Preparation, characterization, and *in vivo* evaluation of valsartan porous matrices using emulsion solvent evaporation technique

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**Abstract**

**Introduction:** Valsartan is a type II Biopharmaceutics Classification System (BCS) classified drug. The poor aqueous solubility restricts its use in developing sustained or controlled release systems for the treatment of chronic hypertensive conditions. The present investigation was conducted with an objective to formulate porous matrices (PMs) of valsartan in order to enhance aqueous solubility. **Materials and Methods:** Polyvinylpyrrolidone (PVP) K30 and poloxamer 407 were used as hydrophilic carriers; hexane was used as a pore-forming agent, ethanol was used as a solvent, and tween 20 was used as an emulgent. The prepared porous matrices were characterized and based on the maximum slope obtained from the Washburn method and other characterization results; the drug PVP K30 (1:1.5) was selected and further evaluated *in vivo* by the rat gut method. **Results:** The prepared porous matrices are white, free-flowing powders. Among prepared formulations drug PVP K30 (1:1.5) showed maximum Washburn slope of 0.0103. The mean particle size was found to be 0.82 µ and D50 (median) value was found to be 0.55 µ. The scanning of particles at various magnifications by scanning electron microscopy (SEM) analysis revealed that the method had effectively induced porosity. The Q value of valsartan from porous matrices was observed at 20 min with a first order regression value of 0.917. The calculated difference factor (F1) when compared with pure valsartan was observed to be 63.32%. From the values obtained, it was evident that the method amplifies the percentage of drug dissolution between sixfold and eightfold when compared to pure drug. From the absorption studies by the rat gut method, the absorption of porous matrices increased threefold. **Conclusion:** Porous matrices of valsartan: PVP K30 (1:1.5 ratio) hold promise for the enhancement of solubility and consecutive formulation of controlled release systems even with poorly soluble drugs.

**Key words:** Hexane, poloxamer 407, porous matrices, polyvinylpyrrolidone (PVP) K30, valsartan, Washburn method

**INTRODUCTION**

Drugs that are administered in the form of solid oral dosage forms undergo various physicochemical changes and become a solution in the surrounding medium. The drug in solution undergoes mass transfer across biological barriers and finally reaches systemic circulation to elicit pharmacological response, i.e., any drug to get absorbed has to initially dissolve in the surrounding medium. In this context, aqueous solubility of the drug is an important physicochemical factor. Drug solubility is a major challenge for effective drug transportation and also the primary rate limiting step in drug absorption and bioavailability. Valsartan (VAL) is angiotensin receptor blocker used in the effective treatment of hypertension and congestive heart failure.
It has a molecular weight of 435.5D with plasma elimination half-life of 6 h. Valsartan has poor aqueous solubility but good membrane permeability resulting in poor drug bioavailability. Enhancing the aqueous solubility of valsartan will increase the bioavailability of drug and also make the drug suitable for controlled release formulations.

In the current investigation, an attempt was made to increase the aqueous solubility of the drug by enhancing wetting efficiency using porous matrices technique. The technique involves preparation of an ethanolic solution of the drug and carrier. To the prepared drug carrier solution another volatile immiscible solvent, hexane was added to prepare an emulsion of hexane/ethanol (H/M) using tween 20 as emulsifying agent. The emulsion was subjected to evaporation at 40°C for about 30 min. Hexane being the dispersed phase, when evaporated results in formation of large pores. Eventually ethanol was also evaporated, resulting in porous matrices with enhanced porosity. Figure 1 portrays the schematic preparation of drug porous matrices. The effect of porous matrices on wettability, surface characteristics, and dissolution characteristics was performed and showed good dissolution enhancement for porous matrices.

MATERIALS AND METHODS

Valsartan was obtained as a gift sample from Dr. Reddy Laboratories Pvt. Ltd., Hyderabad, India. Poloxamer and polyvinylpyrrolidone were gifted from Jubilant Organosys, Noida, Delhi, India. Hexane, ethanol, and Tween 20 were obtained from commercial sources. All other materials used were of analytical grade.

Experimental methodology

Preparation of physical mixtures

The physical mixtures of valsartan and hydrophilic carrier polyvinylpyrrolidone (PVP) K30 in different ratios were prepared by passing equal quantities of materials through sieve #40. The mixtures were transferred to a polybag, which was tightly closed and tumbled upside down for about 200-250 times to attain effective mixing. The obtained mixture was stored in a desiccator for further characterization. The same procedure was followed for poloxamer 407; 20 mg of Tween 20 was added to all the mixtures. The details of drug:carrier ratios and their quantities are given in Table 1.

