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# DESIGN AND DEVELOPMENT OF SPHERICAL AGGLOMERATED CRYSTALS LOADED FAST DISOLVING TABLETS FOR ENHANCING THE SOLUBILITY OF VALSARTAN

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## ABSTRACT

*The objective of the present work was to study the effect of different polymers on the solubility and dissolution rate of Valsartan a poorly water soluble NSAIDs, by spherically agglomeration using methanol, water and dichloromethane as good solvent, poor solvent and bridging liquid, respectively. The quasi-emulsion solvent diffusion technique was used as a method for spherical agglomeration. Spherical agglomeration of Valsartan were prepared by using Poloxomer -F338 and Gelucire 48/16 in the ratio of 1:0.5,1:0.75,1:1. The agglomerates were subjected to various physicochemical evaluations such as practical yield, drug content, solubility, flow properities, average particle size,scanning electron microscopy and dissolution studies. The optical electron microscopy studies showed that the agglomerates posseeses a good spherical shape. This study demonstrated that the successful development of directly compressible spherical agglomerates of Valsartanprepared with selected carrires enhances the in-vitro dissolution property of Valsartan, whichcould provide rapid onset of action and potentially increases oral bioavailability. To study the influence of co-processed superdisintegrants on performance of Valsartan Fast dissolving tablets, a set of three formulations ($F_7$, $F_8$, $F_9$) were prepared using co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. The formulation prepared with co-processed superdisintegrants (Croscarmalose sodium:Crospovidone) in 1:3 ratio ($F_9$) was offered relatively rapid release of Valsartan when compared with other ratios employed in this investigation.*

## KEY WORDS

*Valsartan, Poloxomer -F338, Gelucire 48/16, spherically agglomeration*

## INTRODUCTION

Valsartan is an angiotensin II receptor antagonist effectively used in the management of hypertension [5]. It is rapidly absorbed after oral dose with a bioavailability of about 23%. Peak plasma concentrations occur in 2 to 4 hours and its plasma half-life is about 7.5 hours. This drug has low aqueous solubility and high membrane permeability belonging to class II of the Biopharmaceutical Drug Classification system. Improvement in its solubility and dissolution rate may lead to an enhancement in bioavailability. Thus, rapid Valsartan absorption could be a prerequisite for the quick onset of its action. Because of its high membrane permeability characteristic, extent of Valsartan absorption approaches up to 100%. Therefore, dissolution becomes the rate limiting step for absorption and the quick release of Valsartan in the gastrointestinal tract following oral administration is desirable. The major problem of Valsartan is its very low water solubility, which results into poor dissolution rate. The purpose of the present work was to improve the solubility, dissolution rate and micromeritic properties of Valsartan through spherical crystallization by quasi-emulsion solvent diffusion technique. [1-2] The resultant

crystals can be designated as spherical agglomerates. Spherical crystallization is an effective alternative to improve dissolution rate of drugs. This can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion and neutralization methods. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to Biopharmaceutical classification system. These drugs are poorly water soluble, but once they are dissolved they easily absorbed through the gastrointestinal membrane. Therefore, bioavailability after oral administration can be improved by enhancement of the dissolution rate. One of the approaches dissolution rates is use of spherical crystallization technique. [3-6]

## MATERIALS AND METHODS

Valsartan was obtained from Dr.Reddy's labs, Hyderabad, India. Poloxomer-F338 and Gelucire 48/16 were purchased from SD fine Chemicals Ltd, Mumbai. All other materials used were of analytical grade.

**Preparation of Spherically Agglomerates:**

All spherical agglomerates were obtained by the quasi emulsion solvent diffusion method [7]. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The stabilizers composition was given in Table 1. Valsartan (1.0 g) was dissolved in good solvent N, N-dimethylformamide (25.0 mL). The bridging liquid chloroform (12.5 mL) was added to it. The resulting solution was then poured drop wise into the poor solvent distilled water (100 mL) containing different surfactant like, Poloxomer -F338 and Gelucire 48/16 with a stirring rate of 500 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature [8]. After agitating the system for 30 minutes, the prepared agglomerates were collected by filtration through whatmann filter paper no.42.

**Evaluation of spherical agglomerates:**

**a) Particle size determination:** Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide[8]. About 100 spherical agglomerates size was measured individually, average was taken, and their size range and mean diameter frequency was calculated. Average Particle size is calculated by the following formula, **Average Particle size= £nd/ n**

**b) Drug Content Estimation:**

The percentage drug content in spherical agglomerates was estimated by dissolving spherical agglomerates equivalent to 100 mg of Valsartan in methanol, mixed thoroughly by shaking and the volume was made up to the mark with in 6.8 pH phosphate buffer. The solution was filtered, and the filtrate was diluted suitably with 6.8 pH phosphate buffer and absorbance was measured at 250 nm using UV/Visible spectrophotometer [9].

