



FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF VALSARTAN

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ABSTRACT

In this investigation fast dissolving tablets of valsartan were prepared using different superdisintegrants by direct compression method. FDTs were evaluated for physico-chemical properties and *in vitro* dissolution. Effect of disintegrant on disintegration behaviour of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. The release of valsartan from FDTs was found to follow non-Fickian diffusion kinetics.

Keywords :

INTRODUCTION

Fast dissolving tablets (FDTs) are solid single-unit dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provides a quick onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. FDTs are appreciated by a significant segment of population, particularly children and elderly, which have difficulty in swallowing conventional tablets or capsules^{1,2,3}.

FDTs are prepared by various techniques, mainly direct compression, lyophilization and moulding. The simplicity and cost effectiveness of the direct compression process have positioned this technique as an attractive alternate to traditional granulation technologies⁴. 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 disintegrants⁵.

Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with

left ventricular dysfunction following myocardial infarction, and in the management of heart failure. Valsartan is rapidly absorbed after oral dose with a bioavailability of about 23%. 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 ⁶.

The aim of the proposed work was to formulate and characterize fast dissolving tablets of valsartan for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of hypertension in elderly patients.

MATERIALS AND METHODS

Materials

Valsartan was obtained as a gift sample from Ranbaxy Ltd., Devas (M.P.). Crospovidone, Ac-Di-Sol, Sodium Starch Glycolate and Microcrystalline cellulose were obtained as gift sample from Arihant Trading Co., Mumbai. All

other chemicals and reagent were of analytical grade.

Methods

Preparation of fast dissolving tablets of valsartan

The critical parameters to formulate a fast dissolving tablet are choice of superdisintegrant and optimization of concentration of superdisintegrant. The main criteria for fast dissolving tablets is to disintegrate or dissolve rapidly in oral cavity in 15-60 seconds, without need of water and should have pleasant mouth feel. The super disintegrant (Ac-Di-Sol, Crospovidone, Sodium Starch Glycolate) were used to formulate the tablets. All the ingredients as shown in Table 1 were co-ground in a pestle and mortar and then talc and magnesium stearate were added and mixed for 10 minutes. The mixed blend of drug-excipient was compressed using a single punch tablet machine (Cadmach, Ahemdabad) to produce tablets with 2.75 mm thickness and 9.28 mm in diameter.

Table 1: Formulation of fast dissolving tablets of valsartan.

| Ingredients (mg per tablet) | F1 | F2 | F3 | F4 | F5 | F6 |
|-------------------------------|-----|-----|-----|-----|-----|-----|
| Valsartan | 80 | 80 | 80 | 80 | 80 | 80 |
| Microcrystalline cellulose | 94 | 94 | 94 | 94 | 94 | 94 |
| Crospovidone | 1.8 | - | - | 9.5 | - | - |
| Ac-Di-Sol | - | 1.8 | - | - | 9.5 | - |
| Sodium starch glycolate (SSG) | - | - | 1.8 | - | - | 9.5 |
| Sodium saccharin | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Mint flavour | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Talc | 1 | 1 | 1 | 1 | 1 | 1 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 |

Flow properties of blend

The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio⁷. For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The \tan^{-1} of the (height of the pile/radius of its base) gave the angle of repose.

Blends were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess blend was removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρ_b) and tapped density (ρ_t) were calculated. Hausner ratio (H_R) and Carr index (I_C) were calculated according to the two equations given below:

$$H_R = \rho_t / \rho_b$$

$$I_C = (\rho_t - \rho_b) / \rho_t * 100$$

Evaluation of fast dissolving tablets of valsartan

Uniformity of weight

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight.

Hardness

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

Friability

The friability of sample of six tablets were measured using a Roche Friabilator. Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fine's using 60 mesh screen and the percentage of weight loss was calculated.

$$\% \text{ Friability} = (\text{Loss in weight} / \text{Initial weight}) \times 100$$

Wetting time and water absorption ratio

A piece of paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded

as the wetting time. The same procedure without Rosaline dye powder was followed for determining the water absorption ratio R was determined according to the following equation:

$$R = [(W_a - W_b)/W_b] \times 100$$

where, W_b and W_a were the weights of the tablet before and after use⁸.

Disintegration time

Disintegration time was measured in 900 ml artificial saliva (pH 5.8) according to the USP 24 method without disc at $37 \pm 0.5^\circ\text{C}$ temperature. The disintegration time of 6 individual tablets were recorded and the average was reported⁹.

