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Original Article

Formulation and Evaluation of Valsartan Oral Dispersible Tablets by Direct Compression Method

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ABSTRACT

The objective of the present study is to develop a pharmaceutically stable, cost effective and quality improved robust formulation of Valsartan Immediate Release tablets. The aim of work is related to the formulation and evaluation of 10mg of dispersible tablet. Valsartan belongs to a class of antihypertensive agents called angiotensin II receptor blockers (ARBs). Total nine formulations were prepared by direct compression method in which the concentration of the superdisintegrants is varied to evaluate the effect on the disintegration time of valsartan mouth dissolving tablets. The superdisintegrants, involved in preparation are Sodium starch glycolate, Avicel PH 102, Low HPC. The prepared batches of tablets were evaluated for micromeritic parameters, weight variation, hardness, friability, wetting time, In vitro dispersion time, drug content and In vitro dissolution studies. In Formulations F1, F2, F3, releases 89.83%, 91.10%, 96.20%, respectively, Formulation F4, F5, and F6, which release 85.11%, 88.71% and 90.44% respectively and. Formulation F7, F8, F9, releases 78.26%, 82.26%, 85.31%, respectively, at end of 15 minutes. Amongst all the developed formulations, valsartan mouth dissolving tablets formulated by using sodium starch glycolate as superdisintegrants, having hardness (3.7 Kg/cm²), Friability (0.1356 %), Drug Content (9.925 ± 0.067 mg). and it is fulfilling all the parameters. It has shown good In vitro disintegration time (8.00 ± 1.023 sec), In vitro dispersion time (14.33 \pm 1.24 sec), compared to other superdisintegrants. The optimized Sodium formulation (F3) containing starch glycolate. as superdisintegrant is producing best results compared to other formulations.

Keywords: Immediate release tablets, Sodium starch glycolate (SSG), L-hydroxy propyl cellulose (L-HPC), Direct compression.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.¹

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as– Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques. The pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects.²

Formulate to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such IR products result in relatively rapid drug absorption and onset of accompanying pharmacodynamics effects. However, after absorption of drug from the dosage form is complete, plasma drug concentration decline according to the drugs pharmacokinetic profiles, conventional drug requires therapy periodic doses of therapeutic agents.

Oral drug delivery is the most and preferred desirable method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations. mainly of patient acceptance because and convenience in administration.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance.³

Oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package.⁴

Advantages of immediate release drug delivery systems

- Release the drug immediately.
- More flexibility for adjusting the dose.⁵
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem.
- Immediate release drug delivery systems used in both initial stage and final stage of disease. At the particular site of action the drug is released from the system.⁸

Disadvantages of immediate release drug delivery systems⁶

- Rapid drug therapy intervention is not possible
- Sometimes may require more frequency of administration.
- Dose dumping may occur.
- Reduced potential for accurate dose adjustment.

MATERIALS AND METHODS

Valsartan was obtained as a gift sample from Cadila Pvt Ltd, Goa. Eudragit E 100, Sodium Starch Glycollate, Microcrystalline cellulose were obtained from Karnataka Fine Chem. Bangalore and L-HPC from Strides Arcolab Ltd. Bangalore. All other chemicals used for analytical grade.

Direct compression technique

The drug is mixed with powdered sodium starch glycolate, Eudragit E-100 in a suitable ratio. Mix upto 10 mins then add lactose and magnesium stereate, Mixed thoroughly. Then compress into tablet.⁷ (See figure 1.)

Formulation design

Total nine formulations were prepared in which the concentrations of the superdisintegrants is varied to evaluate the effect on the disintegration time of valsartan mouth dissolving tablets.⁸ (See figure 2 and table 1.)

EVALUATION

Preparation of standard calibration curve

An accurately weighed 10 mg of valsartan was dissolved in 100ml of 0.1N HCl to get a concentration of 100mcg/ml. From this stock solution aliquot suitable dilutions were made in order to get concentration in between the Beer's range of 2-10 μ g/ml. The absorbance was measured at 234 nm using UV spectrophotometer. The standard curve was obtained by plotting absorbance V/s. concentration in μ g/ml.⁸

Compatibility studies of valsartan and formulation components

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. Infrared spectrum of the representative valsartan and excipients were taken. The study was conducted on Thermo Nicolet (FTIR-200). The spectra's were run from 4000 nm to 500 nm wave number.⁹

Micromeritic evaluation

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.¹⁰

$$\tan \theta = h/r$$

 $\theta = \tan^{-1}(h/r)$

Where, θ is the angle of repose h is the height r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. The accurately weighed amount of sample taken in a 25ml measuring cylinder of Borosil measured/recorded the volume of packing and tapped 100 times on a plane hard wooden surface and tapped volume of packing recorded and LBD and TBD calculated by following formula:

LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing.

TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing.

Percentage compressibility

Percent compressibility of powder mix was determined by Carr's compressibility index calculated by following formula.

Carr's index (%) = [(TBD - LBD) x 100] / TBD.

Post-compression parameters

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light.

Uniformity of thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper.⁹

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the same tablets from each formulation was determined. The mean and standard deviation values were also calculated.¹⁰

Friability test

friability of The tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets weighed were initially (W_{initial}) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by,

 $F = W_{initial} - W_{final} \times 100 / W_{initial}$.

% Friability of tablets less than 1% are considered acceptable.

Drug content uniformity

One tablet was weighed and powdered. The whole amount of powdered tablet was transferred into a 100 ml volumetric flask. Add 0.1N HCl up to the mark. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 2ml of filtrate was taken in a 25 ml volumetric flask and diluted up to the mark with 0.1N HCl and analyzed spectrophotometrically at 305 nm. The concentration of valsartan (in μ g/ml) was calculated by using the standard calibration curve of valsartan.

Drug content in mg was calculated by using formula;

$= \frac{\text{Concentration in } \mu \text{g/ml } x \ 100 \ x \ 25}{2 \ x \ 1000}$

Drug content claim was 10mg per tablet. This procedure was followed for 5 tablets from each formulation. The mean and standard deviation values were also calculated.

Weight variation test

Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. The US Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Wetting time

The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petridish (i.d. = 6.5 cm) containing 6 ml of water, a tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined. (See figure 3.)

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petridish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation—

R = 100 x Wa - Wb/Wb

Where, Wb = weight of the tablet before water absorption.

Wa = weight of the tablet after water absorption.

Three tablets from each formulation were performed and standard deviation was also determined.⁷

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and *In vitro* dispersion time was performed. Standard deviation was also determined and *In vitro* dispersion time is expressed in seconds.

In vitro disintegration test

The process of breakdown of a tablet particles smaller is called into as disintegration. The In vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at $37^{0}\pm2^{0}$ C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at $37^{0}\pm2^{0}$ C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

In vitro dissolution studies

In vitro release studies were carried out using USP-type II dissolution apparatus (paddle type). Two objectives in the development of *In vitro* dissolution tests are to show (1) that the release of the drug from the tablet is as close as possible to 100% and (2) that the rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective. (See table 2.)

RESULTS AND DISCUSSION

Standard plot

The standard calibration curve of was obtained by plotting Absorbance vs. Concentration. The standard calibration curve shows the slope of 0.099 and correlation coefficient of 0.9998. The curve was found to be linear in the concentration range of 2-10 μ g/ml (Beer's range) at 234 nm. The calculations of drug content, *In vitro* release and stability studies are based on this calibration curve.¹¹ (See table 3 and figure 4.)

Drug-excipients compatibility studies

To study the compatibility of the drug with various polymers, IR spectra of drug and formulation components were carried out. The IR spectra of the drug and all excipients were shown in figure. The characteristics absorption peaks of valsartan were obtained at 3391.48, 2634.50, 1597.18, and 676.19. The peaks obtained in the spectras of each excipient correlate the peaks of drug spectrum. By correlation, it indicates that drug (valsartan) is compatible with the components.¹² (See figure 5.)

Inference

The results obtained are showed the purity of drug and there is no interaction between drug and polymer. FTIR spectra were recorded in above figure.

EVALUATION OF TABLETS

Pre-compression parameters

Angle of repose (θ)

The values were found to be in the range of $25^{0}.22'$ to $30^{0}.17'$. All formulations showed the angle of repose within 30^{0} .

Bulk density

The loose bulk density and tapped bulk density for all the formulations varied from 0.56 gm/cm³ to 0.62gm/cm³ and 0.67 gm/cm³ to 0.73gm/cm³ respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder.