Preparation of porous matrices

80 mg of pure drug was accurately weighed using Essae electronic balance and dissolved in 25 mL of ethanol. To the above ethanolic drug solution, the required amount of hydrophilic carrier (poloxamer 407) and surfactant (Tween 20) were added with constant stirring with the help of magnetic stirrer. Stirring was continued until uniform dispersion was obtained by placing the beaker in cold water bath to prevent loss of solvent during stirring process. To the obtained polymer dispersion, a required quantity of hexane was added for emulsification. Emulsification was achieved by using REMI high speed homogenizer at 5,000 rpm. The resulting emulsion was transferred into a tray and both the solvents were evaporated at 40°C for about 30 min. The obtained porous matrices were milled in ball mill until 80% of the powder passed through sieve # 80. The procedure was repeated for all drug polymer ratios as well as other hydrophilic carrier PVP K30. A total of 6 formulations with each hydrophilic carrier were prepared with various drug:carrier ratios. The details of the formulations are given in Table 2.

Characterization of porous matrices

The prepared porous matrices were characterized for surface characteristics by scanning electron microscopy (SEM), wetting efficiency by the Washburn method, and micromeritic characteristics such as particle size distribution, density, and flow properties.

Solubility

Solubility of pure drug, physical mixture, and porous matrices was performed to estimate the effect of induced porosity on solubility of the drug. The details of solubility study was given in Table 3. A saturated solution of the drug was prepared by dissolving 50 mg/mL of drug and added to 10 mL of each buffer having pH 1.2, 4.5, 6.8, and water. The test was performed at a physiological temperature, i.e., 37°C. The prepared samples were filtered using 0.22 µ pore size Merck Millex-VV PDFV filters with the aid of a Baba vacuum pump.

Table 1: Physical mixture of Valsartan with carriers

| Ingredients       | Drug:polymer ratio | Category     |
|-------------------|--------------------|--------------|
| Valsartan         | 1:0.5              | 1:1          |
| Valsartan         | 1:1.5              | 1:2          |
| PVP K30/PLX       | 80:80              | Drug         |
| Tween 20          | 40:80              | 120:160 Carrier |
| Wetting/Emulsifying agent | 5:5 | 5:5 |

PLX: Poloxamer
pump. The samples were suitably diluted and concentration of the drug was estimated using the ultraviolet (UV) method.

**Wetting efficiency**

Washburn method[3,4]

Figure 2 represents the setup of components to estimate wetting efficiency. The method involved preparation of a powder column, which contained tightly packed powder under testing. The column was fixed to the stand. A digital weighing balance with \( d^2 = 0.1 \) mg was placed below the column. Wetting liquid such as water was taken in a china dish and placed on the weighing balance and the total weight was recorded as initial weight. The column was lowered until it touched the surface of water. Due to wetting and capillary action, water rose into a column from china dish resulting in a decrease of weight, which was displayed on the digital balance. The change in weight for every 5 s was recorded. The mass of water raised for every 5 s was calculated using following formula.

\[
\eta/\rho^2 \gamma \cos \theta
\]

According to the Washburn method, a graph of time versus mass was plotted, the slope of which was found to be \( \eta/\rho^2 \gamma \cos \theta \). The more the slope, the more is the wetting efficiency.\[5-7\]
The details of washburn slopes obtained is given in Figures 3-6.

**Micromeritic characterization**

Micromeritic characterization of pure drug, physical mixtures, and porous matrices were performed to estimate the effect of porous matrices on powder characteristics. Fundamental properties such as particle size and derived properties such as density and flow properties were estimated.

**Density**

 Derived properties such as bulk density, tapped density, and flow behavior of pure drug, physical mixtures, and porous matrices were estimated using elite tap density apparatus.

**Bulk density and tap density**

A known weight of powder was transferred to a 100 mL graduated measuring cylinder (Borosil) and the volume occupied by powder was recorded; the apparatus was operated for tapping and tap density was estimated as per the methods described in the United States Pharmacopeia Chapter 616 “Bulk Density and Tapped Density.” From the obtained values, Carr’s index and Hausner ratio were estimated to identify flow characteristics.

**Drug content**

Drug content in physical mixtures and porous matrices was estimated by dissolving a quantity equivalent to 80 mg of valsartan in 250 mL of methanol. Suitable dilutions were made and the amount of drug was determined using Elico Spectrophotometer 210 model and the results were analyzed using Spectratreats™ software (Elico).

