ORIGINAL ARTICLE

# Increasing the Oral Bioavailability of Poorly Water-soluble Valsartan Using Non-ordered Mesoporous Silica Microparticles

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## Abstract

**Aim:** To evaluate the use of mesoporous silica SYLOID® 244 FP to increase the dissolution rate of valsartan, antihypertensive poorly water soluble, Biopharmaceutical Classification System Class II drug. **Materials and Methods:** Valsartan was adsorbed on and/or into SYLOID® 244 FP in the ratio of 1:0.5, 1:1, and 1:1.5 via a wetness impregnation method and then processed into tablet by direct compression. To investigate the interaction in between valsartan and SYLOID® 244 FP, X-ray powder diffraction (XRPD) and Fourier transform infrared studies were performed. To examine the effect of SYLOID® 244 FP on the solubility of drug, phase solubility study was performed. Optimization of the study was done using $3^2$ full factorial designs where amount of SYLOID® 244 FP ($X_1$) and volume of ethanol ($X_2$) were selected as independent variables and solubility and % cumulative release were selected as dependent variables. Flowability and wettability of the valsartan-loaded powder were evaluated by bulk and tapped density and by the angle of repose, respectively. Physical stability tests of the valsartan and the valsartan-SYLOID® 244 FP matrix were observed by keeping it over a 1-month storage at 40°C and 75% ± 5% humidity. **Results and Discussion:** The drug excipient interaction study revealed the absence of crystalline form and presence of hydrogen bonds interaction in valsartan-loaded powder. The improvement in the dissolution rate of tablet containing valsartan-loaded matrix is due to the lack of valsartan in the crystalline form and large surface area of the SYLOID® 244 FP. Satisfactory results of physical stability tests of the valsartan and the valsartan-SYLOID® 244 FP matrix were observed. Correspondingly, the solubility of the valsartan-loaded matrix was increased up to 2.83 times. **Conclusion:** Study indicates that valsartan tablet prepared from drug-loaded silica may provide a feasible approach for the development of an oral formulation for this poorly water-soluble drug.

**Key words:** Bioavailability, non-ordered mesoporous silica, valsartan

## INTRODUCTION

Nowadays, the greatest challenge for oral drug delivery systems is to improve the bioavailability of poorly water-soluble drugs. Although several formulation strategies including emulsion-based systems,[1] liquid-solid compact,[2] solid dispersions,[3] and cyclodextrin inclusion complexes,[4] had promising results, use of these technologies in the marketplace has been very limited due to several disadvantages. To overcome these limitations and the growing number of poorly soluble compounds, this underscores the need to explore new formulation approaches.

As *in vitro* dissolution is directly correlated with bioavailability in pharmaceutical research, an emerging approach to enhance dissolution is an encapsulation of hydrophobic amorphous drugs in non-ordered mesoporous silica materials. The outstanding features of non-ordered mesoporous silica materials, including their highly regular mesoporous structure, high surface area, large pore volume, good biocompatibility and thermal stability, have led to these materials becoming important drug carriers. The first report by Vallet-Regi *et al.,* in 2001,[5] used one of the grades of silica as a new drug delivery system indicated that

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**Received:** 18-10-2015
**Revised:** 29-03-2016
**Accepted:** 11-04-2016

mesoporous silica holds great promise in the enhancement of dissolution for poorly soluble drugs.[6-8]

However, in most of the previous studies, dissolution was evaluated directly in drug-loaded powdery mesoporous materials rather than preparing specific dosage forms.[9-12] Since drug-loaded silica can be pressed into tablets without any pharmaceutical excipients by direct compression,[13,14] but the quality of the tablets is not ensured due to the poor compressibility. Finally, Limnelle *et al.,* 2011; Vialpando *et al.,* 2011, and Kiekens *et al.* 2012[15-17] have reported being able to compress drug-loaded silica with suitable excipients into tablets with acceptable quality.

Surprisingly, to the best of our knowledge, there have been no reports to date regarding a pharmaceutical formulation based on preparing non-ordered mesoporous silica as tablet. In fact, tablets are frequently used as a solid dosage form and offer several advantages over other solid dosage forms. The advantages of tablets including the chemical and physical stability to maintain its physical attributes over time and must be able to release the medicinal agents in a predictable and reproducible manner. The tablets also have technological advantages including sufficient strength to withstand mechanical shock during its production packaging, shipping, and dispensing and elegant product identity while free of defects such as chips, cracks, discoloration, and contamination.[18] Tablet based on mesoporous silica could enhance the oral bioavailability of poorly water-soluble drugs by increasing the dissolution rate. Furthermore, drug-release behavior can be modified to obtain adequate drug dissolution followed by gradual and continuous drug release to maintain the plasma drug concentration over an extended period. This modified tablet is expected to improve the solubility and dissolution of poorly water-soluble drugs, as well as improve the safety and efficacy of drug delivery.[20]

In this study, SYLOID® 244 FP mesoporous silica as a carrier was combined with drug to develop modified tablet using direct compression method. From all of the silica-based non-ordered mesoporous materials available, SYLOID® 244 FP was chosen because it has highly developed network of mesopores that provide access to the large surface area, an adjustable pore size in the range of 2.5-3.7 µm, and a high drug-loading capacity.[21-23] Direct compression is a well-established technique for production of the tablet. Microcrystalline cellulose has been the most widely used excipient for preparing tablets via direct compression because it has good binding properties. As drug-loaded mesoporous silica itself has the ability to dissolve rapidly, so it is necessary for the tablets to disintegrate quickly. Hence, easily dissolving lactose as a diluent and crospovidone as a water insoluble disintegrant was added to accelerate the disintegration of the tablet. Sodium lauryl sulfate was added as a lubricant and wetting agent.