Percentage compressibility

Percent compressibility of powder mix was determined by Carr's compressibility index. The percent compressibility for all the nine formulations lies within the range of 13.432 to 17.808. All formulations are showing good compressibility. (See table 4.)

Inference

The pure drug showed angle of repose value 25.22 indicates the good flow properties. The compressibility value 13.432 that indicates the drug has good compressibility property.

Post-compression parameters

See table 5.

Inference

The uniformity of thickness, hardness, friability, uniformity of weight, drug content are within the limits. (See table 6.)

Inference

Wetting time and water absorption ratio of the drug is within the limits. (See table 7 to 10 and figure 6 to 8.)

Inference

The results were found to be 96.2% drug release for f3 formulation.when compared to other formulations it shows good result.All physical chemical characteristics were found to be satisfactory. So I selected f3

formulation containing SSG as super distentegrant. (See figure 9.)

Inference

From the above results the *in vitro* drug release of f3 formulation is high compared to innovator product.

SUMMARY AND CONCLUSION

The present was an attempt to formulate and evaluate mouth dissolving tablets of an anti-hypertensive drug valsartan. For the present study, valsartan was chosen as the existing market product is available only in the form of Tablets in India and is difficult to swallow to the pediatrics and elderly patients leading to patient non-compliance.

Preformulation studies were carried out during the early stages of this work. It has found that valsartan is having maximum absorption at wavelength 234 nm. The drugpolymer compatibility study was carried out to determine the interactions between the drug and the polymers used in the study. The IR spectra's revealed that, polymers and excipients used were compatible with drug.

Prepared tablets were evaluated for Pre-compression Parameters and Post compression parameters. Flow properties -Angle of repose, loose bulk density, tapped density and also % Carr's compressibility was determined to all the formulations which showed good flow property. The shape and color of all formulations were found to be circular and white in color. The thickness found uniform in specific formulations. Amongst all the developed formulations, valsartan mouth dissolving tablets formulated by using sodium starch glycolate as superdisintegrants, F3 having hardness (3.7 Kg/cm²), Friability (0.1356 %), Drug Content (9.925±0.067 mg). and it is fulfilling all the parameters. It has shown good In vitro disintegration time (8.00 ± 1.023 sec), In vitro dispersion time (14.33 \pm 1.24 sec), compared to other superdisintegrants.

All the nine formulations tablets, In vitro disintegration, In vitro dispersion and wetting time found less than 30 seconds. This indicates rapid disintegration. Water absorption ratio showed good absorptivity in all formulations. Hardness and friability of all the formulations indicated tablets were mechanically stable and percentage weight variation and drug content uniformity found within limits. In vitro release studies revealed that 96% of drug releases from SSG, MCC (90%), and L-HPC (85%) for all the formulations were within 15 min.

Amongst all the formulations, formulation containing sodium starch glycolate (F3) as optimized formulation is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration, *in vitro* dispersion time, compared to other superdisintegrants.

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Ingredients (mgs)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Valsartan	10	10	10	10	10	10	10	10	10
Sodium starch glycolate	15	22.5	30						
Avicel PH 102				15	22.5	30			
Low HPC							15	22.5	30
Eudragit E100	10	10	10	10	10	10	10	10	10
Lactose	259	251.5	244	259	251.5	244	259	251.5	244
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3

Table 1. Composition of rapidly disintegrating tablets of valsartan

Table 2. Specifications for the study of *in vitro* dissolution

Dissolution medium	500 ml of 0.1N HCl
Temperature	37 [°] C±1 [°] C
RPM	50
Drug Content	Weight of tablet equivalent to 10 mg of drug
Volume withdrawn	1 ml every 3 minutes
Volume made up to	5 ml
λ_{max}	234 nm
Dilution factor	5

Table 3. Standard calibration curve of valsartan at 234 nm in 0.1N Hcl

S. No.	Concentration (µg/ml)	Absorbance
1	2	0.1820
2	4	0.3924
3	6	0.5921
4	8	0.7955
5	10	0.9886

Formulation code	Angle of repose (θ)	Loose bulk density (gm/cm ³)	Tapped bulk density (gm/cm ³)	% Compressibility
F1	28.23	0.58	0.71	15.492
F2	27.31	0.57	0.70	14.285
F3	25.22	0.56	0.67	13.432
F4	29.37	0.61	0.72	16.666
F5	28.22	0.60	0.70	15.289
F6	27.37	0.59	0.69	14.285
F7	30.17	0.62	0.73	17.808
F8	29.19	0.61	0.71	15.492
F9	28.88	0.60	0.70	14.676

