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# PULSATILE RELEASE TABLETS OF VALSARTAN: DEVELOPMENT, STATISTICAL OPTIMIZATION, AND IN VITRO EVALUATION

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**ABSTRACT:** Pulsatile release tablet containing Valsartan will be developed with an objective to get desired drug release according to Circardian Rhythm of body and attack episodes of Hypertension where blood pressure is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. Core tablet was prepared by direct compression using super disintegrants like sodium starch glycolate. The core tablet was compression coated with different quantities of coating material containing different polymers. A 32 Full factorial design was used for optimization of barrier layer. Total coat weight (X1) and % KLUCEL EXF (X2) were selected as independent variables. The lag time for Valsartan (Y1), CPR at 1st hr after lag time for Valsartan (Y2), time for 90% drug release for Valsartan (Y3), were selected as dependent variables. Tablets were evaluated for various evaluation parameters. Comparative dissolution profiles of all the batches indicate drug release from tablet was inversely proportional to coat weight. From release profile it also found that delay lag time was observed for the press-coated tablet containing a higher amount of KLUCEL EXF in the outer shell. The press coated tablets coated with KLUCEL EXF: KLUCEL HXF IN 64.39:35.61 ratios with 250 mg coat weight are most likely to provide desired delivery of Valsartan.

## INTRODUCTION

The oral route of drug delivery is typically considered the favoured and the most having the highest degree of patient compliance because of user-friendly means of drug administration. Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and

  

increasing patient compliance.Pulsatile drug delivery system (PDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease [1-2]. PDDS can be classified according to the pulse-regulation of *drug release* into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli-induced release and external stimuli-**induced** pulsatile release systems [3-7].

**Press Coated tablet**

An oral press-coated tablet was prepared by using direct compression and wet granulation methods to achieve predetermined lag time. This press-coated tablet containing the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer and hydrophilic polymer. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time. [8-9]

Many pharmacological classes are used to control the blood pressure . Valsartan is a potent, orally active non-peptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension [10-11]. It was first developed by Novartis and has a wide market in the developed and the developing countries. It is also available in combination with other antihypertensive drugs. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category.

## 2. MATERIALS AND METHODS[12-15]

**2.1. Materials**. The drug Valsartan was gifted from Asha chemicals Pvt.Ltd, Ankleshwer . Microcrystalline cellulose, SSG, PVP K30 and Crosscarmellose was purchased from SD fine chemicals. Klucel – EXF grade and Klucel – HXF grade was purchased form Aqualon chemicals. Hydroxy propyl methylcellulose (K4M) were obtained from Fine Chem Industries, Mumbai, India.

**2.2. Analytical Method for Estimation of Valsartan** Construction of calibration curve of Valsartan, Standard stock solution was prepared by dissolving 100 mg of Valsartan in 100 ml of methanol to get concentration of 1 mg/ml. The prepared stock solution was further diluted with

buffer to get working standard solution of 2 to 14 mcg of Valsartan to construct Beer's law plot for the pure drug, the absorbance was measured at λmax at 227 nm, against blank. The standard graph was plotted by taking concentration of drug on X-axis in the concentration range of 2 mcg to 14 mcg and absorbance on Y axis.

**Table 1: Formulation table for preparing core tablets of Valsartan.**

| Ingredients(mg) | Batch C1 | Batch C2 | Batch C3 | Batch C4 |
|---|---|---|---|---|
| **Valsartan** | 150 | 150 | 150 | 150 |
| **Sodium starch glycolate** | 4 | 6 | 8 | - |
| **Microcrystalline Cellulose** | 40 | 38 | 36 | 44 |
| **PVP K30** | 4 | 4 | 4 | 4 |
| **Mg.stearate** | 1 | 1 | 1 | 1 |
| **Talc** | 1 | 1 | 1 | 1 |
| **Total** | 200 | 200 | 200 | 200 |

**2.3 Formulation Development**. For preparing PDDS of Valsartan, initially the immediate release core tablets containing drug were prepared and optimized tablets were compression-coated using mixture of different polymer. Accordingly, various formulation parameters of the inner immediate release core and the coatings were varied and optimized.