**Dissolution rate study**

Dissolution study of pure valsartan, physical mixture, and porous drug matrices was studied using DR8000 dissolution apparatus by paddle method (Lab India). The dissolution study was characterized at 37°C in 900 mL of 6.8 phosphate buffer at 50 rpm. 5 mL of aliquots were withdrawn through a 0.45 µ-filter paper (Merck) at 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, and 60 min. The collected samples were analyzed after suitable dilutions against blank at 250 nm. The dissolution rate and percentage of drug dissolved for pure drug, physical mixtures, and porous matrices were studied and they are represented using box-whisker plots.

**Evaluation of porous matrices**

After thorough characterization of porous matrices based on the results of solubility, wetting efficiency, and dissolution studies, the valsartan formulations with more drug solubility, more Washburn slope, and maximum percentage of drug dissolved were selected and further evaluated for surface characteristics by SEM, particle size distribution by the Malvern method, compatibility by differential scanning calorimetry (DSC), dissolution rate studies, and bioavailability studies by in vivo rat gut method.

**Particle size**

Particle size is one of the significant fundamental properties of powder, which influences various physicochemical properties.
Particle size affects the flow, density, and dissolution rate of drugs. Preparation of porous matrices induces porosity and also reduces particle size, which in turn increase surface area preceding enhanced solubility and dissolution rate of poorly soluble drugs. Particle size was estimated by using Malvern Mastersizer 2000 (Malvern Instruments) and various size distribution statistics such as mode, median, span, and specific surface area were estimated.

**Differential scanning calorimetry study**

DSC thermogram of porous matrices has been studied for the valsartan:PVP K30 (1:1.5) ratio. The thermograms of all porous matrices were recorded using Universal V4.5A DSC analyzer, Divya Laboratories, Mumbai, Maharashtra, India, at a heating rate of 20°C/min from 0°C to 350°C in nitrogen atmosphere.

**Scanning electron microscopy**

To understand the effect of porous matrices on surface characteristics SEM was conducted. The SEM analysis was performed using scanning electron microscope S3400, Hitachi, Marunouchi, Chiyoda-ku, Tokyo, Japan. Prior to examination, the samples were mounted on an aluminum stub using a double-sided adhesive tape and then it was made electrically conductive by coating it with a thin layer of gold (approximately 24 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 KV.

**Dissolution rate and kinetics of drug dissolution**

Dissolution rate study of valsartan porous matrices was conducted using DR8000 dissolution apparatus by the paddle method at 37°C in 900 mL of dissolution medium at 50 rpm. 10 mL of aliquots were withdrawn through 0.45-µ filter paper at 5 min, 10 min, 15 min, 20 min, 30 min, 45 min and 60 min. The collected samples were analyzed after suitable dilutions using UV method against blank at the required wavelength. The dissolution rate of porous matrices was studied using zero order and first order model.

**Difference factor \( F_1 \)**

Difference factor is a model independent approach to estimate the difference in dissolution profiles. The difference factor estimates the percentage of difference between two dissolution curves at

![Figure 3: Washburn slopes of valsartan pure and physical mixtures of PVP K30](image)

![Figure 4: Washburn slopes of porous matrices of valsartan with various ratios of PVP K30](image)

![Figure 5: Washburn slopes of physical mixture of valsartan with various ratios of PLX 407](image)

![Figure 6: Washburn slopes of porous matrices of valsartan with various ratios of PLX 407](image)
each time point. According to the Food and Drug Administration (FDA), the difference factor can be estimated using the following equation.

\[ F_1 = \left\{ \frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} R_t} \right\} \times 100 \]

where \( n = \) number of time points, \( R_t = \) dissolution of reference at time \( t \), \( T_t = \) dissolution of test at time \( t \).

More the percentage difference in dissolution of pure drug when compared to porous matrices, more is the dissolution rate enhancement.

**In vivo rat gut method to study rate of absorption**

The method was investigated by Doluiso et al., to estimate the rate of absorption of drugs from the stomach without collecting blood samples. The method involves estimation of drug concentration before and after entering gastrointestinal (GI) tract. Male albino rats weighing 200-250 g were fasted 24 h prior to surgery; however, drinking water was readily accessible. To prevent coprophagy, the rats were kept in cages having a wide mesh floor. All the precautions were taken as per Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). A prior approval was granted by the Institutional Animal Ethical Committee (IAEC) with protocol number: 10/IAEC/VPC/Pharma/RES/2011-12. The rats were anesthetized approximately 1 h prior to surgery with phenobarbitone injection by the intraperitoneal route. The dose and volume to be injected was calculated precisely as improper dose can cause death of the animal.

