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DESIGN, DEVELOPMENT AND EVALUATION OF STABLE VALSARTAN NANOCRYSTALS WITH CHITOSAN USING MICROWAVE-ASSISTED GRINDING NANOTECHNOLOGY

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Keywords:

Microwave Assisted Grinding Nanotechnology (MAGN), Chitosan, Valsartan, Neusiline, Factorial Design

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ABSTRACT: Solubility and stability are the limiting steps for almost all drugs in the pharmaceutical field toward bioavailability. In the present investigation, microwave reacts with the crystallization solvent to change their crystalline state to stable and highly soluble nanocrystals. Microwave Assisted Grinding Nanotechnology (MAGN) was used to prepare stable nanocrystals of Valsartan, BCS class II, by treating them with Chitosan and neusiline US2. Ternary crystalline particles were designed using 3^2 level full factorial design using Design Expert Software version 12. The optimized batch showed a nano-size range with about a 3.2 times increase in saturation solubility and 2.89 times enhanced cumulative drug release than pure valsartan. Compatibility with excipients, crystallinity and particle size study was confirmed from FTIR, DSC, XRD, and particle analyzer. Physical interactions from FTIR and NMR results also confirmed intermolecular hydrogen bond interaction. The accelerated stability study showed a confirmed stable product due to the absence in any interactions from FTIR and variation of drug content. Formulation of microwave-treated nanocrystals is a novel technique to enhance bioavailability with improved solubility and stability.

INTRODUCTION: Conversion of the drug into a crystalline state and its stabilization without affecting the chemical structure by losing energy to the surrounding is a thermodynamically spontaneous process [1, 2]. The bioavailability of crystalline drugs is dependent upon dissolution rate in a biological fluid, absorption into the blood, and physicochemical and micromeritic properties [3]. Many drugs in the pharmaceutical field belong to Class II in Biopharmaceutical Classification System due to the problem of solubility and dissolution rate of crystalline nature.

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The amorphous nature of the drug might help enhance solubility and dissolution rate but difficult to stabilize the formulation due to the high amount of surface free energy [4–6]. Thus pharmaceutical solids face the problem of solubility in the crystalline phase and stability in size-reduced amorphous formulations [1]. Crystal engineering is one of the novel techniques used to alter crystal habit into a metastable or amorphous form.

Many researchers worked on crystal engineering by using different methods like micronization [7, 8], nanonization [9, 10], co-crystallization [11–13], polymeric dispersion, Spherical crystallization, *etc* [14]. Microwave Assisted Grinding Nanotechnology (MAGN), a newly introduced technique in crystal engineering, shows the interaction between crystalline particles and waves to stabilize the nature of solids. Microwave, a spectrum of

electromagnetic radiation ranging from 1mm to 1m, is used for dielectric heating in industrial applications. This radiation may affect the solvent of crystallization of solids which will change the physical interaction between crystals and thus crystalline properties [14].

Valsartan (VAL), 3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazoyl5-yl) phenyl] phenyl] methyl] amino]-butanoic acid [15] as shown in **Fig. 1**, is a competitive antagonist of binding of angiotensin II to the type-1 of angiotensin II receptor (AT1) subtype. This lowers blood pressure and acts as an anti-hypertensive drug [16].

It is present in unstable, crystalline nature. Hence it has larger particles, ultimately affecting its aqueous solubility. As it has less solubility and high permeability properties, according to biopharmaceutical classification, it belongs to class II [17, 18]. Thus its bioavailability is about 23% [19].

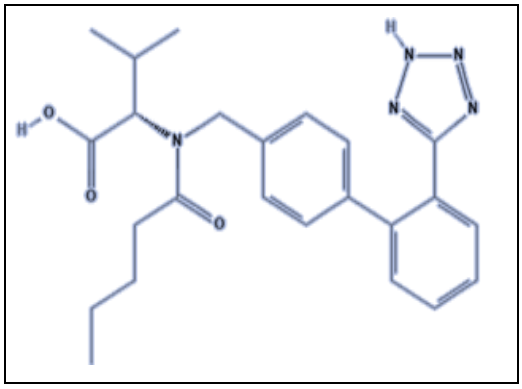

FIG. 1: STRUCTURE OF VAL

This present investigation focuses on enhancing the solubility and dissolution rate of VAL by reducing crystal size to the nano range with the help of MGAN. Nano-sized crystalline solid has stabilized by using chitosan as a hydrophilic stabilizer [20, 21] and neusiline (US2), anamorphous metal silicate, as a surfactant and solubility [22, 23]. The poor dissolution rate of valsartan compromises many problems in industrial use and thus public health. This will increase the dose while also influencing formulation costs and patient compliance [24, 25].

MATERIALS AND METHODS: Lupin Research Park, Pune, MS, India kindly gifted VAL and CH with a 93% degree of deacetylation purchased from Loba chemical, India. Neusiline US2 was obtained as a gift sample from Lupin Research Park, Pune. Neusilin US2 (NS), a synthetic magnesium aluminometasilicate with a high specific surface area (300 m^2/g) was used as a surfactant to enhance solubility in physiological fluid [22, 23]. Distilled water and different reagents used for the study were of analytical grade. Substances or ingredients were used directly without any further purification.

Phase Solubility Study: The phase solubility studies of VAL were performed in distilled water as per the method described by Higuchi and Connors. Excess VAL was added to 10 ml of distilled water in the absence and presence of different concentrations of CH with or without NS.

A solubility tube containing binary and tertiary suspension was kept for 48 h on a mechanical shaker (Bio Technics India) with a stirring speed of 100 rpm at room temperature. The filtrate, obtained after filtration of suspension equilibrium from Whatman filter paper no. 41, was analyzed by UV spectroscopically with necessary dilutions. A straight line equation, $y = 0.0166x + 0.1808$, was generated from the calibration curve of VAL using a maximum wavelength of 256 nm [26–28].