**2.3.1 Precompression Parameters of Valsartan and Core Tablet Powder Blend** Coating powder blend and core tablet powder blend was evaluated for various precompression parameters such as angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index (Table 4).

**2.3.2 Post Compression Parameters of core tablet of Valsartan:**

The prepared core tablets were evaluated for thickness hardness, friability, Uniformity of weight, *in vitro* dissolution study, and drug content. Thickness and diameter: It is measured by using Vernier caliper in mm. Weight variation test: The USP weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average. Hardness: Hardness of the tablets was tested using a Monsanto hardness tester. Thickness was determined by electronic Vernier caliper. Friability: Friability of the tablets was determined in a friability test apperature. Drug content: For drug content (without enteric coating) the core tablets were estimated by the spectrophotometrically at 227 nm (Shimadzu 1800, Japan). Disintegration: Disintegration time of the tablets was determined using a tablet

disintegration test apparatus (Electrolab, India) using pH 1.2 Buffer solutions as fluid (Tables 6).

### 2.3.3 *In vitro* drug release of core tablets of Valsartan:

*In vitro* dissolution studies were carried out using USP Type II (paddle method) apparatus (Electrolab India). Buffer solution 1.2 was used as dissolution medium. Release pattern was studied by taking sample of 5 mL at the specific time intervals and analyzed at 227 nm using a UV spectrophotometer (Shimadzu 1800, Japan).

**2.3.4 Preparation of Pulsatile release tablets of Valsartan** The core tablets were compression coated with different weight ratios (w/w) KLUCEL JXF, KLUCEL HXF, KLUCEL EXF and Ethyl cellulose. Initially 50% of the coat powder was placed in the die cavity then, the core tablet was carefully positioned at the center of the die cavity which was filled with the remainder of the coat powder. It was then compressed around the core tablet by using 10-mm round, flat, plain punches.

**Table 2: Preliminary batches for Pulsatile release tablet of Valsartan**

| Batch | Composition of polymer for particular batch |
|---|---|
| **B1** | KLUCEL JXF: KLUCEL HXF 200mg coating of two polymer |
| **B2** | KLUCEL EXF: KLUCEL HXF 200mg coating of two polymer |
| **B3** | KLUCEL JXF: EC 200mg coating of two polymer |
| **B4** | KLUCEL EXF: EC 250mg coating of two polymer |
| **B5** | KLUCEL EXF: KLUCEL HXF 250mg coating of two polymer |
| **B6** | KLUCEL EXF: KLUCEL JXF 250mg coating of two polymer |
| **B7** | KLUCEL EXF: KLUCEL HXF 300mg coating of two polymer |
| **B8** | KLUCEL JXF: KLUCEL HXF 300mg coating of two polymer |
| **B9** | KLUCEL HXF: KLUCEL CS 300mg coating of two polymer |

### 2.4. Formulation and Optimization by using $3^2$ full factorial design.

A $3^2$ Full factorial design was used for optimization of barrier layer, in which a minimum and a maximum level must be given for each parameter. Responses obtained from all the formulations were analyzed. Dependent variables was be selected against two independent variables (i.e.X1:Total amount of polymer and X2: Ratio of KLUCEL EXF: KLUCELHXF) for Optimization. The outputs were combined into an overall desirability function. The association between the independent and dependent variables was interpreted by response surface plots. The effects of

different factors on regression coefficients were studied using analysis of variance (ANOVA). The relative error (%) was calculated as part of validation of the selected experimental design by using the difference in the predicted and experimental values.