**Preparation of perfusion solution**

Perfusion solution was used for perfusion and removal of the waste from the gut to avoid interferences during sampling. The irrigation of GI tract before administration of porous matrices was performed and the solution contained following molar concentration of salts: 8.474 g of sodium chloride \((1.45 \times 10^{-1} \text{M})\), 0.3399 g of KCl \((4.56 \times 10^{-3} \text{M})\), 1.3873 g of CaCl\(_2\) \((1.25 \times 10^{-2} \text{M})\), and 0.5998 g of sodium dihydrogen phosphate \((5 \times 10^{-3} \text{M})\) were dissolved in distilled water and the volume was up to 1,000 mL.

**In vivo method**

After anesthetizing the rat with phenobarbitone injection by the intraperitoneal route, the small intestine was exposed by midline abdominal incision. Two segments of tygon tubing (Poolay Inc.), 4-cm long were inserted through small slits at the duodenal and ileal ends. Care was taken to handle the small intestine gently and to maintain an intact blood supply. The stomach and cecum were closed off by ligature with care not to occlude any major blood vessels. The tygon tubing was secured with silk suture.

A 20-mL hypodermic syringe (Life long Meditech) was attached to duodenal tubing and 1 mL syringe was attached to the ileal tubing. Intestinal lumen was irrigated using perfusion solution from duodenal tubing and collected at the ileal end. Irrigation was carried out until effluent solution was clear. Any solution remaining in the lumen after irrigation was removed by pumping air through lumen. 10 mL of drug \((1 \text{ mg/mL})\) solution was immediately introduced into the intestine through the duodenal end. 0.1 mL of sample solution was collected at 0 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 35 min, 40 min, and 45 min. The collected samples were measured using the UV method. To assure uniform drug solution concentration throughout the gut segment, aliquots were removed from the two syringes alternatively at various intervals up to 45 min.

Absorption of valsartan alone and optimized porous matrices were studied. A total of 12 rats were used; 6 rats were administered pure drug and 6 rats were administered the optimized porous matrices.

**RESULTS AND DISCUSSION**

The physical mixtures and porous matrices of valsartan and hydrophilic carrier PVP K30 in different ratios were successfully prepared by the emulsion solvent evaporation technique. The prepared porous matrices were characterized for DSC, solubility, micrometric characteristics, wetting efficiency by the Washburn technique.

| Name of the drug | Solubility (mg/mL) | pH 1.2 | pH 4.5 | pH 6.8 | Water | pH7.4 |
|------------------|--------------------|--------|--------|--------|-------|-------|
| Valsartan        |                    | 0.100  | 1.82   | 4.88   | 0.192 | 6.5   |

| Name of the drug | Washburn slopes for wetting efficiency |
|------------------|--------------------------------------|
|                  | Pure drug | Physical mixture | PVP\(^{a}\) K30 | Porous matrices |
| Valsartan        | 0.0037    | 1.0 | 0.5 | 0.0048 | 0.0055 | 0.0068 | 0.0077 | 0.0069 | 0.0076 | 0.0103 | 0.0089 |
| Poloxamer 407    | 0.0047    | 0.0050 | 0.0059 | 0.0074 | 0.0063 | 0.0071 | 0.0084 | 0.0093 |

\(^{a}\)PVP: Polyvinylpyrrolidone
Characterization of porous matrices

The prepared physical mixtures and porous matrices were characterized for solubility, wetting efficiency, and the percentage of drug dissolved to study the effect of the method and carriers on amplification of drug solubility and dissolution.

Solubility

Estimated using various mediums such as water, buffers having pH 1.2, 4.5, 6.8 and 7.4. The solubility of valsartan was found to be more at pH 7.4. The results obtained are given in Table 4.

Wetting efficiency

Washburn method

The graphs of valsartan pure drug, physical mixtures, and porous matrices with carriers poloxamer 407 and PVP K30 are given in Figures 3-6 and the slopes are given in Table 5. From the results obtained, valsartan showed a Washburn slope of 0.0037. The physical mixtures of drugs with carriers showed an increase in wetting efficiency with increase in the amount of carrier when compared to pure drugs; this was due to increase in hydrophilic carrier ratio. The porous matrices of valsartan showed a maximum Washburn slope of 0.0103 with PVP K30 drug:carrier ratio of 1:1.5, whereas the physical mixture of the same showed a slope of 0.0077.

From the above values, it evident that the physical mixtures enhanced the wettability of drugs to a certain extent but porous matrices have more slopes indicating the effect of the method on reduction of contact angle and enhancement of wettability. The rapid wetting was due to formation of porous structures and enhancement of contact surface area facilitating capillary rise of water and wettability.