Valsartan, an effective antihypertensive agent with low solubility (0.0234 µg/mL) and high permeability, is designated as a Class II agent according to the Biopharmaceutical Classification System. Since valsartan is weakly acidic, it is poorly soluble in the acidic environment where its absorption window exists. As the dissolution of poorly water-soluble drugs such as valsartan is the rate-limiting step for absorption, it is important to improve the dissolution rate, and thus, enhance drug absorption and bioavailability.[24] The main objective of the present work was to develop a valsartan tablet formulation with improved drug dissolution using adsorption based drug loading on and/or into SYLOID® 244 FP mesoporous silica. Another objective was to find out minimum effective concentration required to enhance solubility. This work is also expected to expand the use of silica-based non-ordered mesoporous materials as drug delivery systems.

## MATERIALS AND METHODS

### Materials

Valsartan pure drug was provided by Wockhardt Ltd, Aurangabad as a gift sample. Valent-40 tablets were obtained from Poona Medical, Kondhwa, Pune, Maharashtra, India. SYLOID® 244 FP was obtained from Grace Davison Chemicals India Pvt. Ltd., Pune, Maharashtra, India. Microcrystalline cellulose and Crospovidone were obtained from Research Lab Fine Chem. Sodium lauryl sulfate and ethanol were obtained from Otto. Lactose, potassium dihydrogen phosphate (monobasic), and sodium hydroxide were obtained from SD fine Chemicals. All other chemicals and reagents used were of the high analytical grade.

### Loading valsartan on and/or into SYLOID® 244 FP

A wetness impregnation method was used to load valsartan on and/or into the SYLOID® 244 FP. SYLOID® 244 FP was added to an ethanol solution containing valsartan according to given in Table 3. Ethanol was used as the loading solvent because it is safe, non-toxic, and can dissolve large amounts of valsartan. Afterward, the mixture was ultrasonicated in a closed vial for 10 min and brought to adsorption equilibrium under magnetic stirring at room temperature for 24 h to achieve maximum drug loading in the SYLOID® 244 FP pore channels. Finally, the mixture was evaporated at 50°C on a rotary evaporator (Heidolph) until dry to remove the ethanol completely.

The valsartan loading in the matrix was determined by Fourier transform infrared (FTIR), XRPD, differential scanning calorimetry (DSC), and phase solubility studies.

### Characterization of valsartan-SYLOID® 244 FP matrix

#### *FTIR spectroscopy*

Infra-red spectroscopy is used to estimate the interaction between drug molecule and SYLOID® 244 FP. The scans

were evaluating the presence of principal peaks of the drug, shifting and masking of drug peaks due to SYLOID® 244 FP, and appearance of new peaks due to mixture.

**Table 1:** Formula of tablet without SYLOID® 244 FP

| Ingredients | Quantify given for 1 tablet (mg) |
|---|---|
| Valsartan | 40 |
| MCC | 41 |
| Crospovidone | 6.5 |
| SLS | 2.5 |
| Lactose | 90 |

**Table 2:** Formula of tablet with SYLOID® 244 FP

| Ingredients | Quantify given (mg) |
|---|---|
| Valsartan | 40 |
| SYLOID® 244 FP | 40 |
| MCC | 41 |
| Crospovidone | 6.5 |
| SLS | 2.5 |
| Lactose | 50 |

**Table 3:** Composition of factorial batches

| Dependent variable | Independent variable | | |
|---|---|---|---|
| | Low (−1) | Medium (0) | High (1) |
| Amount of SYLOID® 244 FP (mg) | 20 | 40 | 60 |
| Volume of ethanol (ml) | 0.5 | 1 | 1.5 |

**Table 4:** Phase solubility values

| Concentration of SYLOID® 244 FP (mg) | Solubility (µg/ml) |
|---|---|
| 20 | $3.48\times10^{-2}\pm0.0038$ |
| 30 | $3.96\times10^{-2}\pm0.0047$ |
| 40 | $5.04\times10^{-2}\pm0.0061$ |
| 50 | $4.74\times10^{-2}\pm0.0052$ |
| 60 | $4.09\times10^{-2}\pm0.0059$ |

*Value expressed as mean±SD, *n*=3. SD: Standard deviation

### *DSC*

Thermogram of the binary mixture was recorded. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate of 10°C/min from 30°C to 300°C. During the measurement, the sample was purged with nitrogen.

### *XRPD*

The XRPD spectra of binary mixture recorded using high power powder X-ray diffractometer with Cu as target filter having a voltage/current of 40 KV/40 mA at a scan speed of 4°/min. The samples were analyzed at 2θ angle range of 5-50°. Step time was 46.500.[25,26]

### *Phase solubility study*

The most widely used approach to study binary mixture is the phase solubility method, which examines the effect of an SYLOID® 244 FP on the solubility of the drug. Solubility measurements were performed according to the method reported by Higuchi and Connors. In each five beakers, 40 mg of valsartan dissolved in require amount of ethanol and then add different concentrations of SYLOID® 244 FP, i.e., 20, 30, 40, 50, and 60 mg, respectively.