Determination of Stoichiometric Constant: It was calculated by taking various ratios of the molar concentration of VAL and CH. Increasing the molar concentration of VAL and reducing the molar concentration of CH were mixed to form a suspension. Then this binary mixture was filtered with Whatman filter paper no. 41 and analyzed UV spectroscopically at 256 nm [29].

Experimental Work:

Preparation of Crystals of the Ternary Complex:

Selection of Factors: The percentage of CH and percentage of NS were selected as two independent variables X1 and X2 with three levels from preliminary data of the stoichiometric study and phase solubility study. Crystalline formulations were formulated and optimized by using 3^2 levels of full-factorial design with Design Expert version 12.

This gives a total of 9 experimental batches for evaluation of dependable responses Y1; saturation solubility and Y2; percentage drug release as shown in table 1. These factors were studied for obtaining an optimized batch of maximum response [30].

TABLE 1: FACTORIAL BATCHES

Batch	A: CH (%)	B: NS (%)
V_1	5	5
V_2	10	5
V_3	15	5
V_4	5	7.5
V_5	10	7.5
V_6	15	7.5
V_7	5	10
V_8	10	10
V_9	15	10

Formulation of Crystal Particles:

Microwave Assisted Grinding Nanotechnology (MAGN): A selected amount of ingredients were weighed and ground without distilled water in a mortar pestle for about 20 minutes. Then the mixture is transferred to a microwave oven (Panasonic microwave oven, 230V- 50 Hz-1250W) adjusted at 600 W power for two intervals of 3 min. Before starting the second interval, remove the mixture and stirred it to cool down.

Amounts of X1 and X2 were optimized and repeated the same procedure for wet grinding technology using distilled water and ball milling technology without solvent. An optimized ingredients without solvent system was added in an electrically operated ball mill (Shreeji Chemicals, Kandivali, Mumbai) with 100 rpm speed for 48 h.

Then batch was transferred for microwave treatment with 600 W power for two intervals of 3 min. Finally prepared batches were optimized from Y1 and Y2 variables and stored in an air-tight desiccator. These batches were studied for molecular interaction, crystallinity, particle size, solubility, and dissolution rate.

Saturation Solubility Studies: Saturation solubility was studied in distilled water and dissolution medium according to the method explained by Higuchi and Connors. Excess amounts of VAL and prepared particles were added in 10 ml solvent in solubility tubes and shaken on a mechanical shaker for 48 hrs at room temperature with 100 rpm speed. After equilibrium, the solution was filtered and diluted, if required. The filtrate was analyzed for saturation solubility by using UV spectroscopy at 256 nm [10].

Fourier Transformation-infrared Spectroscopy (FTIR): Functional group and bond vibrational frequencies of pure VAL, CH and NS were observed individually by using FTIR (BRUKER – ECO – ATR – ALPHA, Germany) spectroscopy technique. This technique was also carried out for physical mixtures and formulated crystal particles with different methods. The samples were directly placed on the pan and analyzed from 600 to 4000 cm^{-1} spectral range with 24 scans [10].

Percentage Drug Content Studies: Crystal particles from all formulated batches of drugs equivalent to 20mg were weighed accurately and added to 10 ml methanol. This was stirred by using a mechanical stirrer for 24 h at room temperature with 100 rpm speed.

After equilibrium, it was filtered through Whatman filter paper no. 41 and analyzed with required dilution UV spectroscopically at 256 nm wavelength using Shimadzu UV spectroscopy. Percentage drug content was calculated from the following formula

$$\% \text{ drug content} = (\text{actual drug content in methanol}) / (\text{theoretical equivalent drug taken}) \times 100$$

Differential Scanning Calorimetry (DSC): Thermal analysis of pure VAL, CH, NU, physical mixtures, and formulated crystal particles was performed using a DSC analyzer (TA Instruments, SDT Q600 USA). A sample (5 mg) was heated under a nitrogen atmosphere at a heating rate of 200C/ min over the temperature range of 40–2600 C [21, 31].

X-ray Powder Diffractometry (XRPD): The XRPD patterns of all systems were recorded by using an X-ray diffractometer (BRUKER – D2 PHA-SER, Germany) with tube anode Cu, throughout 10–900/2h. The operational data were as low: Generator tension (voltage) 30 kV, Generator current 10 mA [32].

Nuclear Magnetic Resonance (NMR): NMR spectral analysis gives interaction between drug and excipient in the form of a peak for protons. It was recorded on 300 MHz (Bruker, GER) using a spectral window of around 10000 Hz. Samples were dissolved in Deuterated Chloroform (CDCl3) solvent and TMS was used as the internal standard [32].

Particle size Analysis: Particle size was measured using a Horiba particle size analyzer SZ-100 instrument scanned for determination of nano particular scale.

Dissolution Study: A dissolution study was performed in 900 ml simulated gastric fluid of 0.1 N HCl using type 2 Disso apparatus (LABINDIA Dissolution test apparatus, DS 8000). The rate of stirring and temperature was maintained at 50 rpm and 37 ± 0.5 °C respectively. 5ml of aliquot was withdrawn and replaced with fresh buffer after a specific time interval. Dilute the aliquot, if required, and analysed UV spectroscopically for percentage drug release at an absorbing wavelength of 256 nm [28].

Micromeritic Study: Flowability and compressibility values can be determined by the dimensionless quantity of Carr's index (CI) and Hausner's Ratio (HR). It gives a relative picture of particle size and shapes with cohesiveness. Specifically, flowability can be calculated by measuring the angle between the height and slope of the pile formed by pouring the sample through a funnel.

Stability Study: It was carried out in a stability chamber (REMI SC 16S) operated at an environment of temperature 40 °C and 75% RH. The study was conducted for 3 months and samples were withdrawn after 0 days, 15 days, 1 month, 2 months, and 3 months. Samples were evaluated for drug content using UV spectroscopy with methanol as a solvent system at 256 nm and for the interaction between VAL with polymers using IR spectroscopy [20, 32].