**Table 3: Formulation and Optimization by using $3^2$ full factorial design:**

| Coded Values | | | Decoded Values | | |
|---|---|---|---|---|---|
| **Sr no.** | **Total amount of polymer X1)** | **%KLUCEL-EXF: (X2)** | **Sr no.** | **Total amount of polymer (X1)(mg)** | **%KLUCEL- EXF: (X2)** |
| 1 | -1 | -1 | 1 | 200 | 25 |
| 2 | 0 | 0 | 2 | 250 | 50 |
| 3 | 1 | 1 | 3 | 300 | 75 |

**Table 4: Coded and Decoded values for Pulsatile release tablet of Valsartan**

| Sr no. | Coded value for X1 factor | Coded value for X2 factor | Decoded value for X1 factor | Decoded value for X2 factor |
|---|---|---|---|---|
| **F1** | -1 | -1 | 200mg | 25% |
| **F2** | -1 | 0 | 200mg | 50% |
| **F3** | -1 | 1 | 200mg | 75% |
| **F4** | 0 | -1 | 250mg | 25% |
| **F5** | 0 | 0 | 250mg | 50% |
| **F6** | 0 | 1 | 250mg | 75% |
| **F7** | 1 | -1 | 300mg | 25% |
| **F8** | 1 | 0 | 300mg | 50% |
| **F9** | 1 | 1 | 300mg | 75% |

**2.5 Characterization of Pulsatile release tablet of Valsartan** The physical properties such as Uniformity of weight, thickness, hardness friability and Drug content of press coated tablets were given in Table 3.

**2.6 Dissolution Study of Core and Press Coated Tablet** Dissolution of Valsartan tablets were performed in a USP dissolution tester, paddle method (Electrolab, Dissolution tester USP Mumbai, India), under stirring at 100 rpm. The dissolution media consisted of 900 ml of

phosphate buffer (pH 6.8) at 37±0.5 °C. Samples were withdrawn after every 5 min for press coated tablet respectively, then filtered and analyzed at 227 nm using UV spectrophotometer. An equivalent volume of temperature equilibrated fresh buffer was replaced following the removal of each sample.

**2.7 Drug Excipients Compatibility Study** Sample of pure drug, coating polymer, physical mixture of coating material and drug in (1:1) ratio were evaluated for drug–excipients compatibility using Differential scanning colorimeter (DSC) and Fourier transformed infrared spectroscopy (FT-IR).

**Differential Scanning Colorimeter**: Thermograms of pure Valsartan, physical mixture of coating material and valsartan (1 : 1), and mixture of optimized formulations were obtained using DSC (Mettler Toledo DSC, Japan) at a scanning rate of 10 °C/min conducted over a temperature range 30—400 °C.

**Fourier Transformed Infrared Spectroscopy**: FT-IR spectra of drug, mixture of optimized formulation, physical mixture of coating material and drug (1:1) and core tablet mixture were recorded with a FT-IR spectrophotometer (Shimadzu Corporation, Japan) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1:100 and pressed using a hydrostatic press at a pressure of 10 tons for 5 min. The disc was placed in the sample holder and scanned from 4000 to 500 $cm^{-1}$ at a resolution of 1 $cm^{-1}$.

**2.8. Optimization and Validation of the Experimental Design.**

Responses obtained from all the formulations were analyzed using Design-Expert 8 software and were used to generate a study design and the response surface plots. A numerical optimization technique was used to develop the optimized formulation, in which a minimum and maximum level must be given for each parameter. The outputs were combined into an overall desirability function. The association between the independent and dependent variables was interpreted by response surface plots. The effects of different factors on regression coefficients were studied using analysis of variance (ANOVA). The relative error (%) was calculated as part of validation of the selected experimental design by using the difference in the predicted and experimental values.

**2.9 Stability study of optimized batch**: Optimize formulation was placed in a stability chamber at accelerated stability condition 40±2 °C and 75±5% relative humidity for a period of 3 month. At the end of 3 month the dissolution study of tablets were carried out.

