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FORMULATION AND EVALUATION OF VALSARTAN TABLETS EMPLOYING CYCLODEXTRIN-POLOXAMER 407-PVP K30 INCLUSION COMPLEXES

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ABSTRACT

Valsartan, a widely prescribed anti-hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. The objective of the study is to evaluate the feasibility of formulating valsartan–CD (βCD/ HPβCD)–Poloxamer 407 and valsartan–CD (βCD/ HPβCD) –PVP K30 inclusion complexes into tablets and to evaluate the effects of CDs, Poloxamer 407 and PVP K30 on the dissolution rate of valsartan tablets. A comparative evaluation of wet granulation and direct compression methods was made for the preparation of tablets employing drug–CD–Poloxamer 407/PVP K30 inclusion complexes. Drug–CD-Poloxamer 407/PVP K30 inclusion complexes were prepared by kneading method. Tablets each containing 40 mg of valsartan were prepared by wet granulation and direct compression methods employing various CD complexes and the tablets were evaluated for dissolution rate and other physical properties.

Valsartan tablets made by direct compression method disintegrated rapidly when compared to those made by wet granulation method. Tablets formulated employing βCD complexes disintegrated relatively more rapidly than those formulated employing HPβCD complexes. Valsartan dissolution was rapid and higher from the tablets formulated employing drug-CD-Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing valsartan alone and drug – CD complexes in both wet granulation and direct compression methods. In both the methods tablets formulated employing βCD complexes gave higher dissolution rates (K_1) and DE_{30} values when compared to those formulated employing HPβCD complexes. Tablets formulated employing dug–βCD–Poloxamer 407 and drug–βCD–PVP K30 complexes and prepared by direct compression method gave higher dissolution rates, 0.0944 and

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0.0833 min^{-1} respectively when compared to plain tablets (0.0326 min^{-1}) as well as tablets containing drug – βCD complexes (0.0641 min^{-1}). Hence a combination of βCD with Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate of valsartan tablets.

Key words: Valsartan tablets, β Cyclodextrin, HP β Cyclodextrin, Poloxamer 407, PVP K30, Dissolution rate.

INTRODUCTION

Valsartan, a widely prescribed anti-hypertensive drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It is practically in soluble in water and aqueous fluids. As such its oral absorption is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, micro emulsion and self-emulsifying systems are available to enhance the solubility, dissolution rate and bioavailability of poorly soluble BCS Class II drugs[1]. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favourably affected[2,3]. Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies[4,5]. Poloxamer 407 is a polyethylene oxide-polypropylene oxide- polyethylene oxide triblock co-polymer of non-ionic nature and is used as a solubilising agent[6-8]. We reported[9] earlier that combination of cyclodextrins (βCD and HPβCD) with either Poloxamer 407 or PVP K30 has markedly enhanced the solubility and dissolution rate of valsartan, a BCS class II drug than is possible with them individually. The objective of the present study is to evaluate the feasibility of formulating valsartan – CD (βCD/ HPβCD) – Poloxamer 407 and valsartan – CD (βCD/ HPβCD) –PVP K30 inclusion complexes into tablets and to evaluate the effects of CDs, Poloxamer 407 and PVP K30 on the dissolution rate of valsartan tablets. Two methods i.e. wet granulation and direct compression methods were tried for the preparation of valsartan tablets employing valsartan-CD- Poloxamer 407 and valsartan-CD-PVP K30 inclusion complexes. A comparative evaluation of the two methods of preparation was also made.

EXPERIMENTAL

Material and methods

Valsartan, crosspovidone and poly vinyl pyrrolidone (PVP K30) were gift samples from M/s Dr. Reddy Laboratories, Hyderabad. β-Cyclodextrin and HP β- Cyclodextrin were gift samples from M/s. Cerestar Inc., USA. Methanol (Qualigens) and Poloxamer 407, lactose IP, talc and magnesium stearate were procured from commercial sources.

Estimation of valsartan

A UV Spectrophotometric method based on the measurement of absorbance at 225 nm in a phosphate buffer of pH 6.8 was used for the estimation of valsartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 1-10 µg/mL. When a standard drug solution was repeatedly assayed (n = 6), the relative error and coefficient of variance were found to be 0.80% and 1.20% respectively. No interference by the excipients used in the study was observed.

Preparation of drug-CD- poloxamer 407/ PVP K30 complexes

Solid inclusion complexes of valsartan- βCD (1 : 2), valsartan- βCD(1 : 2)- Poloxamer 407 (2%), valsartan- βCD (1 : 2) - PVP K30 (2%), valsartan- HPβCD (1 : 2), valsartan- HPβCD (1 : 2)- Poloxamer 407 (2%), valsartan- HPβCD (1 : 2)- PVP K30 (2%), were prepared by kneading method. Valsartan, βCD and Poloxamer 407/ PVP K30 were triturated in a mortar with a small volume of solvent consisting of a blend of water: methanol (1 : 1). The thick slurry formed was kneaded for 45 min and then dried at 55^{o}C until dry. The dried mass was powdered and sieved to mesh No. 120.

