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# *Journal of Chemical and Pharmaceutical Research*

ISSN No: 0975-7384
CODEN(USA): JCPRC5

*J. Chem. Pharm. Res., 2010, 2(5):534-540*

## Formulation and evaluation of Valsartan film coated tablets

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**ABSTRACT**

*Valsartan used for the treatment of Hypertension, which is a specific angiotensin II receptor blocker (ARB) acting on the $AT_1$ receptor subtype, The purpose of the present work is to formulate and evaluate of Valsartan film coated tablets. In order to obtain the best optimized product, eight different formulations were developed using diluents, binder, glidant, lubricant, and different concentrations of superdisintegrant. Tablets were formulated by direct compression, slugging and wet granulation techniques. Various pre-compressional parameters like bulk density, tapped density, compressibility index and Hausner's ratio and post compressional parameters like weight variation, thickness, hardness, friability, disintegration time, and drug release were studied. Comparatively granulation techniques exhibited the good powder flow than direct compression technique. Based on this investigation results, the drug release from tablets increased with increasing concentration of superdisintegrant. The formulation F-7 was showed good drug release and selected as an optimized formulation and it was concluded that superdisintegrant concentration, granulation technique, binder, and lubricants plays a key role in the formulation development and optimizing the immediate release tablet of Valsartan formulation*

**Key words:** Valsartan, Angiotensin II receptor blocker, Hypertension, Immediate release tablet, Superdisintegrant.

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### INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing. They can be mass produced with robust quality controls and offer different branding possibilities by means of colored film coating, different shapes, sizes or logos [1,2].

Valsartan is rapidly absorbed after oral dose with a bioavailability of about 25%. Peak plasma concentrations occur 2 to 4 hours and its plasma half-life is about 7.5 hours after an oral dose. In management of hypertension, Valsartan is given in a dose of 80 mg once daily [3,4]. The main objective is to formulate a drug product as immediate release oral solid dosage form of Valsartan tablets, which is considered to be a stable, robust quality and pharmaceutical equivalent to that of the reference product for the treatment of Hypertension.

Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants [5]. Immediate release tablets are designed to disintegrate and release their medicaments with no special rate-controlling features, such as special coatings and other techniques [6]. Immediate release tablets are expected to achieve fast tablet disintegration which would dissolve for absorption into the bloodstream [7]. Conventional immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat any unwanted defect or disease [8].

## EXPERIMENTAL SECTION

### Materials

Valsartan (Aurobindo Pharmaceuticals Ltd.), Crospovidone (Anshul agencies, Mumbai), Lactose monohydrate (DMV International), Microcrystalline cellulose, Talc, Magnesium stearate (Signet chemical corporation, Mumbai), PVP K-30 (Boai Nky Pharmaceuticals), Aerosil (Carboit samnol pharma agencies), Opadry brown (Ideal Cures Pvt. Ltd).

### Preparation of Valsartan film coated tablets

The critical parameters to formulate an immediate release tablet are choice and optimization of concentration of superdisintegrant. The super disintegrant (Crospovidone) was used to formulate the tablets. In order to prepare these tables three techniques were used i.e., direct compression, slugging and wet granulations. The mixed blend of drug-excipient was compressed using 18×8 mm oblong punches to produce tablets with 6 mm thickness.

### Flow properties of blend [9]

### Density

A quantity of 2 gms of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Both bulk density (BD) and tapped density (TD) were determined.

### Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations.

### Hausner's ratio

It is usually determined from the ratio between the tapped density (TD) and the bulk density (BD).

**Angle of Repose**

Angle of repose (θ) is the maximum angle possible between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel method and is the measure of the flowability of powder/granules.