RESULTS:

Phase Solubility: Saturation solubility of VAL was carried out in distilled water using a rotatory shaker at 100 rpm speed and finally calculated the concentration using UV spectroscopy at 256 nm.

From **Fig. 2**, it was found to be 291.3 µg/ml and it belongs to a practically insoluble class. Saturation solubility was increased up to 412. 5 µg/ml with a hydrophilic polymer, CH and 609.4 µg/ml with a surfactant, neusiline US2. A ternary phase of VAL with CH and NS showed saturation solubility of 538.75 µg/ml [28]. From **Fig.** below **3**, saturation solubility was increased by both CH and NS.

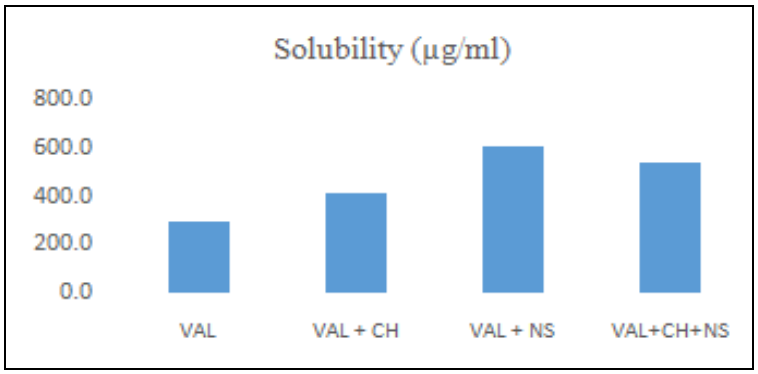

FIG. 2: SATURATION SOLUBILITY STUDY

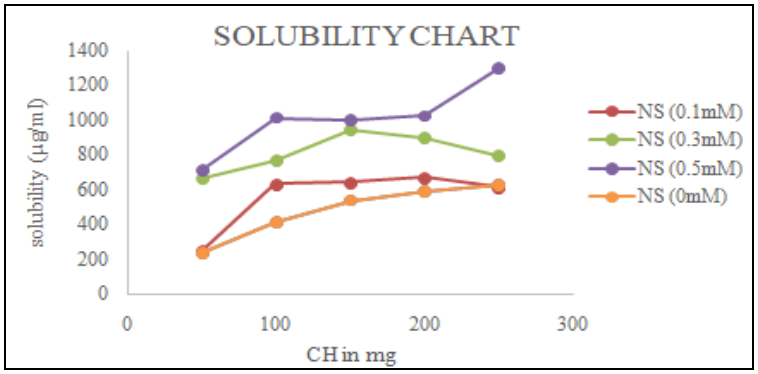

FIG. 3: PHASE SOLUBILITY STUDY

Stoichiometric Constant Determination: It was calculated by plotting a graph of the molar ratio of the drug to CH (r) versus ΔA*r in **Fig. 4** from the data given below in **Table 2.**

TABLE 2: VARIATION OF MOLAR RATIO OF DRUG AND POLYMER

Drug (mM)	CH (mM)	Total	Abs	r	ΔA	ΔA*r
1.1	0	1.1	0.047	1.00	0	0.000
1.05	0.05	1.1	0.161	0.95	0.114	0.109
1	0.1	1.1	0.204	0.91	0.157	0.143
0.95	0.15	1.1	0.153	0.86	0.106	0.092
0.9	0.2	1.1	0.108	0.82	0.061	0.050

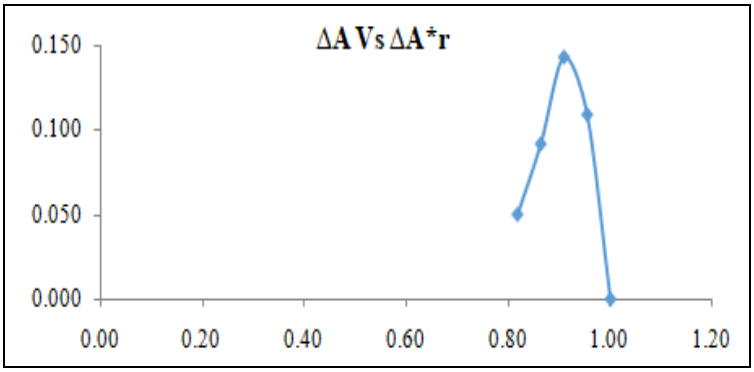

FIG. 4: STOICHIOMETRIC CONSTANT DETERMINATION

FTIR: An interaction study between VAL and excipients was given in **Fig. 5**. It includes all the spectra for VAL and its interaction with others. It shows peaks for interacted functional groups present in compound [2, 28].