Preparation of valsartan- CD - poloxamer 407/ PVP K30 tablets

Compressed tablets each containing 40 mg of valsartan were prepared by (i) wet granulation and (ii) direct compression methods employing Valsartan- CD - Poloxamer 407/ PVP K30 inclusion complexes as per the formulae given in Table 1.

Preparation of tablets by wet granulation method

Lactose was used as filler. Crosspovidone (5%), talc (2%) and magnesium stearate (2%) were incorporated, respectively as disintegrant and lubricants. Purified water was used as granulating fluid in wet granulation method. The tablet granules were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd.,

Ahmedabad) to a hardness of 5- 6 Kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Table 1: Formulae of Valsartan tablets prepared by wet granulation and direct compression methods employing drug-CD–Poloxamer 407/PVP K30 inclusion complexes

Ingredient (mg/tablet)	Valsartan tablet formulation*						
	WT1/ DT1	**WT2/ DT2**	**WT3/ DT3**	**WT4/ DT4**	**WT5/ DT5**	**WT6/ DT6**	**WT7/ DT7**
Valsartan	40	-	-	-	-	-	-
Val - βCD (1 : 2)	-	120	-	-	-	-	-
Val - βCD - P 407 (2%)	-	-	122.4	-	-	-	-
Val - βCD - PVP (2%)	-	-	-	122.4	-	-	-
Val - HPβCD (1 : 2)	-	-	-	-	120	-	-
Val - HPβCD - P 407 (2%)	-	-	-	-	-	122.4	-
Val - HPβCD - PVP (2%)	-	-	-	-	-	-	122.4
Cross povidone	11	11	11	11	11	11	11
Talc	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Lactose	160.2	80.2	77.8	77.8	80.2	77.8	77.8
Total weight	220	220	220	220	220	220	220

* W: Wet Granulation Method; D: Direct Compression Method; Val: Valsartan; P 407: Poloxamer 407; PVP: poly vinyl pyrrolidone.

Preparation of tablets by direct compression method

All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5-6 Kg/cm^2 using 9 mm flat punches. In each case 100 tablets were compressed.

Evaluation of tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution rate study

The dissolution rate of valsartan tablets prepared was studied in phosphate buffer of pH 6.8 using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37 ± 1^{o}C was maintained throughout the study. One tablet containing 40 mg of valsartan was used in each test. Samples of dissolution media (5 mL) were withdrawn through a filter (0.45 μ) at different intervals of time, suitably diluted and assayed at 225 nm for valsartan. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

Analysis of results

Dissolution data were subjected to analysis as per zero order and first order kinetics and the corresponding dissolution rates were calculated. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[10].

RESULTS AND DISCUSSION

The valsartan- CD- Poloxamer 407/PVP K30 complexes were prepared by kneading method. All the solid inclusion complexes of Drug- CD- Poloxamer 407/PVP K30 prepared were found to be fine and free flowing powders. Low coefficient of variation (c.v) values (< 1%) in the percent drug content indicated uniformity of drug content in each batch of solid inclusion complexes prepared.

The feasibility of formulating valsartan- CD - Poloxamer 407/PVP K30 solid inclusion complexes into tablets was evaluated by preparing valsartan tablets employing the solid inclusion complexes by wet granulation and direct compression methods. The formulae of valsartan tablets prepared are given in Table 1. All the prepared tablets were evaluated for drug content, hardness, friability and disintegration time and dissolution rate of valsartan. The physical properties of the tablets prepared are given in Tables 2-3 and the dissolution parameters of the tablets prepared are summarised in Table 4.

Table 2: Physical properties of Valsartan tablets prepared by wet granulation method

Formulation	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration time (min-sec)	Drug content (mg/tablet)
WT1	5	0.7	0-40	40.5
WT2	5	0.5	22-06	40.0
WT3	5	0.7	19-12	39.6
WT4	5	0.4	15-42	39.0
WT5	6	0.6	28-36	39.8
WT6	6	0.5	25-16	40.2
WT7	6	0.5	22-07	38.6

Table 3: Physical properties of Valsartan tablets prepared by direct compression method

Formulation	Hardness (Kg/cm^2)	Friability (% weight loss)	Disintegration time (min-sec)	Drug content (mg/tablet)
DT1	5	0.8	1-01	40.8
DT2	4.5	0.7	1-04	39.8
DT3	5	0.8	1-49	40.4
DT4	5	0.6	7-15	41.0
DT5	5.5	0.6	12-0	40.0
DT6	5.5	0.7	12-03	39.8
DT7	5.5	0.8	11-30	40.6