**Table 1: Formulation batches of Valsartan tablets**

| S. No. | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|
| Dry blend 1 | Valsartan | 320 | 320 | 320 | 320 | 320 | 320 | 320 | 320 |
| 2 | MCC | 298.5 | 296 | - | 280 | 270.4 | 157.4 | 152.6 | 152.6 |
| 3 | LM | - | - | 296 | - | - | 104.9 | 101.7 | 101.7 |
| 4 | Crospovidone | 16 | 8 | 8 | 8 | 12.8 | 20.16 | 24.96 | 24.96 |
| 5 | CSD | 1.6 | - | - | - | - | - | - | - |
| 6 | Mg.st | 3.8 | 3.2 | 3.2 | - | - | - | - | - |
| Granulation 7 | PVP K-30 | - | - | - | 11.2 | 11.2 | 11.2 | 11.2 | 11.2 |
| 8 | Purified water | - | - | - | q.s. | q.s. | q.s. | q.s. | q.s. |
| Prelubrication 9 | CSD | - | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| 10 | Crospovidone | - | 8 | 8 | 8 | 12.8 | 13.44 | 16.64 | 16.64 |
| Lubrication 11 | Mg.st | - | 3.2 | 3.2 | 4.8 | 4.8 | 4.8 | 4.8 | 4.8 |
| 12 | Talc | - | - | - | 6.4 | 6.4 | 6.4 | 6.4 | 6.4 |
| -- | Core tablet weight | 640.0 | 640.0 | 640.0 | 640.0 | 640.0 | 640.0 | 640.0 | 640.0 |
| 13 | Opadry coat | 3% | 3% | 3% | 3% | 3% | 3% | 3% | 3% |
| -- | Coated tablet weight | 660.0 | 660.0 | 660.0 | 660.0 | 660.0 | 660.0 | 660.0 | 660.0 |

*F1- direct compression, F2- & F3- slugging, F4 - F8-wet granulation, MCC-Microcrystalline cellulose, LM-Lactose monohydrate, CSD- Colloidal silicon dioxide, Mg.st -Magnesium stearate, q.s.-Quantity sufficient.*

**Evaluation of Valsartan tablets** [10]

**Weight variation**

Twenty tablets are weighed individually and the average weight is calculated. The individual tablet weights are then compared to the average weight.

**Thickness**

The thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information of the variation between tablets.

**Hardness**

Hardness was determined by taking six tablets from each formulation, using a Monsanto Hardness Tester.

**Friability**

It is usually measured by the use of the Roche friabilator. A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability.

**Disintegration**

The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of suitable liquid held at 37$^{o}$C, preferably in a 1L beaker.

***In-vitro* dissolution study**

The dissolution test was performed using USP dissolution testing apparatus 2 (paddle method); Medium - 0.067M Phosphate buffer, pH 6.8; Volume- 1000 ml; Temperature- 37ºC; RPM – 50; Time intervals- 10, 20, 30 and 45 mins. Absorbance of these solutions was measured at the wavelength of UV-248nm. Separately inject equal volumes (about 10 µl) of the dissolution medium as blank, standard preparation and sample preparation into chromatograph, and the chromatograms was recorded and measure the peak area responses for the analyte peak.

**Accelerated Stability Studies**

Valsartan immediate release tablets 320 mg were evaluated for accelerated stability studies at 40$^{o}$C ± 2$^{o}$C/75% RH ± 5% RH condition, Pack: HDPE container, Storage period: 3 months.

## RESULTS AND DISCUSSION

The formulation F1 prepared by the direct compression method, blend exhibit the poor flow characteristics. The formulations F2 and F3 prepared by the slugging process, whereby blend exhibit passable flow characteristics. The formulations F4-F8 prepared by the wet granulation process, the blend exhibit the good flow characteristics. The results were shown in the Table 2

**Table 2: Preformulation study results of formulations.**

| Formulation | Bulk density (gm/ml) | Tap density (gm/ml) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|
| F-1 | 0.375 | 0.526 | 28.70 | 1.40 |
| F-2 | 0.417 | 0.550 | 24.10 | 1.31 |
| F-3 | 0.414 | 0.542 | 23.61 | 1.30 |
| F-4 | 0.339 | 0.428 | 20.79 | 1.26 |
| F-5 | 0.448 | 0.541 | 17.19 | 1.20 |
| F-6 | 0.425 | 0.535 | 20.56 | 1.25 |
| F-7 | 0.413 | 0.501 | 17.56 | 1.21 |
| F-8 | 0.325 | 0.387 | 16.02 | 1.19 |

The results for weight variation (mg), thickness (mm), hardness (Kg/cm$^2$) and friability (%) were found in the range of 649.35 to 660.90; 5.81 to 6.08; 8.24 to13.11; 0.32 to 0.54 respectively. It was observed that the results of all the above formulations were found to be within the limits. Results for disintegration test (mins) were found to be 2.46 to 8.51. Here formulations F2 & F3, while dispersion in disintegration testing machine the tablets were broken into flakes, the dispersion time was 8-9 mins. From the formulation F4 disintegration was improved with the concentration of superdisintegrant. The results were shown in the Table 3.

