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Development of Discriminative Dissolution Medium for Valsartan

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ABSTRACT

Dissolution is a valuable qualitative tool to asses the biological availability and batch to batch consistency. Discriminative dissolution mediums are highly desirable to differentiate the dissolution profiles of two identical products which are varied in their composition, formulation technique, manufacturing process and site of manufacturing. The objective of present investigation is to develop discriminative dissolution medium for valsartan by using two different marked formulations named as VALZAAR and VALENT. The dissolution studies were performed in four dissolution mediums (0.1N HCl (pH 1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distill water) at three different agitation speeds (50, 75,100 RPM). Model independent approaches such as difference factor (f_1) and a similarity factor (f_2) were used to compare dissolution profiles. Among all the cases in pH 6.8 phosphate buffer at 100 rpm drug releases at faster rate and best suited to maintain sink conditions. Irrespective of other cases pH 4.5 acetate buffer at 50 rpm was considered as a discriminative dissolution medium because of its lesser similarity factor and higher difference factor. From the present experimental investigation the rate of dissolution was found to be influenced by pH of the dissolution medium and speed of the agitation. The usage of 4.5 acetate buffer at 50 rpm was found to be a discriminative dissolution medium for valsartan tablets.

Keywords: Valsartan, Dissolution medium, Difference factor , Similarity factor, Dissolution efficiency

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INTRODUCTION

Valsartan is an ACE inhibitor and effectively used in the treatment of hypertension at a dose of 80 mg per day. It is also used in the management of myocardial infarction, and heart failure[1, 2] Valsartan is a low soluble drug with an oral bioavailability of 23% and peak plasma concentration is achieved with in 2 to4 hours and plasma half life is 7.5 hours up on oral administration.

Discriminative dissolution medium is used to assess the changes in dissolution profile for formulations in which manufacturer changes the composition, equipment and formulation technique[3]. Discriminative dissolution medium is a dissolution medium which has the ability to discriminate the product which passes and another which fails. Dissolution test are used to assess the batch to batch quality and to ensure continuous product quality and performance[4].

With the view of above information an attempt had been made to develop discriminative dissolution medium for valsartan by adopting four different dissolution mediums and paddles are operated at three different agitation speeds.

MATERIALS AND METHODS:

Two marketed brands of valsartan VALZAAR (batch no- C6039007) and VALENT (batch no-PM90017) were obtained from local pharmacy, and named as brand A and brand B. Pure valsartan obtained from NATCO pharmaceuticals, and all other chemicals used in this investigation are analytical grade.

Quality control tests for marketed valsartan tablets:

Weight variation, hardness, friability, drug content, disintegration time, dissolution studies and all other official tests were conducted for marketed valsartan tablets.

Dissolution media:

The four dissolution media employed were 0.1N Hcl, pH 4.5 acetate buffers, pH 6.8 phosphate buffer and distilled water. These media were selected based on the FDA guidance for industry.

In-vitro dissolution studies:

In-vitro dissolution studies are performed by using USP XXVI dissolution test apparatus using 0.1N HCl (pH 1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distill water as dissolution medium. The paddles are allowed to rotate at speed of 50 rpm, 75 rpm and 100 rpm. The dissolution medium was maintained at a temperature of $37 \pm 0.5\ ^{O}C$ and samples are withdrawn at an interval of every 5 min. The volumes of the withdrawn samples were replaced by fresh dissolution medium in order to keep the volume of the dissolution medium as constant.

The withdrawn samples were filtered and absorbance was measured at absorption maxima of 250 nm using UV-visible spectrophotometer.

Comparison of dissolution profile by model independent methods[5,6]:

Model independent approaches includes difference factor (f_1) and a similarity factor (f_2) were used to compare dissolution profiles. The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two dissolution curves.

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/ [\sum_{t=1}^{n} R_t]\} \times 100$$

Where n is the number of time points,

R is the dissolution value of the reference at time t

T is the dissolution value of the test at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two dissolution curves.

$$f_2 = 50 \times \log \{[1+ (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0..5} \times 100\}$$

Where n is the number of time points,

R is the dissolution value of the reference at time t

T is the dissolution value of the test at time t.

RESULTS AND DISCUSSIONS:

The quality control parameters for marketed tablets are recorded. Weight variation of two brands was found to be less than 7.5%, friability was less than 1% and two brands disintegrate with in 15 min. The dissolution studies were performed in four dissolution mediums (0.1N HCl (pH 1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distill water) at three different agitation speeds (50, 75,100 RPM).The dissolution profiles are shown in Figures 1-3. The dissolution rate followed first order kinetics as the graphs drawn in between amount of drug dissolved verses time were found to be linear. In-vitro dissolution parameters i.e., T50 (time for dissolution of 50% of drug), T90 (time for dissolution of 90% of drug), DE (dissolution efficiency),first order rate constant K min^{-1}, difference factor (f_1) and similarity factor (f2) were calculated and are shown in table 1.