- Add 6.8 pH phosphate buffer, stir for 24 h, and then filter it by Whatman filter paper.
- The absorbance of each solution was measured using a Jasco V 630 UV-Vis double beam spectrophotometer by putting reference standard of pH-6.8 phosphate buffer at 250 nm.
- The phase solubility study was conducted in phosphate buffer pH 6.8 to compare with plain drug.

### Preparation of valsartan tablet

#### *Conventional valsartan tablet was prepared by direct compression method without SYLOID® 244 FP*

Valsartan with microcrystalline cellulose as a binder, crospovidone as a disintegrant, and lactose as a diluent was mixed thoroughly. This powder blend was passed through sieve number 100. Sodium lauryl sulfate as a lubricant was added just before compression and then compressed into tablet by direct compression method. The complete formula is given in Table. 1

**Table 5:** % cumulative drug release of trial batches

| Time (min) | A1 | A2 | A3 | B1 | B2 | B3 |
|---|---|---|---|---|---|---|
| 0 | 0.0031 | 0.0020 | 0.0026 | 0.0843 | 0.1058 | 0.0982 |
| 15 | 2.5348 | 1.9851 | 2.0641 | 5.5391 | 7.5967 | 6.8461 |
| 30 | 6.0195 | 5.4685 | 5.9426 | 16.1675 | 18.0938 | 17.5147 |
| 45 | 9.4596 | 8.4676 | 9.1216 | 25.4627 | 27.4937 | 26.3416 |
| 60 | 12.6385 | 11.1383 | 11.6948 | 35.7964 | 36.8972 | 36.0068 |
| 90 | 15.2943 | 14.1594 | 15.0850 | 43.5008 | 44.1641 | 43.9162 |
| 120 | 17.7862 | 16.1239 | 16.8694 | 50.9537 | 51.6742 | 51.0478 |

Where A1, A2, and A3: Prepared valsartan tablets without SYLOID® 244 FP, B1, B2, and B3: Prepared valsartan tablets with SYLOID® 244 FP

### *Valsartan tablet was prepared by direct compression method with SYLOID® 244 FP*

Valsartan (40 mg) was dissolved in ethanol (1 ml) at room temperature. Then, SYLOID® 244 FP (40 mg) was added, and then the suspension was shaken for at least 1.5 h using a mechanical shaker. Next, the solvent was evaporated under reduced pressure in a water bath at 45-50°C for 15 min using a rotavapor. The samples were dried under vacuum at room temperature. The formula for tablet is given in Table 2

Microcrystalline cellulose as a binder, crospovidone as a disintegrant, and lactose as a diluent were mixed thoroughly with the above-dried sample, and then mixed powder was passed through sieve number 100. Sodium lauryl sulfate was added as lubricant just before compression and compressed into tablet using direct compression method.

### *In vitro* dissolution study of tablets prepared with and without SYLOID® 244 FP

*In vitro* drug release of the tablets was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37°C ± 0.5°C and rpm of 50. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 2 h. Samples measuring 2 ml was withdrawn after every 0, 15, 30, 45, 60, 90, and 120 min. Samples were filtered through 10 µm filter. The fresh dissolution medium was replaced every time to maintain sink condition. The collected samples were analyzed at 250 nm using dissolution medium as blank.[19]

Results obtained and given in Table No. 5 were used for comparison of tablets release profile was done.

### Optimization by $3^2$ full factorial design from preliminary study

In $3^2$ randomized full factorial design, the amount of SYLOID® 244 FP ($X_1$) and volume of ethanol ($X_2$) were selected as independent variables, solubility, and % cumulative release was selected as dependent variables. In this design, 2 factors each at 3 levels were evaluated, and experimental trials were performed with 9 possible combinations. In each batch, 40 mg of valsartan as a drug component was added.

## RESULTS AND DISCUSSION

### Evaluation of valsartan-SYLOID® 244 FP matrix

#### *FT-IR study*

Comparison of FTIR spectra of valsartan pure drug [Figure 1a], SYLOID® 244 FP [Figure 1b], and valsartan-SYLOID® 244 FP matrix [Figure 1c] indicates the presence

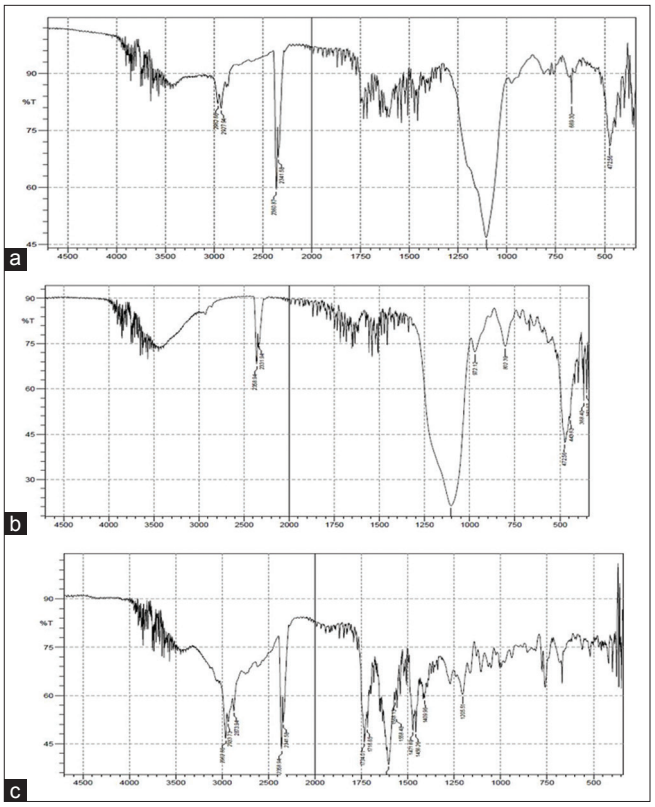


**Figure 1:** Fourier transform infrared spectrum of (a) Valsartan (b) SYLOID® 244 FP and (c) valsartan-SYLOID® 244 FP matrix