Micromeritic characterization

The physical mixtures and porous matrices valsartan with various carriers were subjected to bulk density, tap density, and compressibility index studies. The data obtained are listed in Table 6. From the values obtained, the difference in tap density to bulk density was large for porous matrices when compared to physical mixtures and hence, the compressibility index rose for porous matrices indicating decreased flow properties of prepared porous matrices. The porous matrices of PVP K30 of valsartan have more Carr’s index when compared to poloxamer 407 porous matrices.

From the compressibility index values, the flow was observed to be between satisfactory and poor indicating the requirement of glidants during formulation of tablets using porous matrices. The decreased flow of porous matrices might have been due to increased surface area, which inducts more interparticulate friction resulting in reduced flow characteristics.

**Table 6: Derived properties of valsartan physical mixture and porous matrices with PVP K30 and poloxamer**

| Parameter | Physical mixture | PVP† K30 |
|-----------|-----------------|---------|
|           | 1:0.5 | 1:1 | 1:1.5 | 1:2 | 1:0.5 | 1:1 | 1:1.5 | 1:2 |
| Dₚ (g/mL) | 0.42 | 0.48 | 0.51 | 0.54 | 0.49 | 0.49 | 0.58 | 0.59 |
| Dₜ (g/mL) | 0.61 | 0.60 | 0.62 | 0.63 | 0.63 | 0.69 | 0.76 | 0.81 |
| CI (%)    | 31.1 | 20  | 17.7 | 14.2 | 22.2 | 28.9 | 23.6 | 27.1 |
| Poloxamer 407 |    |     |      |     |      |      |      |      |
| Dₚ (g/mL) | 0.40 | 0.44 | 0.49 | 0.51 | 0.44 | 0.48 | 0.52 | 0.57 |
| Dₜ (g/mL) | 0.62 | 0.61 | 0.69 | 0.7  | 0.59 | 0.6  | 0.69 | 0.74 |
| CI (%)    | 35.4 | 27.8 | 28.9 | 27.1 | 25.4 | 20  | 24.6 | 22.9 |

†PVP: Polyvinylpyrrolidone, CI: Confidence interval

**Table 7: Drug content of valsartan in physical mixtures and porous matrices**

| Physical mixtures | Drug: carrier ratio | % drug content of valsartan | Porous drug matrices | Drug: carrier ratio | % drug content of valsartan |
|-------------------|---------------------|-----------------------------|----------------------|---------------------|-----------------------------|
| PLX 407           | 1:0.5               | 99.99                       | PLX 407              | 1:0.5               | 98.7                        |
|                   | 1:1                 | 99.3                        | 1:1.5                | 100.2               | 102.3                       |
|                   | 1:1.5               | 100.2                       | 1:2.0                | 99.4                | 100.1                       |
| PVP† K30          | 1:0.5               | 100.8                       | PVP K30              | 1:0.5               | 98.6                        |
|                   | 1:1                 | 97.6                        | 1:1.5                | 103.3               | 100.1                       |
|                   | 1:1.5               | 99.1                        | 1:2                  | 100.8               | 100.8                       |

†PVP: Polyvinylpyrrolidone, PLX: Poloxamer

Drug content

Drug content estimation was performed for physical mixtures and porous matrices of valsartan using a suitable analytical method. The preparation of porous matrices involves multiple steps due to which suitable amount of drug loss may occur, resulting in improper interpretation of results. To avoid misinterpretation of data, the drug content was estimated. The percentage of drug content value is given in Table 7.

The percentage of drug content estimated for physical mixtures of valsartan with PVP K30 was between 97.6% and 100.8% and with poloxamer 407 is between 99.3% and 100.2%. The percentage drug content estimated for porous matrices of valsartan with PVP K30 were between 98.6% and 100.8% and with poloxamer 407 between 98.75 and 102.3%. All the formulations showed values within the limits, i.e., 100 ± 15%.

Dissolution study

The percentage of drug dissolved at a specific time interval was studied for pure drug, physical mixtures, and porous matrices of valsartan using suitable medium. For drugs that belong to Biopharmaceutics Classification System (BCS) class II the bioavailability was dissolution-dependent, i.e., drugs with more percentage of dissolution possess better bioavailability. The percentage dissolution studies also indicate the effect of method on the dissolution of drugs and helps in selection of the best formulations. The formulation with more percentage of drug dissolved in less time was considered as the best formulation.
The percentage of drug dissolved of pure drug was studied over a period of 45 min considering United States Pharmacopoeia (USP) dissolution criteria. The dissolution studies of valsartan were performed using 6.8 phosphate buffer. The values obtained are given in Table 8. From the box-whisker plot, it was observed that the percentage of drug dissolved in 45 min for valsartan was 42.7%.