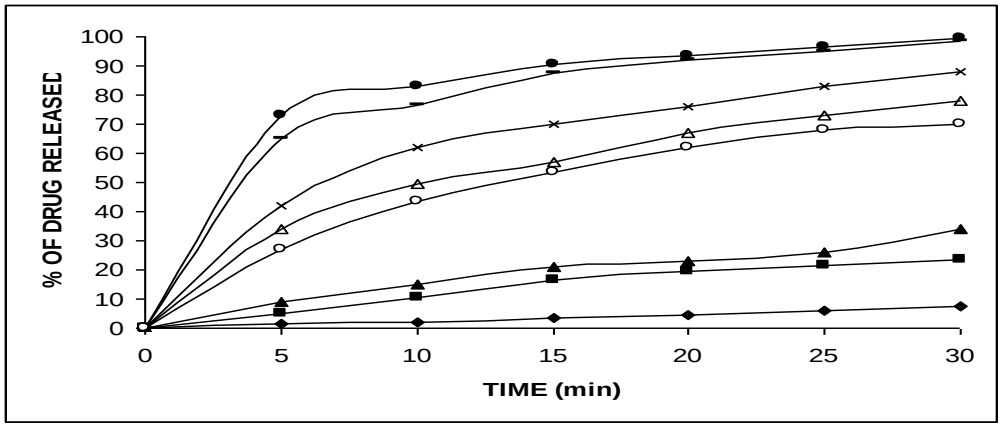

Figure 1: **Comparative Dissolution Profiles of Valsartan in Four Mediums at 50 RPM**

(♦) dissolution profile for valsartan brand B in 0.1 NHCl buffer at 50 rpm
(■) dissolution profile for valsartan brand A in 0.1 NHCl buffer at 50 rpm
(X) Dissolution profile for valsartan brand A in 4.5 acetate buffer at 50 rpm
(▲) dissolution profile for valsartan brand B in 4.5 acetate buffer at 50 rpm
(-) dissolution profile for valsartan brand A in 6.8 phosphate buffer at 50 rpm
(▪) dissolution profile for valsartan brand B in 6.8 phosphate buffer at 50 rpm
(Δ) dissolution profile for valsartan brand A in water at 50 rpm
(○) dissolution profile for valsartan brand B in water at 50 rpm.

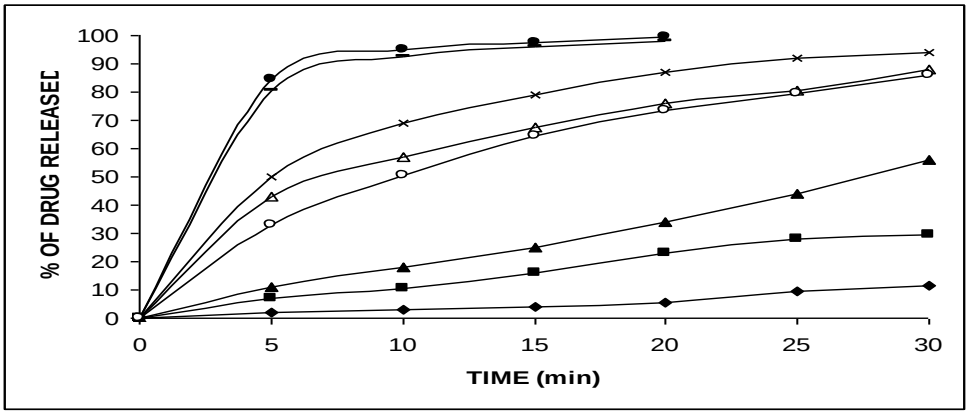

Figure 2: **Comparative Dissolution Profiles of Valsartan in Four Mediums at 75RPM**