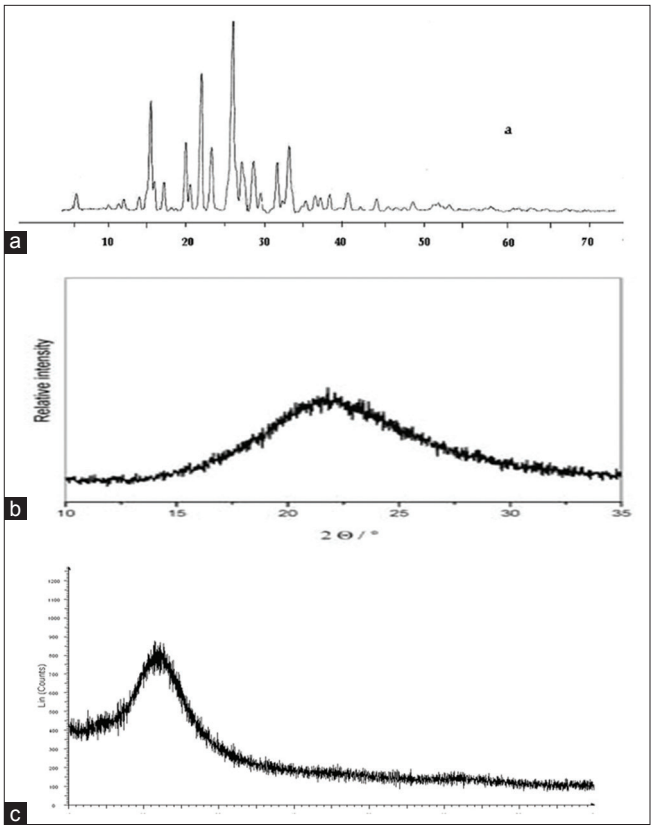


**Figure 2:** X-ray powder diffraction spectrum of (a) valsartan (b) SYLOID® 244 FP and (c) valsartan-SYLOID® 244 FP matrix

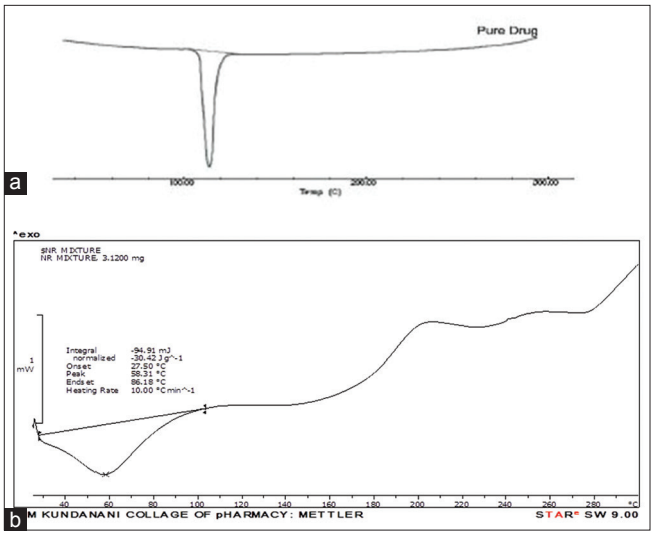


**Figure 3:** Differential scanning calorimetry of (a) Valsartan, (b) valsartan-SYLOID® 244 FP matrix

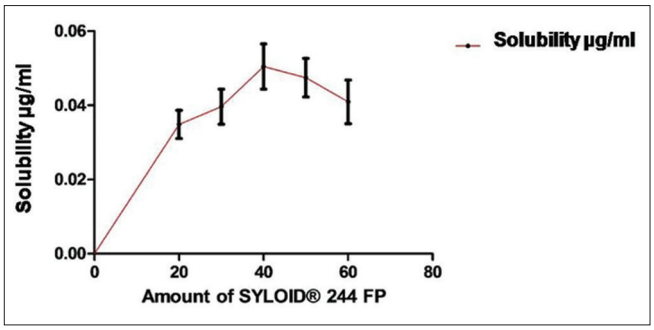


**Figure 4:** Phase solubility graph

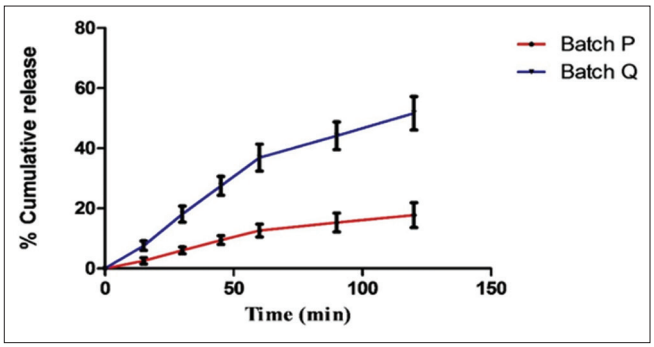


**Figure 5:** Time versus % drug release. Batch P: Average values of valsartan tablets without SYLOID® 244 FP, Batch Q: Average values of valsartan tablets with SYLOID® 244 FP

of new and shifted peaks which confirmed that valsartan was loaded on and/or into SYLOID® 244 FP.