**c) Dissolution studies of agglomerates:**

*In-vitro* dissolution studies of pure drug and spherical agglomerates were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm. Spherical agglomerates equivalent to 100 mg of Valsartan was used for dissolution study at 37±0.5$^0$ C in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 250 nm UV/Visible spectrophotometer. $DE_{30}$%, $T_{50}$, $T_{90}$ and $k^{-1}$ values were calculated from dissolution data [10].

**Preparation of Valsartan tablets:** To study the influence of co-processed superdisintegrants on performance of Valsartan Fast dissolving tablets, a set of three formulations ($F_7$, $F_8$, $F_9$) were prepared using co-processed superdisintegrants (Croscarmalose sodium : Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. Tablets were made from blends by direct compression method. All the ingredients (shown in Table 3) were mixed [11]. The resulting blend was lubricated with magnesium stearate and compressed into tablets using the Cadmach single punch (round shaped,7mm thick) machine.

**EVALUATION OF VALSARTANTABLETS**

**a) Weight variation test [12]:** Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

**b) Drug content[13]:** Twenty tablets were powdered, and powder equivalent to 100 mg of Valsartan was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 250 nm.

**c) Disintegration Time[14]:** The disintegration time was determined in distilled water at 37±0.5$^0$ C using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).

**d) Friability[14]:** Roche friabilator was used to determine the friability. Pre weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\% \text{ friability} = \frac{\text{Weight before friabilation - Weight after friabilation}}{\text{Weight before friabilation}} \text{X } 100$$

**e) Hardness[14]:** Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure.

**f) Wetting Time[14]:** The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing amaranth a water-soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

**g) In vitro dispersion time[14]:** Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at 37± 0.5°C. Time required for complete dispersion of tablet was measured.

**h Fineness of dispersion[14]:** This test was performed by placing two tablets in 100 ml of water and stirring it gently, until the tablets get completely disintegrated. Then the dispersion is passed through a sieve screen with a nominal mesh aperture of 710 µm.

**j) Dissolution studies [14]:** Dissolution studies for Valsartan fast dissolving tablets were performed in pH 6.8 phosphate buffer using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles are allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of 37±0.5 $^o$C and samples are withdrawn at an interval of every 5 min the volume of the withdrawn samples is replaced by fresh dissolution medium in order to kept the volume of the dissolution medium as constant. The withdrawn samples are filtered, and absorbance was measured at absorption maxima of 250 nm using UV-visible spectrophotometer.

**k) *In-vitro* dissolution kinetic studies[14]:** The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants (K), correlation coefficient (r), the times ($t_{50}$) for 50 % drug released (half-life) and dissolution efficiency [D.E.] were calculated. From the slopes of linear plots, the dissolution rates were calculated.

**l)FTIR (Fourier Transform Infra-red Spectroscopy) Studies [15]:** Infrared (IR) spectroscopy studies of Valsartan and its optimized formulations with PVP and cross povidone were recorded in a FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed, and background spectrum was collected under identical conditions. The spectrum for each sample showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived from 16 single average scans collected in the region of 400 - 4000 cm-1 at a spectral resolution of 2 cm-1.

## RESULTS AND DISCUSSION:

Spherical agglomerates of Valsartan were prepared by quasi emulsion solvent diffusion method (QESD) using a three-solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of drug in individual solvent. Accordingly, methanol, dichloromethane, water was selected as a good solvent, bridging liquid, and poor solvent, respectively. Valsartan is highly soluble in methanol, but poorly soluble in water. Also, it is soluble in dichloromethane which is immiscible in water. Hence, this solvent system was used in the present study. In QESD method, when good solvent solution of drug plus bridging liquid were poured in the poor solvent (containing different carriers) under agitation, quasi

emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of
the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. In the present study effect of different polymers on solubility and dissolution rate of spherical agglomerates of Valsartan were studied. Incorporation of polymer during agglomeration significantly enhanced the dissolution. Mixing of drug with a carrier results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug carrier system sink immediately, while pure drug keeps floating on the surface for a longer time interval. The cumulative percentage of drug released from different agglomerates was increased in the following order : Valsartan spherical agglomerates prepared with Poloxomer -F338 > Valsartan spherical agglomerates prepared with Gelucire 48/16.Among all the formulations prepared, spherical agglomerates prepared Valsartanand Poloxomer -F338 in 1:1 ratio showed highest drug release in 60 minutes.