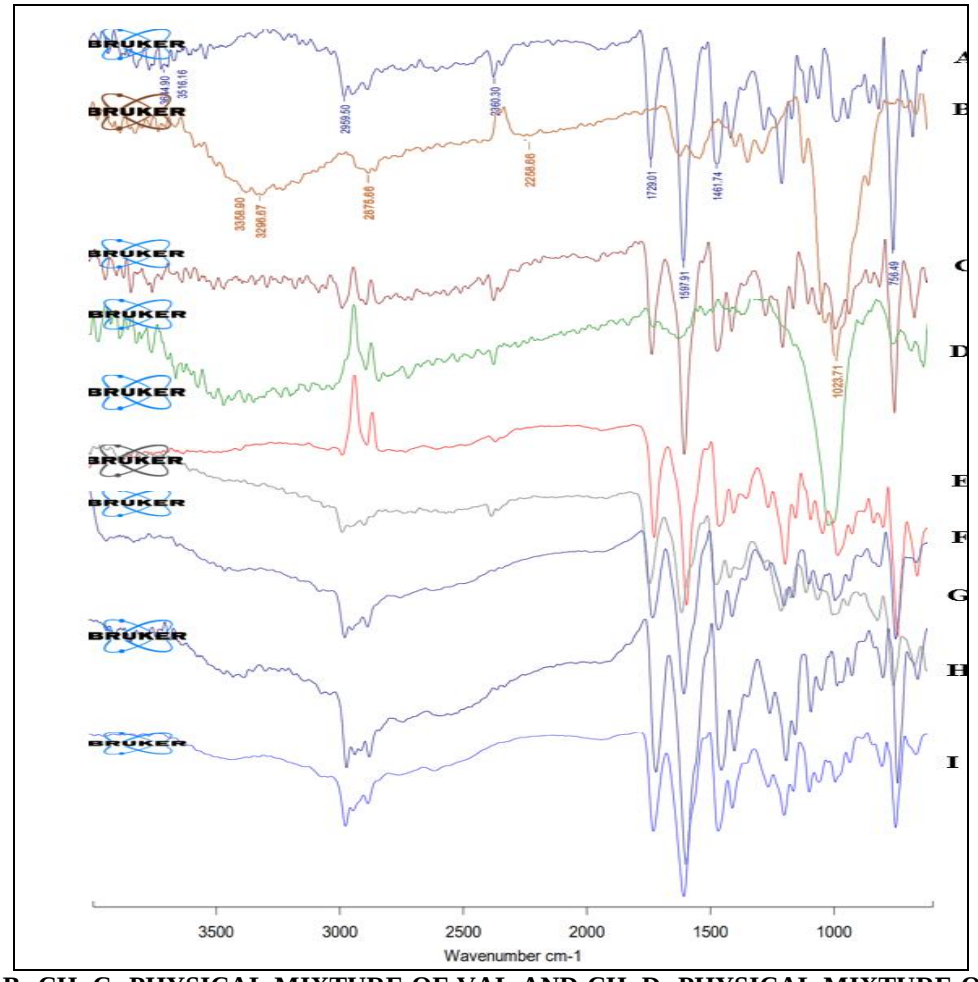

FIG. 5: A: VAL, B: CH, C: PHYSICAL MIXTURE OF VAL AND CH, D: PHYSICAL MIXTURE OF VAL AND NS, E: PHYSICAL MIXTURE OF VAL, CH AND NS, F: FORMULATION OF VAL, CH AND NS, G: VF WET GRINDING BATCH, H: VAL DRUG BALL MILLED AND I: BALL MILLED FORMULATION

DSC: It gives some endothermic peaks in the region of 60°C to 100°C with varying values of enthalpies as shown in **Fig. 6.**

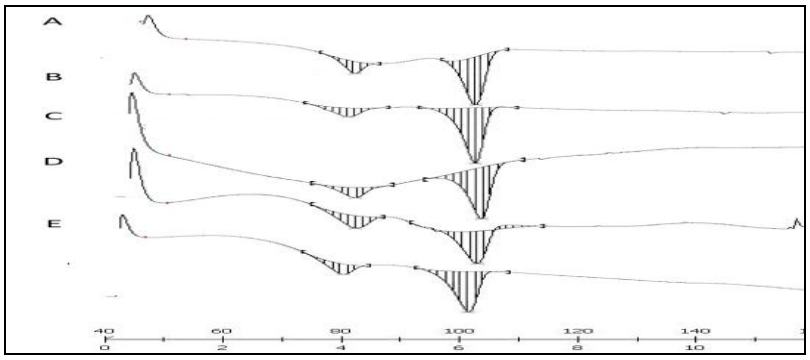

FIG. 6: DIFFERENTIAL SCANNING CALORIMETRY STUDY. A: VAL; B: V0; C: VAL+CH+NS; D: V7 AND E: V5

XRPD Study: It was determined from **Fig. 7** that VAL and their formulation batches showed maximum peak intensity around 2Ɵ values of 21.18 and 14.4356, which showed the crystalline nature of the drug as shown in **Table 3**. Other formulation batches also showed maximum peak intensity around the same 2Ɵ values [2].

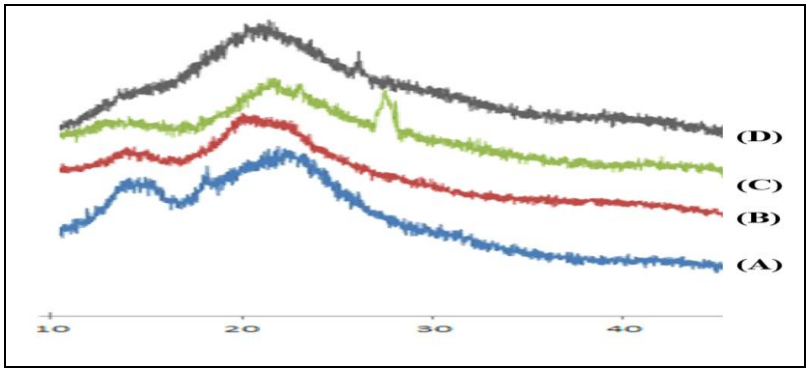

FIG. 7: XRD STUDY. A: VAL; B: V6; C: VAL FBM; D: VAL BM 7

TABLE 3: 2 THETA VALUES OF VARIOUS BATCHES

Batch	2 Theta	
	21.18	**14.4356**
V	1459	1202
V6	1566	1245
VAL BM	1211	758
V6 BM	1769	1264

NMR: Fig. 8 shows sharp peaks of NMR for various protons present in given batches. The splitting of peaks was due to neighboring protons in the chemical structure of a compound.