**RESULT AND**

## DISCUSSION

In order to improve the bioavailability, rapid absorption of the Valsartan is essential for the gastric region as soon as it gets released from the dosage form. Therefore, Valsartan immediate release formulations were developed and optimized. For chronotherapeutic drug delivery, it is essential to have lag time in drug release, and accordingly tablets were compression-coated for controlling the drug release.

### 3.1 Evaluation of Core tablet of Valsartan

**3.1.1 Precompression Parameters of Coating Powder and Core Tablet Powder Blend** The results of angle of repose, bulk density, tapped density and compressibility index indicates that powder blend has passable flow property with good compressibility and suitable for direct compression method.(Table 5).

**Table 5: Results of evaluation of powder blend for core tablets of Valsartan.**

| Drug and formulation blend | Angle of repose (Θ) | Bulk density ($g/cm^3$) | Tapped density ($g/cm^3$) | Comressibiliy index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| **Valsartan** | 32.11±0.34 | 0.47±0.001 | 0.58±0.0005 | 12.45±1.10 | 1.16±0.01 |
| **BatchC1** | 32.01±0.21 | 0.39±0.001 | 0.57±0.001 | 12.28±1.02 | 1.12±0.01 |
| **BatchC2** | 35.21±0.34 | 0.48±0.0005 | 0.52±0.001 | 12.87±1.04 | 1.18±0.01 |
| **BatchC3** | 33.12±0.41 | 0.35±0.001 | 0.56±00005 | 14.21±1.10 | 1.16±0.01 |
| **BatchC4** | 34.02±0.38 | 0.51±0.001 | 0.53±0.001 | 13.43±1.08 | 1.11±0.00 |

### 3.1.2 Post-compression parameters of Core Tablet of Valsartan

The tablets of different batches showed uniform thickness (3.20 ± 0.1 mm) and Uniformity of weight(200 ± 1.48mg). The hardness was found to be 3.10±0.02. The friability, disintegration time and uniformity of content were within the official limits.

**Table 6: Post-compression parameters of Core Tablet of Valsartan**

| Core Tablet | Uniformity of weight (mg) | Thickness (mm) | Hardness ($kg/cm^2$) | Friability test(%) | Uniformity of content(%) | Disintegration Time (sec) |
|---|---|---|---|---|---|---|
| **Batch C1** | 200±1.23 | 3.20±0.1 | 3.10±0.03 | 0.23 | 99.38±1.23 | 72±0.02 |
| **Batch C2** | 200±1.14 | 3.21±0.1 | 3.20±0.03 | 0.12 | 99.28±1.87 | 60±0.02 |
| **Batch C3** | 200±1.48 | 3.20±0.1 | 3.10±0.02 | 0.28 | 100.12±1.78 | 54±0.01 |
| **Batch C4** | 200±1.08 | 3.20±0.1 | 2.90±0.03 | 0.25 | 99.92±1.46 | 230±0.02 |

*Invitro* disintegration times of all four formulations are shown in table 6.From the result it was found that as the percentage of super disintegrants increased(4 to 8%), the disintegration time decreased. Minimum disintegration time (54±0.01sec) was observed with formulation C3 containing 8% sodium starch glycolate.

***Invitro* dissolution of core tablets of Valsartan:** Among all, formulation C3 containing Sodium starch glycolate 8% was found to have has shown better release with initial 32.11% at 5min and 99.08% at the end of 60 min compared to others formulations. So the formulation C3 containing 8% sodium starch glycolate is selected as optimized core tablet for further preparation of compress coated tablet.