Table 4. Pre-compression parameters

Table 5. Evaluation of tablet parameters

Formulation code	Uniformity of thickness (n=3) (mm)	Hardness (n=3) (kg/cm ²)	Friability % (n=10)	Uniformity of weight (n=10) (mg)	Drug content (n=3) (mg)
F1	3.13±0.05	3.87±0.29	0.3633	301.0±2.013	9.790±0.148
F2	3.17±0.06	3.76±0.29	0.2103	300.5±2.153	9.825±0.113
F3	3.18±0.05	3.70±0.29	0.1356	300.5±2.652	9.925±0.067
F4	2.97±0.03	3.76±0.29	0.3496	298.6±2.88	9.889±0.176
F5	3.13±0.05	3.24±0.29	0.3035	300.0±1.032	9.900±0.031
F6	3.15±0.13	3.66±0.29	0.2103	300.1±1.272	9.918±0.021
F7	2.90±0.05	3.24±0.29	0.4739	300.1±2.171	9.700±0.148
F8	2.97±0.03	2.96±0.29	0.4200	299.4±3.045	9.835±0.113
F9	2.98±0.03	2.90±0.29	0.4187	299.6±2.197	9.876±0.054

Table 6. Wetting time and water absorption ratios of formulations

Formulation Code	Wetting Time (n=3)	Water absorption ratio
	Mean \pm SD	Mean ± SD
F1	$\textbf{22.00} \pm \textbf{1.12}$	27.81 ± 1.123
F2	18.00 ± 0.67	19.84 ± 0.663
F3	17.33 ± 1.55	18.45 ± 2.135
F4	24.67 ± 0.36	30.89 ± 1.637
F5	23.67 ± 0.55	29.89 ± 1.653
F6	22.33 ± 1.57	$\textbf{28.08} \pm \textbf{1.428}$
F7	$\textbf{28.33} \pm \textbf{0.59}$	37.89 ± 1.345
F8	$\textbf{26.00} \pm \textbf{1.01}$	36.37 ± 1.965
F9	25.33 ± 0.59	34.09 ± 1.936

Formulation code	In vitro disintegration time (Sec.)	In vitro dispersion time (sec.)
F1	11.67 ± 2.082	$\textbf{20.00} \pm \textbf{1.11}$
F2	09.33 ± 1.143	18.33 ± 0.56
F3	$\textbf{08.00} \pm \textbf{1.023}$	14.33 ± 1.24
F4	19.30 ± 0.556	$\textbf{21.67} \pm \textbf{0.65}$
F5	18.33 ± 0.567	19.67 ± 0.67
F6	16.33 ± 0.587	15.33 ± 1.25
F7	23.67 ± 0.556	23.67 ± 1.23
F8	19.33 ± 0.545	21.67 ± 0.65
F9	17.33 ± 0.567	20.00 ± 1.11

Table 7. In-vitro disintegration time, in vitro dispersion time

Table 8. In vitro drug release profile for F1, F2, F3

Formulation code	Cumulative percent drug release						
F1	3	6	9	12	15		
	62.65	74.49	78.72	85.80	89.83		
F2	66.04	75.98	77.16	88.85	91.10		
F3	67.24	79.00	83.21	93.99	96.20		

Table 9. In vitro drug release profile for F4, F5, F6

Formulation code	Cumulative percent drug release						
F4	3	6	9	12	15		
F4	66.22	76.97	79.15	81.41	85.11		
F5	60.22	75.53	77.70	83.99	88.71		
F6	59.04	70.26	76.45	85.20	90.44		

Table 10. In vitro drug release profile for F7, F8, F9

Formulation code	Cumulative percent drug release						
F7	3	6	9	12	15		
F7	57.26	68.53	71.5	76.98	78.26		
F8	54.96	64.65	73.86	79.55	82.26		
F9	60.11	69.91	75.65	81.50	85.31		

