The percentage drug dissolved of valsartan from physical mixtures and porous matrices is given in Table 9. The box-whisker plots of valsartan with their physical mixtures and porous matrices are given in Figures 7 and 8. Valsartan exhibited maximum 102.1% of drug dissolved with porous matrices of PVP K30. The porous matrices of valsartan with PVP K30 at a ratio of 1:1.5 and 1:2 have not much difference in the percentage drug dissolved. The more percentage of drug dissolved in 1:1.5 ratio of PVP K30 might have been due to presence of more percentage drug content in formulation but still there was not much difference in increasing the carrier ratio from 1:1.5 to 1:2. Among all the prepared ratios 1:1.5 ratio was considered as the best drug:carrier ratio. Moreover, the percentage drug dissolved at 15 min was >Q+5 for 1:1.5 ratio whereas, it was <Q+5 at 15 min for 1:2 ratio.

From the characterization of pure drug, physical mixtures and porous matrices based on solubility, wetting efficiency and percentage drug dissolved valsartan porous matrices with PVP K30 at 1:1.5 ratio were selected for further evaluation.

**Evaluation of best porous matrices**

After thorough characterization, the best porous matrices for each drug were selected and they were further evaluated to establish

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**Table 8: Percentage of pure drug dissolved in respective mediums**

| Time in min | % drug dissolved |
|-------------|------------------|
|             | Valsartan        |
| 0           | 0                |
| 5           | 11.14±0.12       |
| 10          | 16.34±0.09       |
| 15          | 21.78±0.73       |
| 20          | 27.83±0.62       |
| 30          | 36.66±1.24       |
| 45          | 42.71±1.31       |

**Table 9: Percentage of dissolved valsartan from physical mixtures and porous matrices**

| Time | Pure | 1:0.5 | 1:1 | 1:1.5 | 1:2 | (VAL:PLX 407) physical mixture % drug dissolved |
|------|------|-------|-----|-------|-----|-----------------------------------------------|
|      |      |       |     |       |     | (VAL:PVP K30) physical mixture % drug dissolved |
| 0    | 0    | 0     | 0   | 0     | 0   | 0                                             |
| 5    | 11.14| 17.1  | 22.8| 29.4  | 30.2| 13.6                                          |
| 10   | 16.34| 23.8  | 34.7| 39.3  | 41.6| 20.9                                          |
| 15   | 21.78| 31.1  | 38.5| 45.7  | 49.6| 28.5                                          |
| 20   | 27.8 | 37.6  | 46.8| 51.4  | 60.2| 34.4                                          |
| 30   | 36.6 | 45.7  | 52.6| 55.6  | 64.8| 42.8                                          |
| 45   | 42.7 | 54.3  | 57.6| 62.5  | 74.6| 52.4                                          |

| Time | Pure | 1:0.5 | 1:1 | 1:1.5 | 1:2 | (PM:PLX 407) porous matrices % drug dissolved |
|------|------|-------|-----|-------|-----|-----------------------------------------------|
|      |      |       |     |       |     | (PM:PVP K30) porous matrices % drug dissolved |
| 0    | 0    | 0     | 0   | 0     | 0   | 0                                             |
| 5    | 11.14| 40.7  | 52.7| 69.6  | 63.4| 38.3                                          |
| 10   | 16.34| 46.4  | 60.7| 77.9  | 74.6| 42.9                                          |
| 15   | 21.78| 55.2  | 69.3| 89.4  | 83.9| 54.4                                          |
| 20   | 27.8 | 64.4  | 80.5| 97.3  | 85.6| 62.5                                          |
| 30   | 36.6 | 80.7  | 89.6| 99.2  | 94.3| 77.4                                          |

**Figure 7:** Comparative box-whisker plot of valsartan using PVP K30 physical mixture and porous matrices

**Figure 8:** Comparative box-whisker plot of valsartan using poloxamer 407 physical mixture and porous matrices
the effect of porous matrices method on the particle size, surface characteristics, dissolution rate, and bioavailability. Particle size analysis was performed by the Malvern method, surface characteristics by SEM, and in vitro dissolution rate studies and bioavailability studies by in vivo rat gut method.