All the tablets prepared were found to contain valsartan within 100 ± 5% of the labelled claim. Hardness of the tablets was in the range 5.0- 5.5 Kg/cm^2. Percentage weight loss in the friability test was less than 0.45% in all the cases. In both wet granulation and direct compression method plain tablets formulated employing valsartan alone disintegrated within 1 min. All the tablets prepared by direct compression method employing CD (βCD/ HPβCD) – Poloxamer 407/ PVP K30 inclusion complexes also disintegrated rapidly and fulfilled the official (I.P.) disintegration time specification of uncoated tablets. Tablets formulated employing βCD complexes (DT2, DT3, DT4) disintegrated relatively more

rapidly than those formulated employing HPβCD complexes (DT5, DT6, DT7). Whereas tablets prepared by wet granulation method employing CD (βCD/ HPβCD) – Poloxamer 407/ PVP K30 inclusion complexes disintegrated slowly and the disintegration times of these tablets were in the range 15-28 min. As such these tablets did not fulfil the official (I.P.) disintegration time specification of uncoated tablets.

Table 4: Dissolution parameters of Valsartan tablets prepared by wet granulation and direct compression method

Formulation	Wet granulation method		Direct compression method	
	Dissolution rate (K_1 x 10^2) (min^1) (x ± s.d.)	**Dissolution efficiency (DE_{30}) (%) (x ± s.d.)**	**Dissolution rate (K_1 x 10^2) (min^1) (x ± s.d.)**	**Dissolution efficiency (DE_{30}) (%) (x ± s.d.)**
T1	1.52 ± 0.01	19.81 ± 0.07	3.26 ± 0.01	23.69 ± 0.07
T2	2.90 ± 0.06	17.19 ± 0.14	6.41 ± 0.06	27.92 ± 0.14
T3	5.80 ± 0.08	19.74 ± 0.05	9.44 ± 0.08	29.06 ± 0.05
T4	3.79 ± 0.11	20.31 ± 0.07	8.33 ± 0.11	25.32 ± 0.07
T5	1.17 ± 0.02	6.11 ± 0.01	4.71 ± 0.02	19.83 ± 0.01
T6	1.76 ± 0.02	7.21 ± 0.01	6.93 ± 0.02	24.48 ± 0.01
T7	1.69 ± 0.03	8.40 ± 0.02	3.49 ± 0.03	15.89 ± 0.02

The dissolution rate of valsartan from the tablets prepared was studied in 900 mL of phosphate buffer of pH 6.8. Dissolution of valsartan from all the tablets prepared followed first order kinetics with r (correlation coefficient) above 0.9406. The dissolution parameters (K_1 and DE_{30}) of various tablets are summarized in Table 4. Valsartan dissolution was rapid and higher from the tablets formulated employing drug- CD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing valsartan alone in both wet granulation and direct compression methods. In both the methods tablets formulated employing βCD complexes gave higher dissolution rates (K_1) and DE_{30} values when compared to those formulated employing HPβCD complexes. Tablets formulated employing valsartan-βCD-Poloxamer 407 (WT3) and valsartan-βCD-PVP K30 (WT4) gave higher dissolution rates, 3.81 fold and 2.50 fold respectively when compared to plain tablets (WT1) in the wet granulation method. Tablets formulated employing valsartan-βCD- Poloxamer 407 (DT3) and valsartan- βCD-PVP K30 (DT4) gave respectively 2.90 fold and 2.55 fold increase in the dissolution rate when compared to plain tablets (DT1) in direct compression method. Tablets formulated employing dug – βCD – Poloxamer 407 and drug – βCD – PVP

K30 complexes and prepared by direct compression method gave higher dissolution rates, 0.0944 and 0.0833 min^{-1} respectively when compared to plain tablets (0.0326 min^{-1}) as well as tablets containing drug – βCD complexes (0.0641 min^{-1}). Hence a combination of βCD with either Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate of valsartan tablets.

CONCLUSION

(i) Valsartan tablets made by direct compression method disintegrated rapidly when compared to those made by wet granulation method. Tablets formulated employing βCD complexes disintegrated relatively more rapidly than those formulated employing HPβCD complexes.

(ii) Valsartan dissolution was rapid and higher from the tablets formulated employing drug- CD- Poloxamer 407/ PVP K30 inclusion complexes when compared to the tablets containing valsartan alone and drug – CD complexes in both wet granulation and direct compression methods.

(iii) In both the methods tablets formulated employing βCD complexes gave higher dissolution rates (K_1) and DE_{30} values when compared to those formulated employing HPβCD complexes.

(iv) Tablets formulated employing dug – βCD – Poloxamer 407 and drug – βCD – PVP K30 complexes and prepared by direct compression method gave higher dissolution rates, 0.0944 and 0.0833 min^{-1} respectively, when compared to plain tablets (0.0326 min^{-1}) as well as tablets containing drug –βCD complexes (0.0641 min^{-1}).

(v) A combination of βCD with Poloxamer 407 or PVP K30 is recommended to enhance the dissolution rate of valsartan tablets.

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