**Table 7: Dissolution time for core tablets of Valsartan**

| Time(min) | Batch C1 | Batch C2 | Batch C3 | Batch C4 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 5 | 35.40 | 28.30 | 32.11 | 4.1 |
| 10 | 47.12 | 51.14 | 56.78 | 7.8 |
| 15 | 54.23 | 63.24 | 69.11 | 9.34 |
| 20 | 65.21 | 66.21 | 75.23 | 12.23 |
| 30 | 75.34 | 78.28 | 88.12 | 23.28 |
| 45 | 84.14 | 90.47 | 93.28 | 33.17 |

| | | | | |
|---|---|---|---|---|
| 60 | 97.24 | 99.12 | 99.08 | 51.16 |

**Figure 1: Dissolution of valsartan core tablet formulation with Sodium starch glycolate 4 %(C1), 6% (C2), 8%(C3) & Microcrystalline Cellulose (C4)**

### 3.2 Evaluation of Pulsatile release tablet of Valsartan

#### 3.2.1 Effect of Polymer on drug release

From the dissolution profile of preliminary batches B1-B3 was found that core tablet coated with high viscosity grade of KLUCEL JXF and KLUCEL HXF, KLUCEL EXF and Ethyl cellulose in different proportion cause highly retardation of drug release and lag time of drug release was around 8 to 10 hours. This is due to forma thick viscous stiff gel layer around the core tablet on being exposed to the dissolution fluids.This viscous gel layer will retards seeping of dissolution fluids into the core tablets and reduce the diffusion of drug from the core to negligible level and decreases the drug release from the formulation. So, KLUCEL EXF and KLUCEL HXF were selected in different ratio for achieving the proper lag time in compress coated tablet. It also indicates that the lag time of press coated tablet increased with increase in viscosity of KLUCEL. Ethyl Cellulose was not able to maintain proper lag time and lag time was found to less than 4 hours and premature release observed. So, KLUCEL EXF and KLUCEL HXF were selected in different ratio for achieving the proper lag time in compress coated tablet. It also indicates that the lag time of press coated tablet increased with increase in viscosity of KLUCEL.

#### 3.2.2 Post-compression parameters of Pulsatile release tablet of Valsartan

The tablets of different batches showed uniform thickness and uniformity of weight. The hardness was found to be 5.20±0.02. The friability and drug content were within the official limits.

**Table 8: Post-compression parameters of Pulsatile release tablet of Valsartan**

| Batches | Uniformity of weight(mg) | Thickness (mm) | Hardness test (kg/cm$^2$) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| **F1** | 400±1.25 | 5.10±0.12 | 5.30±0.017 | 0.012 | 99.78±0.05 |
| **F2** | 400±1.38 | 5.12±0.40 | 5.40±0.026 | 0.015 | 99.21±0.01 |
| **F3** | 400±1.12 | 5.02±0.30 | 5.10±0.018 | 0.011 | 99.32±0.023 |
| **F4** | 450±1.45 | 5.65±0.23 | 5.80±0.016 | 0.010 | 100.14±0.025 |
| **F5** | 450±1.58 | 5.69±0.40 | 5.60±0.028 | 0.012 | 99.20±0.05 |
| **F6** | 450±1.61 | 5.64±0.35 | 5.20±0.021 | 0.014 | 99.14±0.014 |
| **F7** | 500±1.32 | 5.87±0.12 | 5.40±0.018 | 0.012 | 99.35±0.012 |
| **F8** | 500±1.12 | 5.85±0.14 | 5.80±0.016 | 0.014 | 99.92±0.025 |
| **F9** | 500±1.25 | 5.12±0.12 | 5.80±0.021 | 0.010 | 99.21±0.05 |

### 3.2.3 *Invitro* drug release of Pulsatile release tablet of Valsartan

*In-vitro* drug release profile of all nine formulations is shown in table 9. The release profiles from the press coated tablets were found the typical sigmoidal curves with a lag time. For drug delivery systems designed for Pulsatile delivery, it is desirable that the system remains intact and shows minimal drug release in the physiological environment of the stomach and triggers drug release in the lower GIT. From the release profile influence of change in the ratio of KLUCEL EXF to KLUCEL HXF and coat weight on drug release was demonstrated. It showed that lag time increases with increasing concentration of KLUCEL EXF. From release profile of all nine batches it was observed that drug release from tablet was inversely proportional to coat weight. Drug release rate was highly regarded in formulation F7, F8 and F9 which contain a higher level of coat weight(300 mg). From all the batches, formulation F1shows > 90% of drug released before the lag time of 6h.The intermediate drug release retardation was observed from the batches F2, F3 and F6 while significant retardation was observed from the batches F4 and F5 containing higher amount of KLUCEL EXF in the outer shell. Formulation F4 and F5 show less than 10% of drug release at the end of 6 hr and nearer 99% of drug release at the end of 9hr. Hence, it can be said that the batches F4 and F5showed desirable drug release.