### *X-ray powder diffraction (XRPD)*

The XRPD Spectra of pure drug and drug loaded with SYLOID® 244 FP is given in Figure 2. As compared with valsartan pure drug spectra, there were absence characteristic peaks of valsartan were detected in the valsartan-loaded SYLOID® 244 FP matrix spectra indicating that valsartan

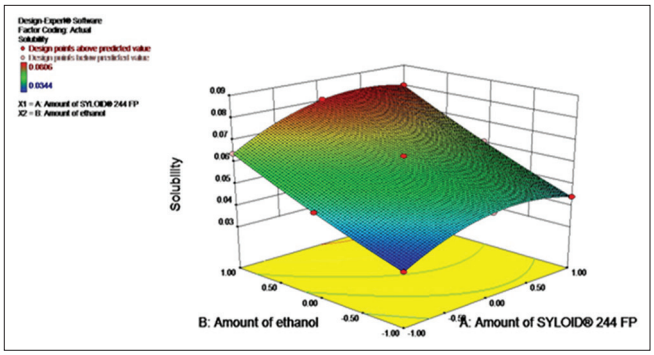


**Figure 6:** Three-dimensional surface graph for solubility

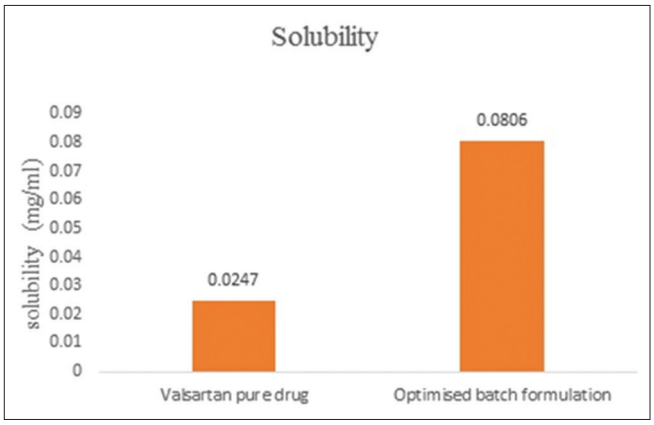


**Figure 7:** Comparison of solubility

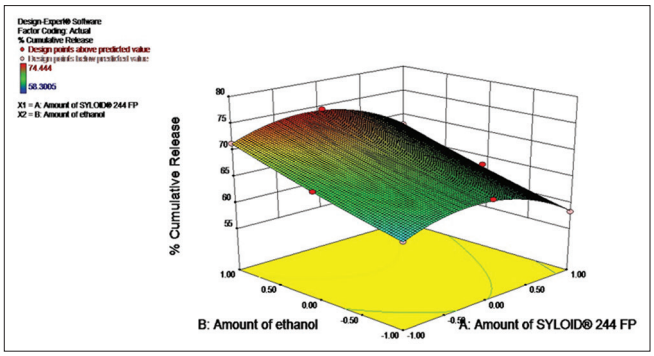


**Figure 8:** Three-dimensional surface graph for % cumulative release

was almost completely converted from a crystalline to an amorphous state.

### *DSC*

As compared with valsartan pure drug, changes in melting point, peak onset, and appearance of the peak of DSC spectra of valsartan-loaded SYLOID® 244 FP matrix given in Figure 3 ultimately confirmed that valsartan was loaded on and/or into SYLOID® 244 FP.

### *Phase solubility*

Valsartan pure drug shows solubility in pH 6.8 phosphate buffer was found to be 0.0284 ± 0.0037 µg/ml.

The phase solubility study was conducted in phosphate buffer pH 6.8 show rises in solubility up to $5.04 \times 10^{-2} \pm 0.0061$. From this, it was confirmed that valsartan was loaded on and/or into SYLOID® 244 FP. The phase solubility curve also in Figure 4 and values given in Table 4 revealed that increase in the concentration of SYLOID® 244 FP increase the solubility of valsartan but up to a concentration of 40 mg. Therefore, in further optimization study, the amount of SYLOID® 244 FP (0 level) was fixed to 40 mg.

## Formulation of tablet by direct compression method

### *In vitro dissolution study of trial batches*

Graph given in Figure 5 indicates that the % cumulative release of tablet containing SYLOID® 244 FP was increased and greater than that of the tablets without SYLOID® 244 FP, so ultimately results in the enhancement of the dissolution rate. The improvement in the dissolution rate of tablet containing valsartan-loaded matrix is due to the lack of valsartan in the crystalline form and large surface area of the SYLOID® 244 FP.