Content uniformity

Twenty tablets were powdered, and 10 mg equivalent weight of valsartanin tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of artificial saliva (pH 5.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with artificial saliva (pH 5.8). The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 282 nm.

***In vitro* dissolution study**

The release of from FDT was determined using USP dissolution testing apparatus 2 (paddle method; Veego Scientific, Mumbai). The dissolution test was performed using

900 ml of artificial saliva, pH 5.8 at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45μ membrane filter and diluted to suitable concentration with artificial saliva, pH 5.8. Absorbance of these solutions was measured at 265 nm using a Thermospectronic-1 UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION

Several Technologies are available to manufacture orally disintegrating tablets. The most common preparation methods are molding, lyophilization or freeze drying, direct compression, spray drying and sublimation. In the present investigation FDTs of valsartan were prepared by direct compression method. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tabletting⁹. Values for angle of repose were found in the

range of 17.50 to 19.79°. Carr's index of the prepared blends falls in the range of 3.110 to 10.554 % and this is also supported by Hausner factor values which were in the range of 1.031 to 1.105. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture. All the tablets were prepared under similar conditions. All the formulations exhibited white color, odorless, convex in shape with smooth surface. The characteristics of prepared FDTs of valsartan are shown in Table 2. The average weight of the FDTs prepared by direct compression method was 180.00 to 189.38 mg. Weight variation of FDTs was within 0.801 %. Hardness and friability of all formulations were within acceptable limits. Hardness of tablets prepared by direct compression was 3.0 to 4.2 kg/cm². The friability of all formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping.

Disintegration time is very important for FDTs which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of prepared FDTs was in the range

of 10 to 35 seconds and the order was Crospovidone < Ac-Di-Sol < SSG. This finding is in agreement with results obtained from wetting time, since SSG swells with more gelling than Ac-Di-Sol and Crospovidone, which extend disintegration time as a result. As the concentration of superdisintegrants in the formulations increased the disintegration time was found to decrease.

Wetting time is used as an indicator from the ease of the tablet disintegration in buccal cavity. It was observed that wetting time of tablets was in the range of 15 to 32 seconds. It was observed that type of the disintegrant affected the wetting of the tablets. On comparing superdisintegrants the formulation containing SSG take more wetting time than Ac-Di-Sol and Crospovidone. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time. Crospovidone and Ac-Di-Sol perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling¹⁰.

The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with

water the tablets containing SSG swelled, the outer edge appeared gel-like. Tablets containing Crospovidone quickly wicks water and were hydrated, but were soft as compared with tablets prepared with Ac-Di-Sol and SSG. The centers of the tablets with SSG and Ac-Di-Sol remained dry and hard.

The drug content of the prepared tablets was in the range of 79.94 to 80.01 mg per tablet. The correlation of variation was found to be less than 0.010%, indicating uniformity of the drug content in the prepared tablets.

Table 2 : Characteristics of prepared FDTs of valsartan.

| Code | Average Weight (mg) | Hardness (kg/cm ²) | Friability (%) | Disintegration Time (sec) | Wetting Time (sec) | Water absorption ratio |
|----------------|---------------------|--------------------------------|----------------|---------------------------|--------------------|------------------------|
| F ₁ | 180.00±0.007 | 3.2±0.02 | 0.51±0.03 | 24±2.00 | 15±1.00 | 122±0.12 |
| F ₂ | 181.68±0.101 | 3.0±0.10 | 0.05±0.07 | 29±2.00 | 23±0.00 | 116±0.09 |
| F ₃ | 180.10±0.024 | 3.2±0.02 | 0.61±0.05 | 35±0.00 | 32±1.00 | 102±0.29 |
| F ₄ | 189.08±0.105 | 4.0±0.01 | 0.15±0.03 | 10±1.00 | 08±0.00 | 158±0.97 |
| F ₅ | 189.20±0.213 | 3.4±0.04 | 0.35±0.04 | 12±1.00 | 17±1.00 | 131±0.95 |
| F ₆ | 189.38±0.199 | 4.2±0.00 | 0.75±0.01 | 21±2.00 | 19±2.00 | 125±1.05 |

In vitro dissolution studies of the prepared FDTs was preformed in artificial saliva (pH 5.8) using USP dissolution apparatus type 2. At 5% superdisintegrant level the drug release at the end of 12 minutes were found to be 87.09, 72.04 and 58.78 % with Crospovidone, Ac-Di-sol and SSG respectively (Figure 1). It was observed that as the concentration of superdisintergrant increased the drug release also increased. With reference to the type of superdisintergrant, the release rate was found to follow the order: Crospovidone > Ac-Di-sol > SSG.