**Table 9: Cumilative % Drug Release of Pusatile release formulation of F1 to F9**

| T im e (hr) | CPR | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | F |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2.7 | 2.2 | 2.6 | 1.8 | 1.6 | 2.4 | 2.1 | 1.1 | 1.5 |
| 2 | 4.2 | 2.81 | 2.83 | 2.80 | 2.5 | 3.1 | 2.2 | 2.5 | 2.1 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 3 | 7.6 | 3.41 | 3.9 | 3.40 | 2.9 | 3.4 | 3.2 | 3.8 | 3.4 |
| 4 | 28.2 | 4.25 | 4.15 | 5.05 | 3.1 | 3.65 | 5.65 | 4.1 | 3.7 |
| 5 | 58.2 | 8.42 | 5.58 | 7.82 | 4.08 | 3.88 | 7.89 | 4.3 | 4.26 |
| 6 | 93.8 | 12.2 | 10.9 | 9.7 | 8.3 | 5.92 | 9.14 | 5.23 | 6.78 |
| 7 | 97.2 | 64.6 | 80.1 | 83.2 | 86.14 | 7.15 | 11.2 | 7.74 | 8.92 |
| 8 | 98.1 | 85.2 | 94.05 | 93.16 | 94.26 | 10.8 | 15.2 | 11.2 | 12.7 |
| 9 | 98.4 | 97.16 | | 96.46 | 96.44 | 16.35 | 23.16 | 17.56 | 18.75 |
| 10 | | | | | 97.39 | 75.20 | 75.3 | 23.3 | 25.3 |
| 11 | | | | | | 97.30 | 94.14 | 75.2 | 80.1 |
| 12 | | | | | | | | 96.20 | 97.26 |

**Figure 2: *Invitro* dissolution study of Batch F1 to F9**

### 3.3 Drug-Excipient compatibility study:.

From the I.R. Spectrum, it was observed that there were no changes in these main peaks in IR spectra of drug at 1731cm-1 3745cm-1 2873cm-1 which show there were no physical interactions between drug and polymers. The peaks obtained in the spectra of drug and polymers mixtures correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers (Fig.4).

### Differential Scanning Calorimetry (DSC):

The DSC thermogram shows that the sharp endothermic peak at189.35 °C corresponding to the melting point of Valsartan and similarly at189.35 °C for Valsartan and Excipient respectively, which shows that there is no interaction between polymers and drug (Fig.3).

**Fig. 3 :(a) DSC Thermogram of Valsartan (b)DSC Thermogram of Valsartan and Excipient**

**Figure 4:(a)FTIR spectra of Valsartan (b) FTIR spectra of Valsartan and Excipient**

### 3.4 . *Data Analysis*

The optimization technique which on the basis of few experiments and of statistical analysis of the results can provide an efficient and economical method for the prediction of the optimal composition.

### 3.4.1. Optimization.

Responses obtained from evaluation study of all 9 formulations were fed into Design-Expert software using $3^2$ full factorial design and constrains are given in Table . From the contour plot and Surface plot it can be established that when total amount of polymer coating and % KLUCEL EXF increased it showed decreased CPR at first hour after lag time for Valsartan. The relationship between variables was elucidated using surface plot and contour plot. The effects of X1 and X2 on lag time, CPR at 1st hr after lag time for Valsartan and time for 90% drug release for Valsartan are given in figure . It shows that both variables affecting significantly.