**Table 6:** Solubility optimization by $3^2$ full factorial design

| Batch code | Amount of ethanol (ml) | Amount of SYLOID® 244 FP (mg) | *Solubility (mg/ml) |
|---|---|---|---|
| A | 0.5 | 20 | $3.44\times10^{-1}\pm0.0041$ |
| B | | 40 | $4.78\times10^{-1}\pm0.0058$ |
| C | | 60 | $4.42\times10^{-1}\pm0.0084$ |
| D | 1 | 20 | $4.79\times10^{-1}\pm0.0071$ |
| E | | 40 | $6.29\times10^{-1}\pm0.0061$ |
| F | | 60 | $6.08\times10^{-1}\pm0.0039$ |
| G | 1.5 | 20 | $6.40\times10^{-1}\pm0.0087$ |
| H | | 40 | $8.06\times10^{-1}\pm0.0057$ |
| I | | 60 | $8.01\times10^{-1}\pm0.0049$ |

*Value expressed as mean±SD, *n*=3. SD: Standard deviation

## Optimization by $3^2$ full factorial design method

### *Solubility optimization*

Optimization results observed in Figure 6 and in Table 6 of all 9 batches was done using design expert and maximum solubility, i.e., $8.06\times10^{-2} \pm 0.0057$ mg/ml was observed in batch H. So, we conclude that batch H was the optimized batch. which is confirmed from the Figure 8.

### *Solubility comparison in between pure drug and optimized batch formulation*

This bar diagram of Figure 7 clearly showed that enhancement of solubility up to $8.06 \times 10^{-2} \pm 0.0057$ mg/ml of optimized batch, which contains valsartan-SYLOID® 244 FP matrix than pure drug.

### *Evaluation of pre-compression parameter*

Powders ready for compression into a tablet by direct compression were evaluated as shown in Table 7.

The angle of repose of the powder blend of all the formulations was found in range of $18.25° \pm 0.31°$ to $22.50° \pm 0.14°$, which is in the good or acceptable range indicates the good flow property necessary for the proper flow of powder blend into the die cavity. The bulk density obtained for all the formulations was in the range of $0.51 \pm 0.12$ to $0.57 \pm 0.22$ (g/cm$^3$) and the tapped density in the range of $0.61 \pm 0.52$ to $0.69 \pm 0.25$ (g/cm$^3$). The Carr's index of the powder blend of all the formulations was found in the range of $12.48 \pm 0.16$ to $19.35 \pm 0.27$%, which is good or in the acceptable range means showing good or fair flowability for proper flow of powder blend. Lower Hausner ratio (<1.25) indicates better flow properties. All these results indicated that the powder mixture possesses good flow of powder blend into the die cavity and compressibility properties.

**Table 7:** Pre-compression parameters

| Formulation code | *Angle of repose (θ) | *Bulk density (g/cm$^3$) | *Tapped density (g/cm$^3$) | *Carr's index (%) | *Hausner ratio |
|---|---|---|---|---|---|
| A | 22.50±0.14 | 0.53±0.01 | 0.64±0.17 | 13.72±0.10 | 1.14±0.02 |
| B | 19.86±0.19 | 0.51±0.12 | 0.67±0.02 | 15.26±0.14 | 1.25±0.15 |
| C | 21.43±0.24 | 0.56±0.26 | 0.69±0.25 | 19.35±0.27 | 1.12±0.08 |
| D | 18.27±0.32 | 0.52±0.09 | 0.65±0.01 | 14.61±0.12 | 1.23±0.11 |
| E | 20.18±0.10 | 0.55±0.11 | 0.68±0.38 | 18.51±0.02 | 1.15±0.05 |
| F | 15.34±0.16 | 0.54±0.03 | 0.66±0.41 | 14.63±0.15 | 1.24±0.19 |
| G | 19.59±0.18 | 0.57±0.22 | 0.63±0.08 | 17.81±0.07 | 1.16±0.01 |
| H | 18.45±0.11 | 0.54±0.35 | 0.61±0.52 | 15.65±0.59 | 1.18±0.03 |
| I | 18.25±0.31 | 0.56±0.18 | 0.66±0.19 | 12.48±0.16 | 1.13±0.18 |

*Value expressed as mean±SD, *n*=3. SD: Standard deviation

**Table 8:** Post-compression parameters

| Formulation code | *Thickness (mm) | *Hardness (kg/cm²) | Friability % | *Weight variation | *% Drug content |
|---|---|---|---|---|---|
| A | 4.10±0.01 | 3.8±0.3 | 0.36 | 177.12±0.62 | 96.35±0.21 |
| B | 4.15±0.02 | 4.0±0.2 | 0.28 | 179.65±0.84 | 98.69±0.82 |
| C | 4.17±0.06 | 4.0±0.5 | 0.30 | 180.41±0.41 | 97.48±0.36 |
| D | 4.14±0.04 | 4.1±0.2 | 0.35 | 182.35±0.26 | 98.44±0.12 |
| E | 4.16±0.03 | 4.0±0.4 | 0.31 | 181.52±0.79 | 98.52±0.87 |
| F | 4.19±0.07 | 4.2±0.4 | 0.38 | 184.17±0.11 | 98.29±0.35 |
| G | 4.17±0.03 | 4.1±0.3 | 0.33 | 178.81±0.55 | 98.19±0.31 |
| H | 4.13±0.05 | 4.0±0.4 | 0.29 | 181.75±0.29 | 99.86±0.28 |
| I | 4.12±0.07 | 4.0±0.5 | 0.42 | 180.92±0.71 | 99.67±0.18 |