To study the influence of co-processed superdisintegrants on performance of Valsartan Fast dissolving tablets, a set of three formulations ($F_7$, $F_8$, $F_9$) were prepared using co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Valsartan was found to be affected by nature of the superdisintegrant used in the preparation of tablets. The formulation prepared with co-processed superdisintegrants (Croscarmalose sodium: Crospovidone) in 1:3 ratio ($F_9$) was offered relatively rapid release of Valsartan when compared with other ratios employed in this investigation.

**CONCLUSION:**

Present study concluded that spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compatibility, wettability, flowability and bioavailability. These spherical agglomerates also showed excellent physicochemical characters as compared with plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process.

**Table 1: Composition of Valsartan Spherical Agglomerates**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Valsartan (g) | 1 | 1 | 1 | 1 | 1 | 1 |
| Poloxomer -F338 (g) | 0.5 | 0.75 | 1 | | | |
| Gelucire 48/16 (g) | | | | 0.5 | 0.75 | 1 |
| N, N-dimethylformamide | 25 | 25 | 25 | 25 | 25 | 25 |
| Dichloromethane(ml) | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| Water (ml) | 62.5 | 62.5 | 62.5 | 62.5 | 62.5 | 62.5 |

**Table 2: Particle size and % of Drug content of Valsartan spherical agglomerates**

| Formulation | Particle size(µm) | % of Drug content |
|---|---|---|
| FI | 256 | 99.26 |
| F2 | 278 | 99.54 |
| F3 | 294 | 99.36 |
| F4 | 312 | 99.41 |
| F5 | 334 | 99.39 |
| F6 | 356 | 96.27 |

**Table 3: *In-vitro* dissolution kinetics of Valsartan spherical crystals prepared with different carriers.**

| S.No. | Formulation | $T_{50}$ (min) | $T_{90}$ (min) | $DE_{30}$ (%) | K ($min^{-1}$) | Correlation coefficient values | |
|---|---|---|---|---|---|---|---|
| | | | | | | Zero Order | First order |
| 1 | $F_1$ | 20.2 | 67.1 | 35.43 | 0.034 | 0.9466 | 0.9870 |
| 2 | $F_2$ | 17.2 | 57.0 | 39.51 | 0.040 | 0.9250 | 0.9836 |
| 3 | $F_3$ | 15.4 | 51.2 | 41.49 | 0.044 | 0.9135 | 0.9768 |
| 4 | $F_4$ | 23.5 | 78.0 | 32.14 | 0.029 | 0.9544 | 0.9919 |
| 5 | $F_5$ | 22.0 | 73.1 | 34.34 | 0.032 | 0.9480 | 0.9888 |
| 6 | $F_6$ | 19.6 | 65.2 | 36.09 | 0.035 | 0.9438 | 0.9857 |

**Table 4: Composition of ingredients for Valsartan fast dissolving tablets**

| S.No | Ingredients | $F_7$ | $F_8$ | $F_9$ |
|---|---|---|---|---|
| **1** | Valsartan crystals prepared with Poloxomer -F338 in 1:1 ratio | 160 | 160 | 160 |
| **2** | Croscarmalose sodium+ Crospovidone | 15 | 15 | 15 |
| | Manitol | 45 | 45 | 45 |
| **3** | Micro crystaline cellulose | 76 | 76 | 76 |
| **4** | Talc | 2 | 2 | 2 |
| **5** | Magnesium streate | 2 | 2 | 2 |
| | **Total weight** | 300 | 300 | 300 |

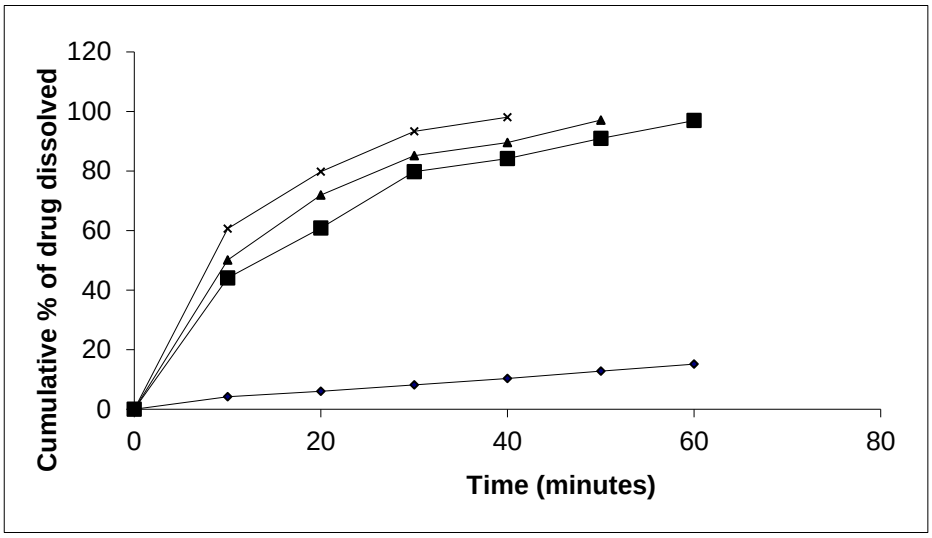
**Table 5: Physical parameters of Valsartan fast dissolving tablets**