In dissolution study the formulation F-7 was meet the dissolution profile with innovator, and the dissimilarity and similarity factors were found to be 1.27, 94.02 and formulation F-8 was reproducility formulation to the F-7, dissimilarity and similarity factors were found to be 1.21, 95, both are within the limits. It was observed that as the concentration of

superdisintergrant increases, the drug release also found to be increased. The results were shown in the Table 4 and Fig. 1.

**Table 3: Post compression tests results**

| Formulation | Average weight (mg) | Average thickness (mm) | Average hardness ($kg/cm^2$) | Friability (%) | Average disintegration time (mins) |
|---|---|---|---|---|---|
| F2 | 649.35 ± 3.422 | 5.81 ± 0.049 | 11.84 ± 0.338 | 0.32 | 8.45 ± 0.189 |
| F3 | 651.00 ± 2.772 | 5.84 ± 0.036 | 13.11 ± 0.331 | 0.44 | 8.51 ± 0.117 |
| F4 | 659.35 ± 1.631 | 6.08 ± 0.033 | 12.36 ± 0.375 | 0.37 | 5.23 ± 0.102 |
| F5 | 660.90 ± 1.744 | 6.04 ± 0.029 | 10.20 ± 0.313 | 0.49 | 4.11 ± 0.103 |
| F6 | 658.40 ± 1.313 | 5.99 ± 0.025 | 8.46 ± 0.347 | 0.51 | 3.42 ± 0.104 |
| F7 | 660.70 ± 1.080 | 6.01 ± 0.026 | 8.24 ± 0.222 | 0.53 | 2.46 ± 0.059 |
| F8 | 660.20 ± 1.005 | 5.99 ± 0.027 | 8.26 ± 0.205 | 0.54 | 2.53 ± 0.069 |

**Table 4: Dissolution profiles of the formulation trails**

| Sampling time | Cumulative percentage of drug release | | | | | | |
|---|---|---|---|---|---|---|---|
| | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| 0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |
| 10 | 68.5 ± 1.91 | 67.2 ± 1.70 | 45.8 ± 1.56 | 60.4 ± 1.36 | 60.2 ± 1.39 | 61.9 ± 0.57 | 61.5 ± 0.69 |
| 20 | 71.2 ± 2.04 | 69.1 ± 1.71 | 66.9 ± 1.54 | 75.4 ± 1.50 | 78.2 ± 1.19 | 81.7 ± 0.41 | 81.1 ± 0.40 |
| 30 | 75.6 ± 2.09 | 71.6 ± 1.62 | 78.4 ± 1.72 | 85.4 ± 1.51 | 86.5 ± 0.97 | 93.1 ± 0.56 | 92.6 ± 0.40 |
| 45 | 78.3 ± 2.03 | 76.0 ± 1.70 | 81.5 ± 1.96 | 91.4 ± 1.55 | 94.3 ± 1.05 | 99.4 ± 0.24 | 99.9 ± 0.02 |

Stability studies were conducted, The drug product is subjected to accelerated stability at 40°C ± 2°C, 75% RH ± 5% RH for 3 months. As per the stability results, the formulation exhibits the no notable changes. Valsartan tablets are stable and comply with that of the specification in the USP.

**Table 5: Physical and chemical parameters of Valsartan tablets (F-7) after 1, 2 & 3 months at 40°C/75% RH (packing: HDPE containers)**

| S. No. | Parameter | Initial | 1st month | 2nd month | 3rd month |
|---|---|---|---|---|---|
| 1 | Description | Dark brown, ovaloid with beveled edges, debossed with NVT on one side and 320 on other side. | Dark brown, ovaloid with beveled edges, debossed with NVT on one side and 320 on other side. | Dark brown, ovaloid with beveled edges, debossed with NVT on one side and 320 on other side. | Dark brown, ovaloid with beveled edges, debossed with NVT on one side and 320 on other side. |
| 2 | Avg. weight (mg) | 660.7±1.08 | 660.9±1.05 | 660.7±1.03 | 661±1.02 |
| 3 | Avg. thickness (mm) | 6.01±0.026 | 6.01±0.025 | 6.01±0.023 | 6.01±0.028 |
| 4 | Avg. hardness ($kg/cm^2$) | 8.24±0.22 | 8.23±0.17 | 8.25±0.21 | 8.24±0.16 |
| 5 | Avg. disintegration time (min) | 2.46±0.059 | 2.45±0.056 | 2.49±0.061 | 2.47±0.064 |

Considering formulation 1, in this formulation the die cavity was not filling properly, because of its poor flow of blend. Here, required weight of tablets was not getting. In formulations 2 & 3, while dispersion in disintegration testing machine the tablets were broken into flakes, the dispersion time was 8-9 mins, and also the appearance of tablets were not much good. In formulation 4, in this batch the effect of PVP K-30 as binder and combination of lubricants (magnesium stearate, talc) was studied. Here the tablets obtained were good appearance but the drug release was poor.

