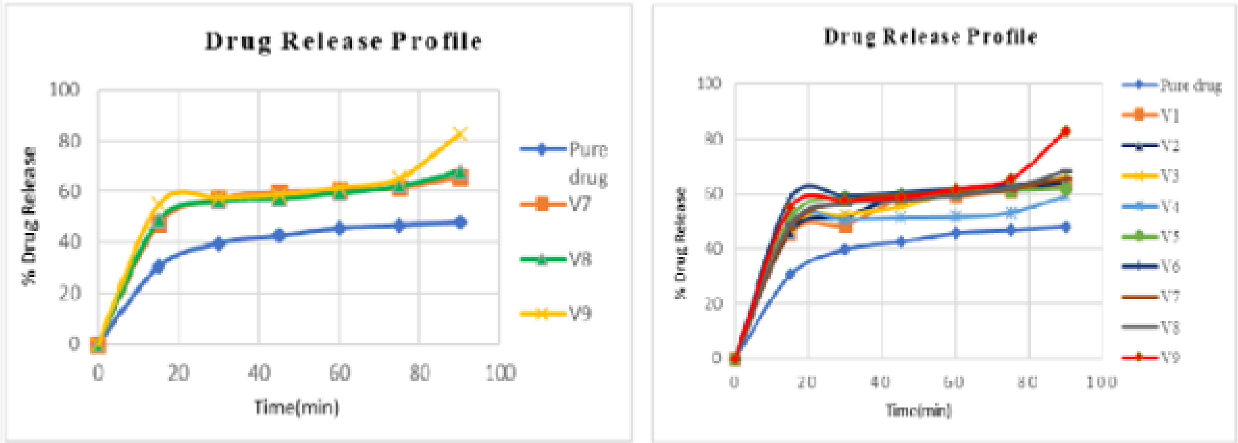
Figure No. 5: SEM images of (A), (B) pure drug valsartan, (C), (D) MSC agglomerates of V9 batch

In-vitro dissolution study

The drug release from MSC Valsartan agglomerates was found to be 82%, whereas pure drug only showed a 47% release in the same time period. The agglomerated form of Valsartan exhibited a faster drug release compared to the native drug, likely due to the increased drug surface area in the agglomerated form and smaller size.



(A) (B)



(C) (D)

Figure No. 6: %DR profiles of pure drug and MSC agglomerates at (A) 60% amplitude, (B) 70% amplitude, (C) 80% amplitude for sonication times of 1, 2, and 3 minutes
(D) V1-V9 batches at 60%, 70%, 80% amplitude

Stability Study

The stability study of the agglomerates of valsartan, as presented in Table No. 3, revealed no significant change in the drug content. This indicates that the prepared agglomerates of valsartan demonstrated satisfactory stability, meeting the regulatory requirements.

Table No. 3: Drug content of valsartan agglomerates after stability study

Batch Codes	0 Days	15 Days	30 Days
V9	94.88 ± 0.01	93.91 ± 0.05	92.88 ± 0.03

V. CONCLUSION

Melt sonocrystallization was successfully utilized to prepare irregular agglomerates of Valsartan with a rough surface and porous structure, leading to improved micrometric properties. These agglomerates exhibited enhanced solubility and dissolution rate compared to the pure drug. Consequently, it can be inferred that the agglomerates prepared using the melt sonocrystallization technique have the potential to serve as a reliable and effective method for improving processability parameters and enhancing the drug's solubility and dissolution properties.

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