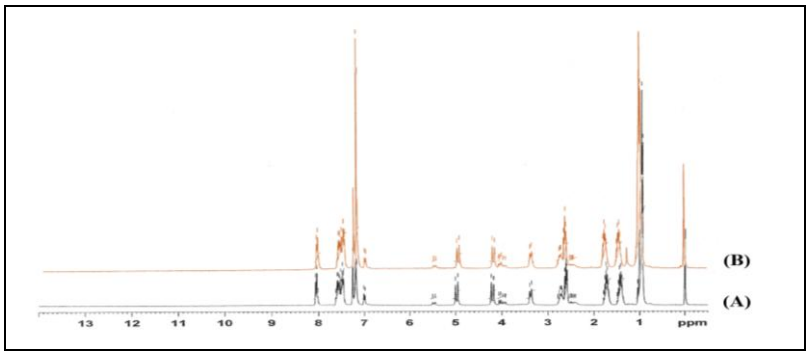

FIG. 8: NMR (A: VAL; B: V6)

Particle size Analysis: The mean particle size of microwave-assisted ball-milled and V8 was 28.2 nm ± 1.6 nm and 24.6 nm ± 1.7nm, as shown in **Fig. 9.** Z- Average values were found to be 731.2 nm and 540.7 nm, respectively.

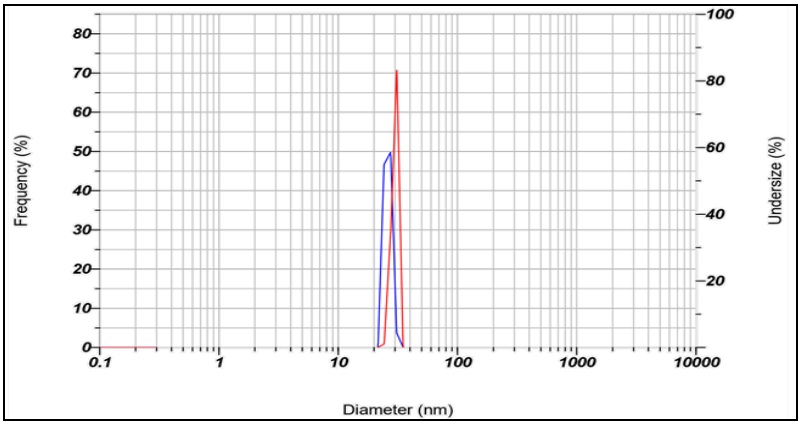

FIG. 9: PARTICLE SIZE ANALYSIS

Saturation Solubility: The saturation solubility of batches having varying factors was analyzed and optimized by design expert software. It suggests a quadratic model for optimizing maximum saturation solubility, which is given in figure 10. Analysis of variance for a quadratic model, having F- value of 6806.85 with a p-value < 0.0001, is significant. ANOVA gives significant terms A, A2 and B2 having p-value < 0.0500, where A and B are % CH and % NS, respectively. The coded equation for a quadratic model is

$$\text{Saturation Solubility} = 843.24 + 294.18*A + 0.0*B - 3.015 * AB - 193.778 * A^2 + 14.0567 * B^2$$

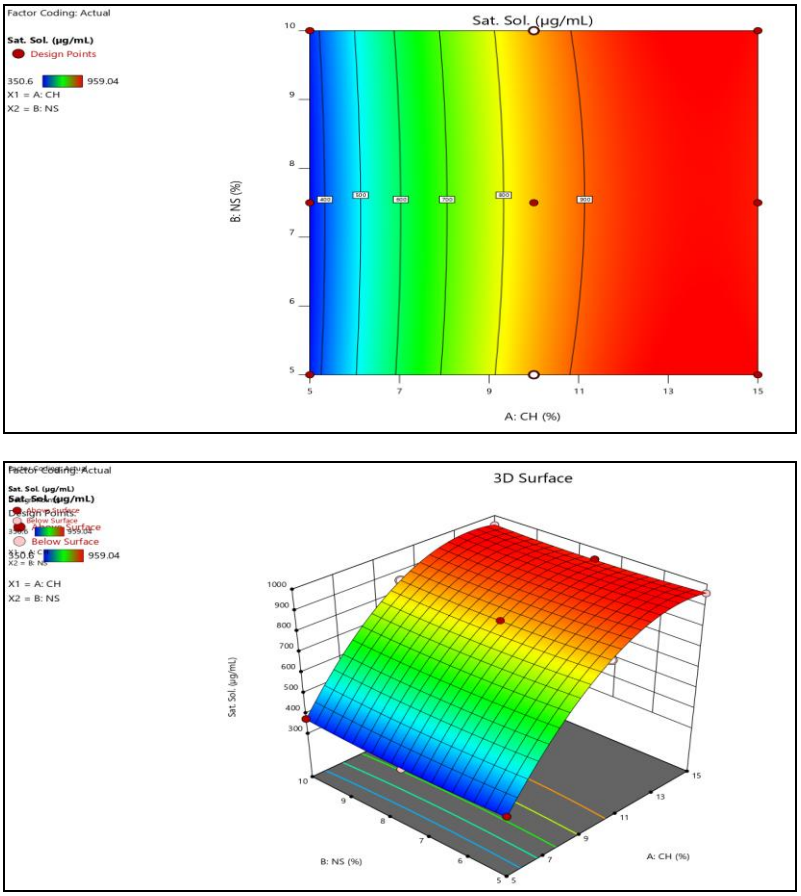

FIG. 10: CONTOUR PLOT OF SATURATION SOLUBILITY STUDY AND 3D PLOT OF SATURATION SOLUBILITY STUDY

Dissolution Study: The percentage cumulative drug release was calculated for all the batches and compared with VAL. VAL showed 28.73 % drug release due to its stable crystalline form. Maximum drug release was obtained for the V8 batch, as shown in **Fig. 11** [33].