**Table 6: Dissolution profiles of Valsartan tablets (F-7) after 1, 2 & 3 months at 40°C/75% RH (packing: HDPE containers)**

| Time interval (mins) | % of avg. drug release | | | |
|---|---|---|---|---|
| | Initial | 1st month | 2nd month | 3rd month |
| 0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 | 0.0±0.0 |
| 10 | 61.9±0.57 | 61.1±0.58 | 62.0±0.70 | 62.5±0.53 |
| 20 | 81.7±0.41 | 82.3±0.23 | 82.1±0.52 | 82.3±0.42 |
| 30 | 93.1±0.56 | 92.6±0.44 | 93.4±0.33 | 93.2±0.37 |
| 45 | 99.4±0.24 | 99.5±0.32 | 99.9±0.17 | 99.7±0.27 |

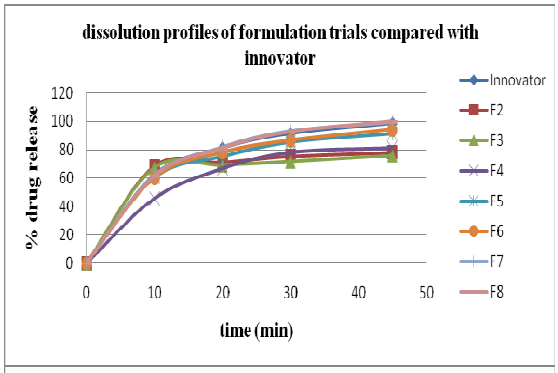


**Fig. 1: Dissolution profiles of formulation compared with Innovator**

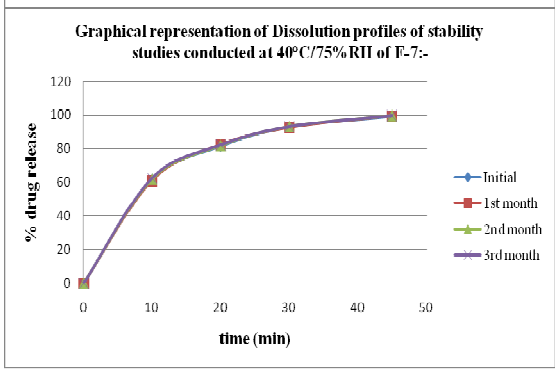


**Fig. 2: Graphical representation of dissolution trials profiles of stability studies conducted at 40°C/75% RH of F-7.**

In formulation 5, the disintegrant concentration was increased. Here initial drug release was good, but it was not maintained up to the end point of dissolution process. In formulation 6, was made by increasing the intragranular concentration of disintegrant and used combination of diluents (microcrystalline cellulose, lactose monohydrate) for effective drug release. In this, drug release was good, but it was not matched to the Innovator.

In formulation 7, the disintegrant concentration was further increased. Drug release was very good and it was matched to the innovator drug release profile. The dissimilarity and similarity factors were found to be 1.27, 94.02, indicated that the drug release profile was super-imposable with the innovator drug release profile. Formulation 8, was reproducibility formulation to the F-7, the dissimilarity and similarity factors were found to be 1.21, 95. It indicated that formulation F-8 was successful reproducible batch to the previous formulation. It was noted that the formulation 7 optimized, which was made by the wet granulation technique exhibit the optimum parameters comparatively with the Innovator.

## CONCLUSION

Based on these results it can be concluded that, the Valsartan film coated tablets were formulated in this research investigation was found to be pharmaceutical equivalent to that of the reference drug. In this research concentration of super disintegrant, granulation technique, lubricants were taken a key role in the formulation development and optimizing the immediate release tablet formulation of Valsartan. Accelerated stability studies were conducted for the optimized formulation F-7 as per ICH guidelines; the results were revealed that the formulation exhibit the no notable changes.

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