*Value expressed as mean±SD, *n*=3. SD: Standard deviation

**Table 9:** % cumulative release of factorial design batches

| Time (min) | *A | *B | *C | *D | *E | *F | *G | *H | *I |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.91±0.21 | 1.02±0.11 | 0.95±0.18 | 1.02±0.17 | 1.13±0.15 | 1.08±0.29 | 0.93±0.20 | 1.24±0.31 | 1.04±0.24 |
| 15 | 8.69±1.02 | 12.76±1.17 | 9.53±1.21 | 10.63±1.51 | 13.57±2.12 | 11.33±1.72 | 12.36±1.75 | 17.85±2.74 | 15.26±2.75 |
| 30 | 22.93±3.09 | 26.46±3.41 | 25.59±2.85 | 24.36±2.10 | 30.40±2.90 | 26.72±2.45 | 29.13±2.84 | 33.72±3.17 | 29.67±3.48 |
| 45 | 37.06±4.14 | 39.27±4.21 | 41.26±3.49 | 37.99±3.87 | 44.24±3.98 | 41.74±4.71 | 42.67±3.98 | 49.92±4.57 | 45.84±3.82 |
| 60 | 45.39±5.56 | 49.09±5.81 | 49.05±4.12 | 46.71±4.99 | 53.82±5.75 | 51.37±5.90 | 51.71±4.48 | 58.25±5.74 | 54.91±4.79 |
| 90 | 51.85±5.74 | 58.63±6.98 | 55.76±6.18 | 56.55±5.87 | 63.58±5.11 | 57.85±6.08 | 62.68±5.97 | 65.26±6.74 | 62.91±6.98 |
| 120 | 58.65±6.56 | 65.16±7.19 | 62.43±7.97 | 63.02±6.88 | 69.39±6.87 | 66.53±7.79 | 68.16±6.48 | 74.40±6.07 | 71.40±7.47 |

*Value expressed as mean±SD, *n*=3. SD: Standard deviation

**Table 10:** Various model fittings for optimized batch formulation

| Model | $R^2$ | K |
|---|---|---|
| Zero order | 0.8994 | 1.4821 |
| T-test | 4.601 | Passes |
| Matrix | 0.9836 | 13.6406 |
| Peppas | 0.9743 | 5.9757 |
| Hix. Crow. model | 0.9403 | −0.0172 |

### *Evaluation of post-compression parameters*

The results of post compression parameters are given in Table 8

#### *Appearance*

The tablets were visually observed for any defect in appearance and defects such as capping; chipping, and lamination were not found.

#### *Thickness*

The thickness of tablets was measured by using digital Vernier caliper. The thickness of tablets was found between 4.10 ± 0.01 mm and 4.19 ± 0.07 mm.

#### *Hardness*

The hardness of tablets was determined using Monsanto hardness tester. It was found in the range of 3.8 ± 0.3 to 4.2 ± 0.4 kg/cm². Hardness values were satisfactory and indicated the good mechanical strength of tablets.

#### *Friability*

Percentage weight loss (friability) of the tablets of each formulation was measured and was found to be <1.0% for all the formulations which was considered acceptable.

#### *Weight variation*

Weight variation of the tablets of each formulation was measured and was found to be within the permissible limits (±7.5%) for all the formulations which were considered acceptable.

#### *Drug content*

Drug content of all tablets was found within 96.35% ± 0.21% to 99.67% ± 0.18%. Uniformity of drug content was observed in tablets from each batch as per IP limits.

### *In vitro dissolution study*

The values of % cumulative release of factorial design batches was given in Table 9

From Figure 9a, maximum cumulative drug release was observed in the formulation G (68.1695% ± 6.4873%) as compare to formulation A and D (58.650% ± 6.5685% and 63.020% ± 6.8846%, respectively) in 2 h.

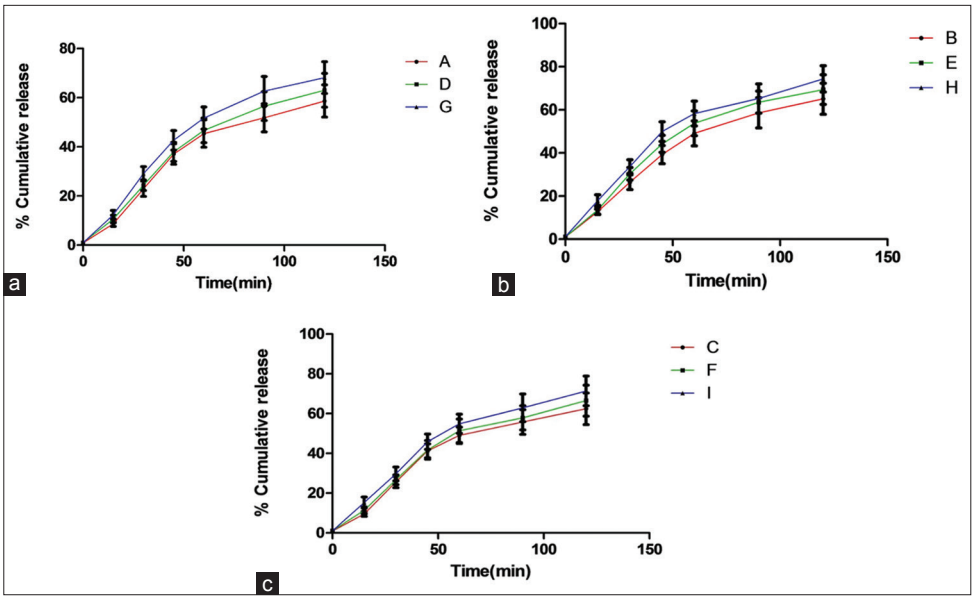


**Figure 9:** (a) Time versus % cumulative release (Batch A, D, and G). For batch A, D, and G, the amount of SYLOID® 244 FP was fixed to 20 mg (−1) and the amount of ethanol varies to 0.5 ml (−1), 1 ml (0), and 1.5 ml (+1). (b) Time versus % cumulative release (Batch B, E, and H). For batch B, E, and H, the amount of SYLOID® 244 FP was fixed to 40 mg (−1) and the amount of ethanol varies to 0.5 ml (−1), 1 ml (0), and 1.5 ml (+1). (c) Time versus % cumulative release (Batch C, F, and I). For batch C, F, and I, the amount of SYLOID® 244 FP was fixed to 60 mg (−1) and the amount of ethanol varies to 0.5 ml (−1), 1 ml (0), and 1.5 ml (+1)