**Figure 5(a): Surface plot for Y1 Surface plot for Y2 Surface plot for Y3**

**Figure 5(b) Contour plot for Y1 Contour plot for Y2 Contour plot for Y3**

**Figure 5: (a) Surface plot and (b) contour plots for Total coat weight (X1) and % KLUCEL EXF (X2) on lag time for Valsartan (Y1), CPR at 1st hr after lag time for Valsartan (Y2), time for 90% drug release for Valsartan (Y3)**

### 3.4.2. Check point cum optimized batch:

Pulsatile tablets should release minimum amount of drug at 6 hours. Ideally, release should start after 6 hours of dissolution study. Difference of drug release between 6 to 9 hours should be maximum and 90% of drug release is desirable within 9 hours.

**Criteria for the optimized batch:**

Drug release at 6 hours: 0-10%.

Drug release after lag time provide burst release: 70-80%

Time required to release 90% of drug: 8-9hours.

**Table 10:Desirability for response**

| Dependant variable | Individual desirability | Desirability |
|---|---|---|
| Y1 | 1.0000 | 0.9678 |
| Y2 | 0.90656 | |
| Y3 | 1.0000 | |

**Table11: Check point batch**

| Dependant variable | Observed value | Predicted value | %Relative Error |
|---|---|---|---|
| Y1 | 6.01 | 5.99 | 0.3327 |
| Y2 | 74.12 | 73.17 | 1.2817 |
| Y3 | 8.60 | 8.55 | 0.5813 |

**Table 12: Composition for final optimized formulation of Pulsatile release tablet of Valsartan**

| Core tablet | |
|---|---|
| **Ingredients** | **Quantity(mg)** |
| **Valsartan** | 150 |
| **Sodium starch glycolate** | 8 |
| **Micro crystalline cellulose** | 36 |
| **PVP K30** | 4 |
| **Mg.stearate** | 1 |
| **Talc** | 1 |
| **Total** | 200 |
| **Coating Material** | |
| **KLUCEL-EXF** | 160.97 |
| **KLUCEL-HXF** | 89.025 |

| | | |
|---|---|---|
| | | |

**3.5 Stability study**: Stability study of optimized batch from the results of stability study, it was observed that the optimized formulation F5 was stable for the three month at 40°C ± 2°C / 75% ± 5% RH as specified by the ICH guidelines. The lag time before and after storage was found to be similar. Dissolution profiles before and after storage are nearly overlapable. The change in the drug release pattern i.e. dissolution profile was not significantly different from the previous tablet dissolution profile. Student t – test between before and after one year of storage showed insignificant difference (tcal< ttab.). It conforms that there must be adequate storage container.

**Table 13: Post compression parameters of Pulsatile release tablet of Valsartan tablet before and after stability period**

| Parameter | Before stability | After stability |
|---|---|---|
| Weight variation (mg) | 450± 0.40 | 449± 1.2 |
| Hardness (kg/cm2) | 5.54± 0.09 | 5.34± 0.08 |
| Friability (%) | 0.47± 0.07 | 0.58± 0.05 |
| Drug content (%) for Valsartan | 99.23± 1.2 | 98.25± 1.4 |

**Figure6: Comparison of *in-vitro* Release Profile of Batch F5 Tablets before and after Stability Study**

## CONCLUSION

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place, at the right time and in the right amount, thus providing spatial, temporal, and smart delivery and increasing patient compliance. To formulate pulsatile release tablet of Valsartan, different grades of polymers were used. Comparative dissolution profiles of all the batches indicate drug release from tablet was inversely proportional to coat weight. From release profile

it also found that delay lag time was observed for the press-coated tablet containing a higher amount of KLUCEL EXF in the outer shell. The press coated tablets coated with KLUCEL EXF: KLUCEL HXF in 64.39:35.61 ratios with 250 mg coat weight are most likely to provide desired delivery of Valsartan.

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