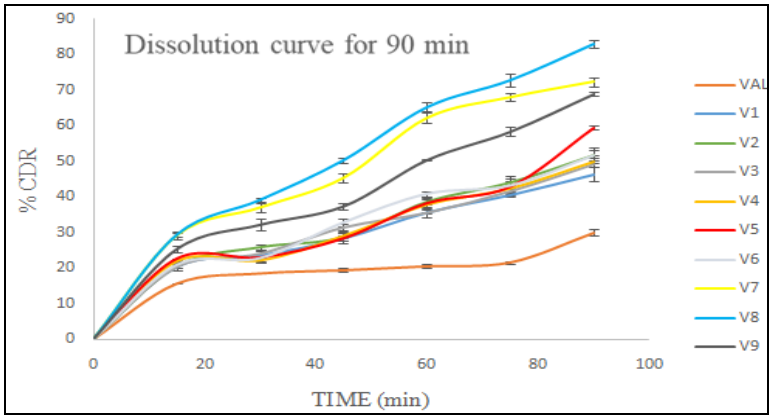

FIG. 11: DISSOLUTION RATE STUDY

The cumulative drug release profile was analyzed using a design expert tool to optimize batches for further studies. ANOVA was significant for the suggested quadratic model, as shown in **Fig. 12**, F-value 27.27 with a p-value of 0.0105 (*i.e.*, less than 0.05000).

A, A^2, and B^2 were the significant factors with p- a value less than 0.0500. The coded equation for a suggested model is-

$$\%CDR = 58.68 + 12.735 * A + -0.267 * B + -0.995 * AB + 8.465 * A^2 + -9.02 * B^2$$

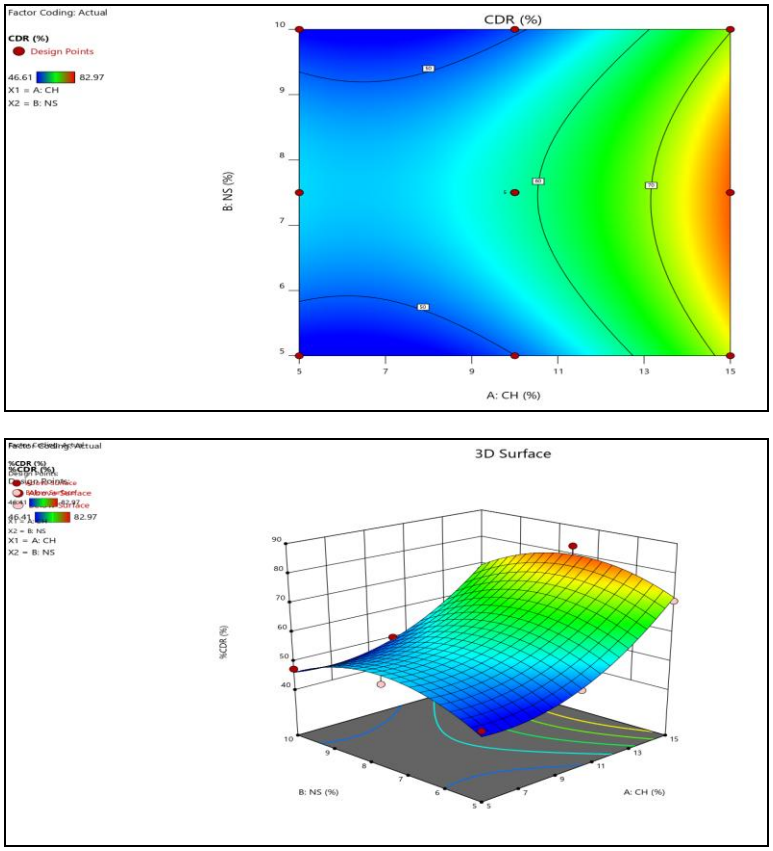

FIG. 12: CONTOUR PLOT OF DISSOLUTION RATE STUDY AND 3D PLOT OF A DISSOLUTION RATE STUDY

Drug Content: Percentage drug content was found to be in the range of 97.75%, and 103.77% and saturation solubility of V8 was found to be 1658.4 µg/ml.

Stability Study: An accelerated stability study was conducted for 60 days using FTIR interactions, as shown in **Fig. 13**. It indicates extended environmental conditions are ineffective on the drug content of batches.

This was confirmed by studying interaction and functional group variation from IR spectroscopic investigation, as given in **Fig. 13.**

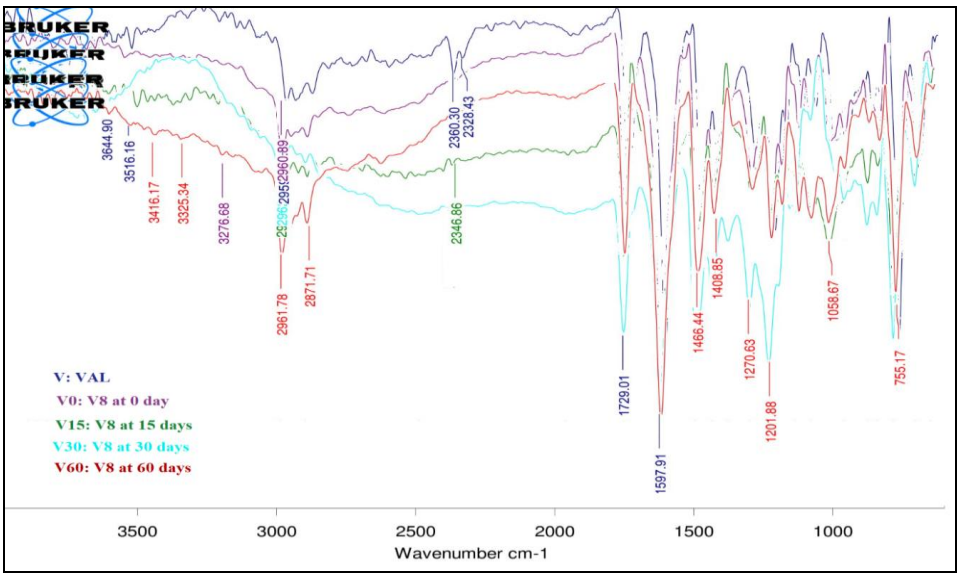

FIG. 13: STABILITY STUDY OF VAL AND FORMULATION (A: VAL, B: VAL (0 DAY), C: VAL (15 DAYS), D: VAL (30 DAYS), E: VAL (60 DAYS))

Micromeritic Study: HR, CI, and angle of repose value for drug, formulation batch without ball milling and with ball milling was calculated and given in **Table 4.**

TABLE 4: MICROMETRIC DETERMINATIONS

Batch code	HR	CI	Angle of repose
VAL	1.38 ± 0.	27.69	42.14
V8	1.12 ± 0.	10.34	25.77
Vb	1.13	11.11	29.75

DISCUSSION: Valsartan, a BCS II drug, was selected based on crystallinity and solubility profile. (1) Chitosan, a hydrophilic polymer, and neusiline US2, a surfactant, were used to change API's crystallinity with the variation of solubility [10, 11].