**Particle size analysis using Mastersizer 2000**

Particle size analysis was performed using Malvern Mastersizer 2000 for pure drug and porous matrices of valsartan with PVP K30 (1:1.5 ratio).

Particle size distribution report was obtained by taking volume (%) on y-axis and size (µm) on x-axis. Table 10 gives various particle size data obtained by the Malvern method. The D50% (median) obtained for pure drug valsartan was found to be 28.743 µ. The porous matrices of valsartan showed the D50% (median) of 2.337 µ. Table 10 gives the specific surface area of pure drug and of porous matrices. The specific surface area of porous matrices increased distinctly when compared to pure drug. This was due to decrease in particle size as well as induction of porosity. The details of particle size distribution curves are represented in Figures 9 and 10.

**Differential scanning calorimetry study**

The DSC thermogram of valsartan porous matrices with PVP K30 showed no characteristic peaks. A broad peak with small loss in weight indicates the conversion of drug into amorphous form. From the DSC curves it is understood that the crystallinity of pure drug and physical mixtures were good and showed characteristic endothermic peak at 118°C. In case of porous matrices, the endothermic peak obtained was very broad and no sharp peak was observed, which concludes that by solvent evaporation method the drug converted to amorphous form, which might be one of the reasons for rapid drug dissolution.

**Scanning electron microscopy**

To evaluate surface characteristics, SEM studies were conducted. The SEM photographs of valsartan pure drug and best porous matrices formulation were given in Figures 11 and 12. The scanning of particles at various magnifications reveals that the method has effectively induced porosity.

| Sample name | Size parameters | Specific surface area (m²) | Span |
|-------------|-----------------|----------------------------|------|
| Valsartan pure | D50% (µ) | 28.743 | 1.251 |
| Valsartan porous matrices 1:2 (PM:PVPK30) | D50% (µ) | 2.337 | 3.973 |

**Table 10: Representing various particle size parameters of pure drugs and optimized porous matrices**

Figure 9: Particle size distribution of valsartan pure drug using Malvern Mastersizer 2000

Figure 10: Particle size distribution of valsartan porous matrices (1:1.5) using Malvern Mastersizer 2000

Figure 11: Valsartan pure

Figure 12: Porous matrices of valsartan-PVP K30
Dissolution rate study and kinetics of drug dissolution

Dissolution rate study was performed to estimate the amount of drug dissolved per unit time. With increased porosity the dissolution rate of porous matrices was much higher than that of pure drug. The Q value of pure drug was not achieved within 60 min, whereas the Q value of valsartan porous matrices is obtained within 20 min. The dissolution data of porous matrices of valsartan was treated with zero and first order kinetic expressions. It was observed that the dissolution of porous matrices was best fitted with first order release. The dissolution studies were also conducted for marketed valsartan tablets, Diovan 80 mg (Novartis). Diovan 80 mg is a biconcave round film-coated tablet with scoring and embossing. On one side, the tablet is embossed with the letters “D” and “V” and on the other side, it is embossed with “NVR.” The dissolution of marketed tablet is performed with the same dissolution conditions. The cumulative percentage drug dissolved in optimized porous matrices of valsartan, pure drug, and divan 80 mg was given in Table 11.

The regression values for valsartan porous matrices were observed to be 0.9176. The kinetic parameters such as zero order and first order slopes and regression values are given in Table 12.

Difference factor

The difference factor F1 was calculated to estimate the effect of method on percentage dissolution enhancement. The values obtained are given in Table 13. From the values of difference factor F1, it was clearly evident that there was a large percentage difference in the dissolution profiles of pure drug when compared to porous matrices. The difference factor obtained for valsartan was 63.32%. From the values obtained, it was evident that the method amplifies the percentage drug dissolution between sixfold and eightfold when compared to pure drug. The cumulative percentage of drug release for pure and porous Matrices of valsartan:PVP K30 (1:1.5) is shown in Figure 13.

Absorption rate studies

Absorption rate studies were conducted using in vivo rat gut method to estimate the effect of the method on drug absorption rate, i.e., bioavailability. A prior approval with protocol no. 10/IAEC/VPC/Pharma/RES/2011-12 was granted. The study was conducted for pure drug as well as best porous matrices. The percentage of drug unabsorbed for all samples is given in Tables 14 and 15. From the table, the percentage of unabsorbed of valsartan in 45 min is 67.8 ± 0.69%. The percentage of unabsorbed of porous matrices of valsartan is 24.2 ± 3.76%. From the absorption studies by the rat gut method, it was clearly understood that enhancing dissolution rate and wettability for type II BCS class drugs enhances absorption rate and bioavailability.