The data obtained from *in vitro* dissolution studies were fitted to zero-order, first-order and Korsemeyer-Peppas equation. The zero-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer-Peppas equation¹¹:

$$m_t/m_\infty = k t^n$$

where m_t/m_∞ is fraction of drug released, k is kinetic constant, t is release time and n is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe

the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism; when $n = 1$, the release rate is independent of time (zero-order) (case

II transport), $n = 0.5$ for Fickian diffusion and when $0.5 < n < 1.0$, diffusion and non-Fickian transport are implicated. Lastly, when $n > 1.0$ super case II transport is apparent. 'n' is the slope value of $\log m/m_{\infty}$ versus \log time curve¹¹.

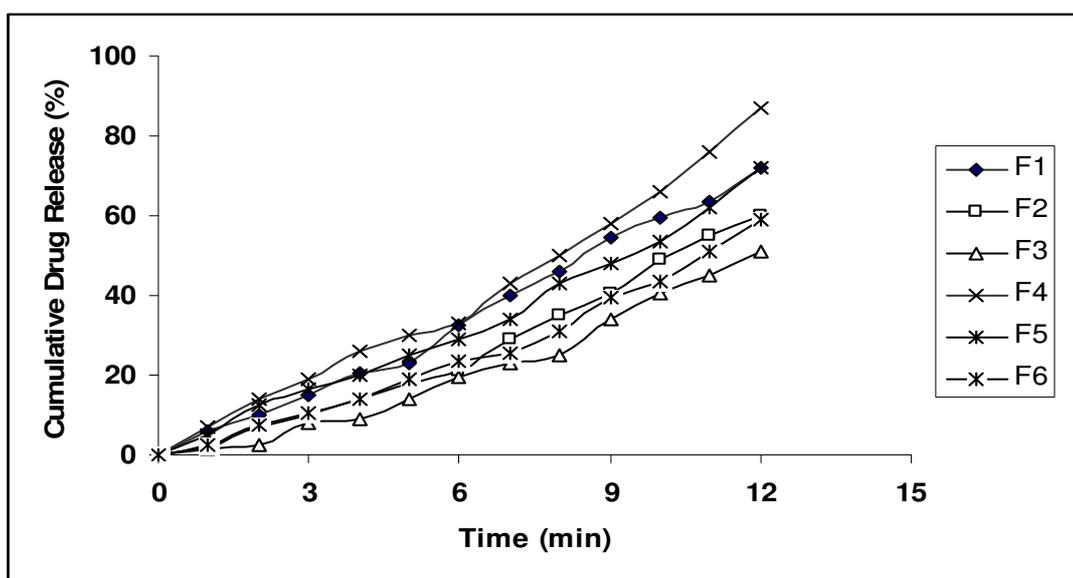


Fig. 1 : *In vitro* release of valsartan from fast dissolving tablets.

Regression analysis was performed and regression values 'R²' were 0.990 to 0.995 for different formulations (Table 3). Slope values ($0.5 < n < 1.0$) suggest that

the release of valsartan from fast dissolving tablets followed non-Fickian diffusion mechanism.

Table 3: Fit of different kinetic models for release of valsartan from FDTs.

| Code | Zero-order | | First-order | | Korsmeyer-Peppas | |
|----------------|----------------------------|----------------|--|----------------|------------------|----------------|
| | k ₀ (mg/min) | R ² | k ₁ (min ⁻¹) | R ² | n | R ² |
| F ₁ | 1.623 | 0.987 | 0.041 | 0.943 | 0.935 | 0.991 |
| F ₂ | 1.403 | 0.984 | 0.035 | 0.941 | 0.904 | 0.995 |
| F ₃ | 1.387 | 0.982 | 0.033 | 0.955 | 0.902 | 0.993 |
| F ₄ | 1.715 | 0.990 | 0.047 | 0.949 | 0.878 | 0.990 |
| F ₅ | 1.698 | 0.989 | 0.041 | 0.965 | 0.905 | 0.992 |
| F ₆ | 1.399 | 0.986 | 0.036 | 0.953 | 0.933 | 0.990 |

CONCLUSION

In the present study it can be concluded from the characterization of fast dissolving tablets of valsartan that formulation containing Crospovidone is most acceptable. It was also observed that to further increase the drug release from FDTs, solubility enhancement of valsartan is required and is under investigation. Further *in vivo* studies in human volunteers are required to correlate *in vitro* release data.

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