Phase Solubility and Stoichiometric Constant Determination: The increment in solubility of polymer and surfactant might be due to the enhancement of hydrophilic interaction and reduction in surface tension of distilled water, respectively, with VAL. But the ternary phase of VAL with CH and NS showed solubility results within the above polymeric and surfactant interacted solubility. Thus VAL to CH ratio was confirmed for crystal engineering study from the stoichiometric constant graph given in figure4 and found to be 1: 0.1 from the peak.

FTIR: The compatibility study means no change in the drug chemical nature in the presence of excipients and lack of direct effect of excipients on drug chemical structure. Thus it varies some physical properties without changing morphology and structural arrangements. IR spectroscopy of VAL shows peaks at 1729.01, 756.49, 1461.74, and 1597.91 cm-1, which reveals the presence of acidic -C=O, aromatic ring, -CH2 bending, -C=,N stretching or conjugated -C=C- aromatic as shown in **Fig. 5A.** It also shows peaks at 3644.90, 3516.16, 2360.30, and 2959.50 cm^{-1} for the group of acidic -OH, secondary -N-H, non-conjugated C=N stretching and -CH SP3. Hydrophilic CH shows peaks from **Fig. 5B** at 1023.71, 3358.90, 3296.67, 2875.66, and 2258.66 cm^{-1} for ethereal C-O, alcoholic group, primary amine, -CH SP3, and C-N bond. All these peaks were present in a physical mixture of VAL and CH with a negligible shift in **Fig. 5C**. It indicates an absence of any interaction with the physical mixture and physical compatibility. NS, as a synthetic magnesium aluminometasilicate, doesn't show any sharp peak with IR spectroscopy **Fig. 5D** and also does not interfere with peaks of VAL in a physical mixture [24]. Thus, like CH, NS not only shows an absence of interference with VAL physically but also shifts slightly as shown in **Fig. 5E.** All those peaks were also present in formulation by different grinding/

milling methods as shown in **Fig. 5F, G** and **I** with slight changes. A binary physical mixture of VAL and CH shows a very slight increase in peak values for the acidic group and a decrease for the amine group but inversely happened for a physical mixture of VAL and NS, which might be due to very weak Vander Waal force between the metal atom and lone pair of electrons present on nitrogen. In the case of a ternary physical mixture, slightly increase the peak value for both the acidic OH group and amine group, which might be due to van der Waal force or hydrogen bond between them.

This change in peak value is comparatively more in the formulation, which reveals the formation of a hydrogen bond between OH and the primary amine group of the compound. But it could not show a sharp peak for primary amine in IR spectroscopy. Hence VAL interacted only physically with polymer and surfactant. The absence of any chemically interacted bond or peak showed a chemically compatible formulation of microwave treatment with simple grinding and ball milling.

DSC: VAL shows two sharp endothermic peaks at 101.5 °C and 79.24 °C, which could represent its melting point and glass transition temperature with integral enthalpy -71.18 mJ and 15.80 mJ, respectively. A broad exothermic peak after 180 °C represents the decomposition of a drug. Microwave-treated valsartan shows a shift of endothermic peak to 101.08 °C and 78.80 °C with enthalpy of -45.10 mJ and -9.09 mJ as shown in **Fig. 14**. Thus decrease in melting point with enthalpy value could be due to the interaction of microwave energy with crystalline nature or solvent of crystallization present in the crystal lattice of VAL.

This shifting was, more in a ternary physical mixture, at 100.46 °C and 78.97 °C with reduced enthalpy. Peak reduction may indicates changing crystallinity and increased stability of the drug in a physical mixture, but the variation is too small to confirm it with a physical mixture.

But endothermic peaks significantly shift to lower values than in drug or physical mixture. It is present at 99.82 °C and 99.64 °C in V7 and V5 batches, respectively, indicating valsartan is more stable in formulation than drug or physical mixture. This reducing effect could confirm weak interaction between drugs and polymers, showed in infrared spectroscopy [34].