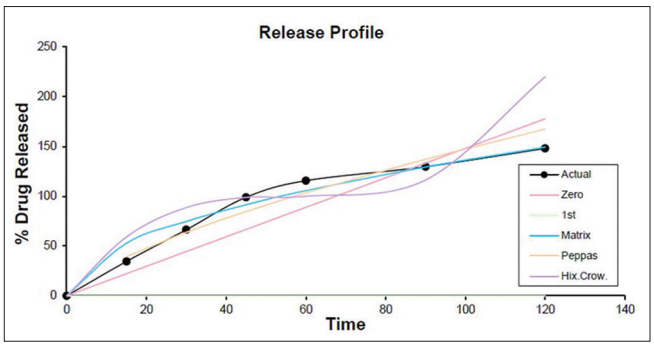


**Figure 10:** Model fitting

From Figure 9b, maximum cumulative drug release was observed in the formulation H (74.40% ± 6.0798%) as compare to formulation B and E (65.1608% ± 7.1994% and 69.3904% ± 6.8710%, respectively) in 2 h.

From Figure 9c, maximum cumulative drug release was observed in the formulation I (71.4008% ± 7.4786%) as compare to formulation C and F (62.4395% ± 7.9746% and 66.530% ± 7.7918%, respectively) in 2 h.

Optimization of all 9 batches was done using design expert and maximum % cumulative release, i.e., 74.4009% ± 6.0798% was observed in batch H. So, we conclude that batch H was the optimized batch.

### *Kinetic modeling of dissolution data*

The optimized formulation batch H was subjected to various mathematical models to understand the release pattern. The study was carried out using the PCP-Disso-v3 software. The values of coefficient of regression suggest the best fit kinetic model.

The value of the coefficient of regression was 0.9836, and from Table 10 Figure 10 it was concluded that and the best fitted kinetic model for optimized batch was found to be matrix model.

### Comparison of optimized formulation with conventional tablet and marketed tablet

Comparative study was done in between tablet with and without SYLOID® 244 FP (X and Y, respectively) and marketed product (Z) by considering % cumulative release as a factor and its graphical representation is as shown in Figure 11.

From Figure 11, we found that % cumulative release profile was increased up to 74.40% ± 6.0798% for tablet prepared with SYLOID® 244 FP compare to conventional tablet without SYLOID® 244 FP and marketed tablet which was 17.7862% ± 4.9672% and 40.0685% ± 5.0084%, respectively.

### Stability profile of optimized batch

The stability studies of optimized formulation revealed that no significant changes were observed in the physical parameters when stored at temperature and humidity conditions of 40°C ± 2°C/75 ± 5% RH (Climatic zone IV condition for

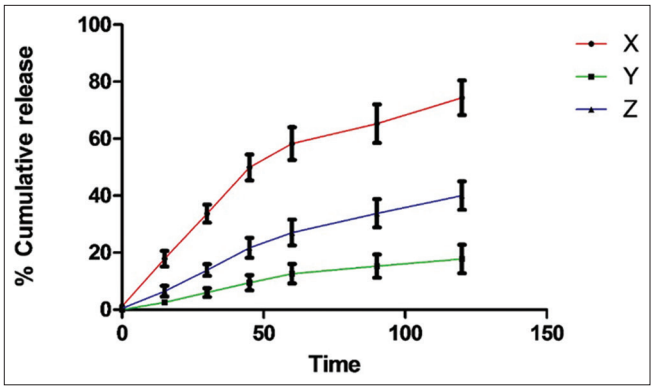


**Figure 11:** Comparison of time versus % cumulative release graph. X: Optimized batch, Y: Conventional tablet without SYLOID® 244 FP, and Z: Marketed tablet (Valent 40)

accelerated testing) to access their long-term stability. Tablets were taken and retested for drug content after an interval of 7, 15, and 30 days. Percent drug content was found in ranged from 96.21 ± 0.41 to 99.61 ± 0.37 indicating no significant reduction in the content of the active drug was observed over a period of 1-month; the percent drug content was found within a specified limit of IP. Therefore, no evidence of degradation of drug quantity was observed.

## CONCLUSION

Enhancement in the solubility of valsartan-loaded SYLOID® 244 FP matrix was observed as compared with valsartan pure drug. Furthermore, the improvement in dissolution profile of valsartan-loaded SYLOID® 244 FP-containing tablets was observed as compared with conventional and commercially available valsartan tablets. This study ultimately indicates that non-ordered mesoporous SYLOID® 244 FP is a promising carrier, which enhances the oral bioavailability of poorly water-soluble drugs. Preparing tablet dosage form containing drug-loaded silica may represent a new approach for the development of better absorbed oral formulations for poorly soluble drugs.

Conclusively, the current study attained the successful design, preparation, and evaluation of drug-loaded SYLOID® 244 FP-containing valsartan tablets.

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**Source of Support:** Nil. **Conflict of Interest:** None declared.