| S.No. | Parameters | $F_7$ | $F_8$ | $F_9$ |
|---|---|---|---|---|
| 1 | **Average weight (mg)** | 99±0.3 | 99±0.1 | 100±0.2 |
| 2 | **Drug content (%)** | 98.54 | 99.8 1 | 99.19 |
| 3 | **Disintegration time (sec)** | 163 | 147 | 125 |
| 4 | **Friability (%)** | 0.44 | 0.28 | 0.13 |
| 5 | **Hardness(kg/sqcm)** | 4.2 | 4.2 | 3.8 |
| 6 | **Wetting time (sec)** | 117 | 112 | 92 |
| 7 | ***In-vitro* dispersion time (min)** | **223** | **202** | **152** |
| 8 | **Fineness of dispersion** | **pass** | **pass** | **pass** |

**Table 6: *In-vitro* dissolution kinetics of Valsartan fast dissolving tablets**

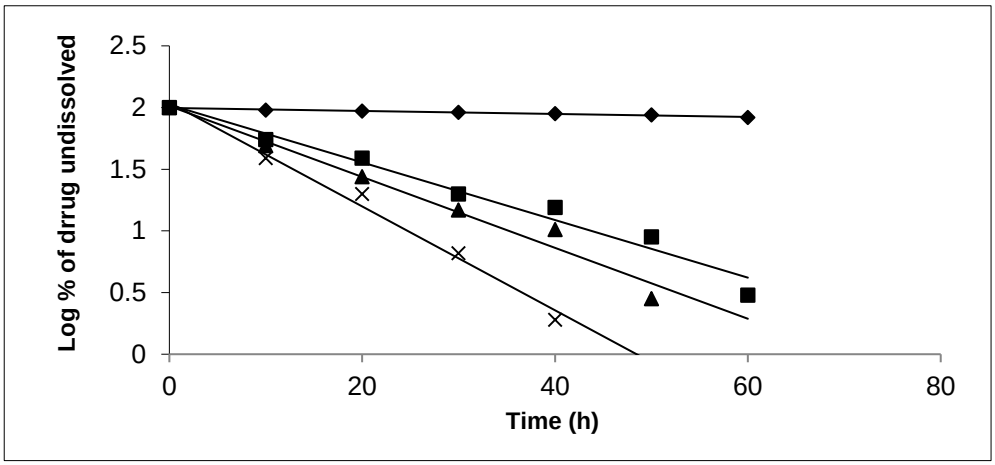
| S.No. | Formulation | $T_{50}$ (min) | $T_{90}$ (min) | $DE_{15}$ (%) | K ($min^{-1}$) | Correlation coefficient values | |
|---|---|---|---|---|---|---|---|
| | | | | | | Zero Order | First order |
| 1 | $F_7$ | 6.6 | 22.0 | 48.28 | 0.104 | 0.8425 | 0.9851 |
| 2 | $F_8$ | 5.3 | 17.7 | 54.87 | 0.131 | 0.8349 | 0.9864 |
| 3 | $F_9$ | 3.7 | 12.3 | 62.38 | 0.180 | 0.8484 | 0.9932 |

**Figure 1: *In-vitro* dissolution profile of Valsartan fast dissolving tablets with co-processed superdisintegrants**




**(-◆-) Valsartanpure drug**
**(-■-) Valsartantablets prepared with crospovidone and croscarmalosesodium in 1:1 ratio by coprocessing technique**
**(-▲-)Valsartantablets prepared with crospovidone and croscarmalosesodium in 1:2 ratio by coprocessing technique**
**(-×-) Valsartantablets prepared with crospovidone and croscarmalosesodium in 1:3 ratio by coprocessing technique**

**Figure 2: First order plots of Valsartan tablets with co-processed superdisintegrants**




**(-◆-) Valsartan pure drug**
**(-■-) Valsartantablets prepared with crospovidone and croscarmalosesodium in 1:1 ratio by coprocessing technique**
**(-▲-)Valsartantablets prepared with crospovidone and croscarmalosesodium in 1:2 ratio by coprocessing technique**
**(-×-) Valsartantablets prepared with crospovidone and croscarmalosesodium in 1:3 ratio by coprocessing technique**

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