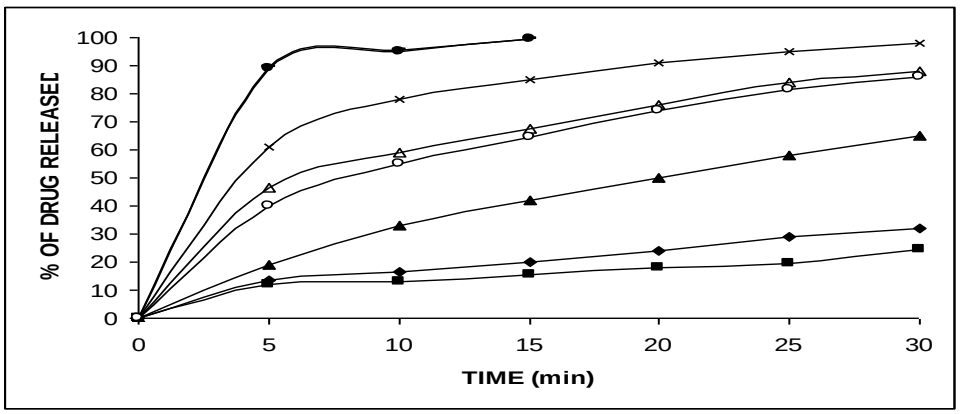

Figure 3: **Comparative Dissolution Profiles of Valsartan in Four Mediums at 100 RPM**

Table 1: In-vitro Dissolution Parameters Of Valsartan Marketed Tablets

S.No	Dissolution Medium	RPM	Zero order coefficient		First order coefficient		$K_{(min^{-1})}$		T_{50}(min)		T_{90}(min)	
			A	B	A	B	A	B	A	B	A	B
1	pH 1.2	50	0.98	0.950	0.99	0.97	0.009	0.002	70	284	233	945
		75	0.96	0.87	0.97	0.99	0.012	0.003	56	189	187	628
		100	0.88	0.86	0.92	0.94	0.013	0.009	51	70	178	233
2	pH 4.5	50	0.98	0.71	0.99	0.98	0.066	0.014	10.4	47.6	34.5	158
		75	0.97	0.62	0.99	0.99	0.100	0.031	6.9	21.8	22.8	72.4
		100	0.95	0.66	0.99	0.97	0.105	0.036	6.6	19.1	21.2	63.4
3	pH 6.8	50	0.60	0.42	0.99	0.96	0.156	0.140	4.4	4.9	14.7	16.4
		75	0.65	0.60	0.98	0.98	0.265	0.264	2.6	2.8	8.7	8.9
		100	0.74	0.73	0.98	0.98	0.365	0.357	1.94	1.99	6.3	6.5
4	pH 7	50	0.75	0.84	0.98	0.98	0.051	0.043	13.6	16	45	53
		75	0.64	0.78	0.97	0.99	0.064	0.061	10.8	11.3	35.9	37.7
		100	0.59	0.74	0.96	0.99	0.069	0.065	10	10.6	33	35.4

Two dissolution profiles are found to be similar if similarity factor (f_2) is more than 50 and difference factor (f_1), is less than 15.The similarity factor was found to be more than 50 and difference factor was found to be less than 15 in case of pH 6.8 phosphate buffer at 50,75,100 and in water at 50,75,100 rpm.

Two dissolution profiles are found to be dissimilar if similarity factor (f_2) is less than 50 and difference factor (f_1), is more than 15.The similarity factor was found to be less than 50 and difference factor was found to be more than 15 in case of pH 4.5 acetate buffer at 50, 75,100 and in 0.1 N HCl at 50,75 rpm.

Table 2: Dissolution Efficiency, Difference Factor (F_1), Similarity Factor (F_2) For Valsartan Marketed Tablet

S.NO	Dissolution medium	RPM	Dissolution efficiency DE_{30} (%)		Difference factor(f_1)	Similarity factor(f_2)
			A	B		
1	pH 1.2	50	7.7	1.6	67	46
		75	8.2	2.3	60	44
		100	13	10.6	25.5	66
2	pH 4.5	50	46.3	11.5	69	17
		75	52.8	13.8	60.2	21.6
		100	60.5	24.3	47.4	24
3	pH 6.8	50	61.1	66.6	3.9	68.4
		75	73.3	75.8	2.45	81.8
		100	77.1	77.9	0.53	96.4
4	pH 7	50	37	31.8	10.3	58
		75	44.1	38	6.3	68
		100	46.1	42	5.4	72

Among the all the cases in pH 6.8 phosphate buffer at 100 rpm drug releases at faster rate and best suited to maintain sink conditions. Irrespective of other cases pH 4.5 acetate buffer at 50 rpm was considered as a discriminative dissolution medium because of its lesser similarity factor and higher difference factor.

CONCLUSION:

From the present experimental investigation the rate of dissolution was found to be influenced by pH of the dissolution medium and speed of the agitation. The usage of 4.5 acetate buffer at 50 rpm was found to be a discriminative dissolution medium for valsartan tablets. The usage of 6.8 phosphate buffer at 100 rpm was found to be best to maintain sink conditions.

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