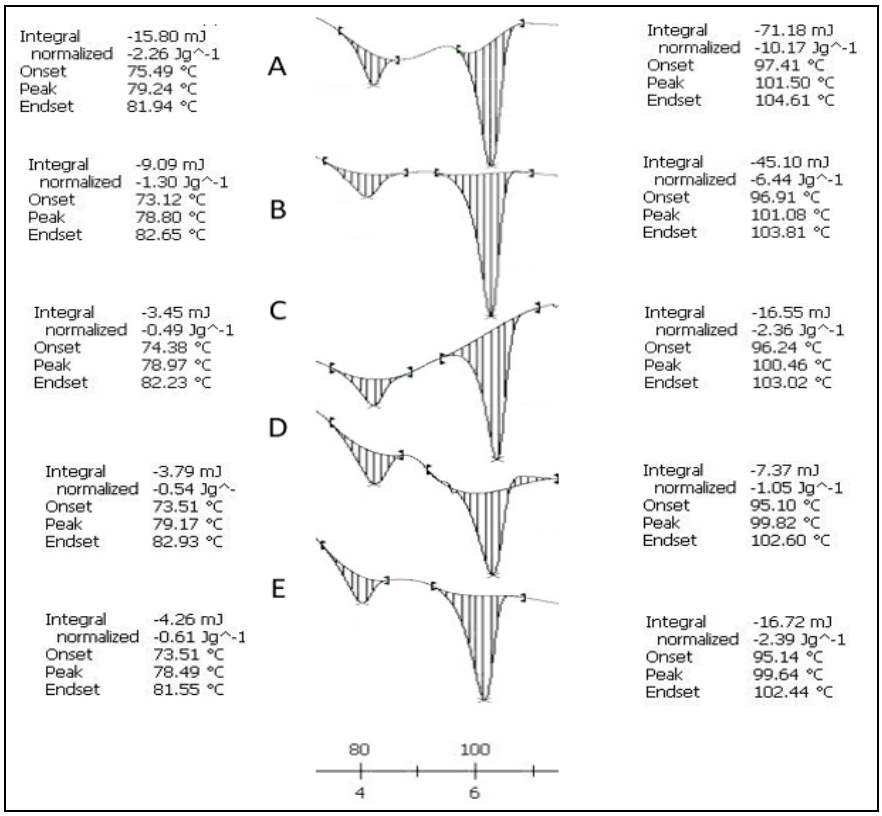

FIG. 14: DIFFERENTIAL SCANNING CALORIMETRY ENDOTHERMIC AND GLASS TRANSITION PEAKS WITH ENDOTHERMIC ENERGY. A: VAL; B: V0; C: VAL+CH+NS; D: V7 AND E: V5.

XRPD Study: The peak intensity of VAL showed crystalline nature in **Fig. 7**. But the peak was not very sharp, indicating the crystalline nature of the rubbery state of the drug. V6 formulation was maintained and somewhat enhanced the crystalline nature of the drug due to an increase in peak intensity. From the results of XRD and DSC, it was confirmed that the effect of microwave radiation on the physical interaction of ternary complex which enhances the stability with increment in crystallinity of the drug. Ball milling is the physical phenomenon of attrition and the impact of balls on the particles of a drug. As well as the rubbery state of VAL was also responsible for a reduction in peak intensity, thus, it reduces the crystallinity. But peak intensities were enhanced in the formulation's presence of CH and NS. This might be due to the physical interaction of microwaves with hydrophilic polymer and rubbery drug molecules.

NMR: NMR peaks are used to identify types of protons attached to different types of carbon in a drug or complex molecule. The splitting of the peak gives proton present on the neighboring carbon atom. Chemical shifts for different functional groups are present within a range which confirms the structure of VAL. Peaks of all types of protons in the formulation are present at the same chemical shift value as that of drug with slight downshift. This downshift might be due to the weak interaction of VAL with excipients [35].

Particle size Analysis: Ball milling helps to reduce the particle size of crystals up to the nanoparticle range. Thus crystal particles formed by using the ball milling technique were present in the nano-size range and their crystalline nature was confirmed by DSC and XRD analysis.

Saturation Solubility: The planar contour graph and the 3D surface graph showed that increasing the percentage of chitosan increases saturation solubility, and increasing the percentage of NS reduces it in the middle range and then improves with less significance than lower. Hence the highest amount of chitosan and the lowest amount of NS is required to obtain maximum saturation solubility [35].

Dissolution Study: The percentage cumulative drug release was calculated for all the batches and compared with VAL. VAL showed 28.73 % drug release due to its stable crystalline form. As hydrophilic polymer and surfactant interact physically, VAL in formulation shows more drug release. Maximum drug release was obtained for the V8 batch.

The drug release profile showed an increase in the release of drugs with increasing surfactants. The polymer showed a rise in drug release and then reduced at higher concentrations. This might be due to the entrapment of hydrophilic polymer with crystalline Val, which retard the drug release. Enhancement of drug release of V8 was about 2.89 times more than VAL, due to variation of a crystalline form of the drug. Thus dry grinding with microwave assistance is one of the techniques to enhance drug release of BCS II drugs.

Drug Content: There was no significant loss of drug during batch manufacturing. Thus deviation of drug content was comparatively small. As well as saturation solubility of V8 was enhanced by 5.69 times with that of VAL.

Stability Study: All drug peaks were present in the formulation batch, indicating an absence of interaction between drug and polymers. At accelerated environmental conditions, peaks of VAL were not altered within formulation over 90 days. This confirms the stability of the formulation, which might be due to the presence of CH polymer [36].

Micromeritic Study: The cohesiveness of the particles will enhance the angle and reduce flowability. As inter particular cohesiveness/ friction increases, these dimensionless values will also increase. It was observed that all these dimensionless quantities are more for VAL than microwave-treated batches. Size-reducing technology will affect slightly on flowability and compressibility properties.

Thus it proves the enhancement of cohesiveness between particles and reduces inter particular gaps due to changes in particle size and shape. This might be due to a reduction in a crystallization solvent which can be confirmed by the DSC and XRPD study. Hence MAGN helps to improve the micromeritic properties of solid forms [37, 38].

CONCLUSION: Valsartan, crystalline drug showing glass transition temperature, belongs to BCS II having low aqueous solubility and bioavailability. MAGN can be used for size reduction, modification of physicochemical properties and maintaining stability without any chemical effect of excipient. This technique enhances bioavailability by reducing solubility barrier and increasing stability for BCS II drugs. Chitosan, natural hydrophilic polymer, alter its stability might be due to weak hydrogen bonding and van der Waal interaction. Neusiline, a synthetic surfactant, used for enhancing solubility of drug while microwave treatment. A compatibility study of FTIT, DSC and stability in microwave treatment confirmed the stability of excipients with VAL. The saturation solubility of VAL is increased by almost two times in the preliminary study and 5.69 times in formulation V8. The cumulative drug release of V8 was increased by 2.89 times. The FTIR study confirmed all the batches were stable in an accelerated environment.

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