The kinetics of absorption by zero order and first order were studied for pure drug and porous matrices. The obtained slopes and regression values of valsartan pure drug and optimized porous matrices are given in Figures 14 and 15. The regression values of drugs and their porous matrices are given in Table 16.

The zero order regression value of pure valsartan is 0.9753, whereas the first order regression value for the pure drug is 0.9638.

| Table 11: Cumulative % drug dissolved of optimized porous matrix |
|-----------------|-----------------|-----------------|
| Time (min)      | Pure            | PM:PVP K30 (1:1.5) | Marketed formulation Diovon 80 mg |
| 10              | 18.32±0.14      | 77.4±2.34        | 63.2±1.98 |
| 20              | 26.14±1.32      | 87.1±3.11        | 78.9±1.74 |
| 30              | 34.65±2.14      | 96.8±2.65        | 86.2±1.31 |
| 40              | 37.12±1.31      | 99.7±2.69        | 97.9±1.11 |
| 50              | 41.22±1.55      | 100.6±1.94       | 100.2±1.56 |
| 60              | 48.75±0.86      | 100.6±2.79       | 98.2±1.98 |

| Table 12: Kinetics of drug dissolution |
|---------------------------------------|
| Drug matrices                         | Zero order slope | Zero order slope | First order slope | First order slope |
|---------------------------------------|------------------|------------------|------------------|------------------|
| Valsartan                             | 0.455            | 0.8065           | -0.0211          | 0.9176           |

| Table 13: Model independent difference factor (F1) for dissolution profiles of porous matrices compared to pure drug |
|------------------------------------------------------------------------------------------------------------------|
| Name of the drug | F1 (%) |
| Valsartan         | 63.322 |

Figure 13: Cumulative % of drug release for pure, porous matrices of valsartan:PVP K30 (1:1.5) and marketed Diovan formulation

Figure 14: Zero order plot of drug absorption from pure drug and porous matrices
From the regression values, it was understood that valsartan pure drug follows zero order absorption. The zero order absorption was due to the presence of less drug in the solution owing to its poor solubility. From the absorption studies, it was clearly evident that absorption of valsartan was dissolution rate-limited.

The zero order regression values of valsartan porous matrices with respective carriers was 0.9474, whereas the first order regression value for the porous matrices was 0.9938. From the regression values, it was understood that the porous matrices follow first order absorption. The first order absorption was due to the presence of more drug in the solution owing to its enhanced solubility by the method. From the absorption studies of porous matrices, it was clearly evident that the porous matrices enhanced dissolution rate and absorption was no more dissolution rate-controlled.

**CONCLUSION**

The objective of the present investigation was to sufficiently amplify the dissolution rate and bioavailability of the antihypertensive class of drugs such as valsartan using porous matrices method. Novel carriers such as PVP K30 and poloxamer 407, and at least possible concentrations were used in the successful preparation of porous matrices. The characterization and evaluation of porous matrices for wetting efficiency and percentage drug dissolution, particle size analysis, DSC studies, SEM studies, and bioavailability studies revealed the following conclusions. The porous matrices of valsartan drug showed better wetting efficiency compared to physical mixtures concluding the effect of induced porosity. Porous matrices of valsartan with PVP K30 at 1:1.5 ratio showed the maximum wetting efficiency with a slope of 0.0103. The percentage of drug dissolved in 45 min is more for porous matrices of valsartan: PVP K30 (1:1.5 ratio). The DSC analysis reveals that the drug and carrier has no intermolecular interaction, whereas the DSC of porous matrices reveals that the drug is converted to amorphous nature resulting in enhanced solubility. Particle size analysis by Malvern Mastersizer reveal that the porous matrices have less particle size and the specific surface area of porous matrices is increased significantly when compared to pure drug. The SEM photographs conclude that the method effectively induces porosity, which is responsible for increased specific surface area and rapid dissolution rate. The dissolution rate study reveals that porous matrices follow first order drug release due to the presence of more drug in the solution. The bioavailability studies by in vivo rat gut method concludes that enhancing wetting and dissolution rate enhance bioavailability of BCS class II drugs. From the in vivo absorption studies, the absorption of drug follows first order, whereas for pure drug it follows zero order due to saturation of drug solution.

Hence, porous matrices of valsartan:PVP K30 (1:1.5 ratio) have met the objectives of the study. From the above, it was concluded that the abovementioned porous matrices hold promise for the enhancement of solubility and consecutive formulation of controlled release systems even with poorly soluble drugs.

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**Conflicts of interest**

There are no conflicts of interest.
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