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FORMULATION AND EVALUATION OF VALSARTAN SR TABLETS USING HYDROPHILIC AND HYDROPHOBIC POLYMER

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ABSTRACT

The aim of the study was to formulate SR tablets of Valsartan Sodium using different hydrophilic and hydrophobic polymers on in vitro release rate from Valsartan Sodium sustained release tablets . Different types of polymers like HPMC, carbopol and Ethyl cellulose were used as Sustained release polymers. Formulation 12 showed sustained drug release for 12 hours so it was selected as the best formulation among all the formulations. The Final trial was packed in PVC/PVDC blister packing and kept at 40°C/75%RH±5% for 3 months and 25°C±2°C/60%RH±5% up to 24 months. Formulation found to be robust and stable.

Kew words: Valsartan, Sustained Release, HPMC, Carbopol

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. The conventional dosage forms such as tablets and capsules are the major oral preparations among all dosage forms to have a wide acceptance of 50-60%. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. Oral drug delivery has been the most widely utilized route of administration among the all route because of certain advantages such as unit dosage form, low cost, cheapest for packaging etc. In the last two decades the drug delivery technology has developed rapidly and many novel oral drug delivery.

Apart from these advantages this route suffers from certain drawbacks like patient noncompliance, multiple dosing and therapeutic failures. In order to overcome these drawbacks of conventional drug delivery there is a need for development of new drug delivery system or modified drug delivery system. Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system.

Valsartan is an angiogenesis II receptor antagonist that is used for the treatment of hypertension. Valsartan acts by blocking the binding of angiotensin II and angiotensin I receptor in many tissues thereby blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively. The most preferred route for this drug is oral delivery in the form of tablets. Valsartan have poor water solubility, low bioavailability (approximately 20-25%), and shorter half-life (nearly 6 hours). Since Valsartan has low bioavailability and shorter half-life, developing a sustained release system can maintain the plasma drug concentration in therapeutic window and increase the therapeutic efficacy of drug. Hence the present work has been proposed. The aim of this proposed work is to formulate, characterize and evaluate sustained release tablets of Valsartan.

MATERIALS AND METHODS

Materials: Valsartan was obtained as a gift sample form Wochard Pharmaceuticals, Aurangabad. All other chemical and solvents used are of analytical grade.

Compatibility Studies: The compatibility studies for the selected polymers such as HPMC, Ethyl cellulose and carbopol 940 along with the drug had been studied using the Kbr pellet method using the bruker instruments.

Pre-formulation Studies: These studies almost all drugs are marketed as tablets, capsules or both. Prior to the development of these major dosage forms, it is essential that certain fundamental physical and chemical properties of the drug molecule and other divided properties of the drug powder are determined. This information decides many of the

subsequent events and approaches in formulation development. This first learning phase is known as pre-formulation. The following parameters such as Bulk density, Tapped density, Hausner's ratio, Compressibility index, Flow properties, Particle size determination, Moisture content, Determination of solubility has been carried out for the granules of valsartan SR.

Preparation of tablets by wet granulation: Weighed all raw materials, and sifted all the ingredients separately through a specified stainless steel sieve. Valsartan, lactose, Microcrystalline Cellulose, and HPMC K4M CR are sifted through 40#. Transferred all the dry mixing stage materials to Rapid Mix Granulator, and mixed for 5 minutes at speed of 120rpm with impeller and chopper off.

Granulation parameter: The binder solution was prepared by adding povidone k30 into isopropyl alcohol under stirring to get clear solution. Binder solution was added into dry mix in the Rapid Mixing Granulator for 210 seconds at impeller speed of 120rpm and followed by kneading for 1minute at impeller speed of 180rpm and chopper off to form a proper consistency granule. The above wet granules were screened through 20#. The sifted mass was transferred to Fluidized Bed dryer and dried in Fluidized bed dryer at 60°C for 30 min. Loss on drying was found to be 2.54 % at 105°C for 5min. The dried granules were passed through 20#. The above sized granules and pre-sifted and aerosil 200(40 mesh) were loaded into blender and blended for 10 minutes. Magnesium Stearate was sifted through 60# and added in to blender and lubricated for 3 minutes. The lubricated granules were unloaded in a cleaned polybag labelled properly. The above lubricated blend was used for compression. Compression was done on 16 station cadmach tablet compression machine (wockhardt, Aurangabad) using 9.50 mm 9.50 mm, Round, plain, standard concave punches.

Tab 1: Parameters to be maintained during the formulation of the Valsartan SR tablet

Parameters	Impeller(rpm)	Chopper (rpm)	Time (sec)
Dry mixing	120	Off	300
Binder addition	120	Off	210
Kneading	180	Off	60

Preparation of tablets by Slugging method: Weighed all raw materials, and sifted all the ingredients separately through a specified stainless steel sieve. Following are the ingredients, Valsartan, MCC and polymer are sifted through 40 mesh. Transferred all the dry mixing stage materials to blender, and mixed for 15 minutes. Magnesium Stearate was sifted through 60# mesh and added in to blender and lubricated for 3 minutes. The lubricated granules were unloaded in a clean polybag and labeled properly. The above lubricated blend was used for Slugging. Slugs are made by using 19mm Punches. The above prepared slugs were milled by using multi mill with 4.00 mm screen, obtained product passed through 20 mesh. Above obtained granules are mixed in a blender for 5 mins. To the mixed blend add 60# mesh passed Magnesium Stearate and Colloidal Silicone Dioxide then lubricate it for 3 mins. The above lubricated blend is compressed using 9.50mm standard concave punches.

Table.2.Slugging Parameters

Parameter	Observation
Weight Of the Slug	1260 mg
Thickness	4.3-4.4 mm
Hardness	80N-90N

Table.3.Composition of 350 mg Valsartan matrix tablet (Weight in mg)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Valsartan	81.13	81.13	81.13	81.13	81.13	81.13	81.13	81.13	81.13	81.13	81.13	81.13
HPMC K4M	60	80	100	120	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	60	80	100	120		-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	60	80	100	120
Mcc	94	84	74	64	94	84	74	64	94	84	74	64
Lactose	94	84	74	64	94	84	74	64	94	84	74	64
Iso propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Pvp k30	14	14	14	14	14	14	14	14	14	14	14	14
AerosIl SD 200	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Mg.stearate	2.10	2.10	2.10	2.10	2.10	2.10	2.10	2.10	2.10	2.10	2.10	2.10
Core tablet weight	350	350	350	350	350	350	350	350	350	350	350	350

Table.4.Composition of 350 m Valsartan g matrix tablet (Weight in mg)

Ingredients (mg)	F13	F14	F15	F16	F17	F18	F19	F20
Valsartan	81.13	81.13	81.13	81.13	81.13	81.13	81.13	81.13
Carbopol 971P	60	80	100	120	-	-	-	-
Ethyl cellulose	-	-	-	-	60	80	100	120
Mcc	101.057	91.057	81.06	71.06	101.057	91.057	81.06	71.06
Lactose	101.057	91.057	81.06	71.06	101.057	91.057	81.06	71.06
Mg. stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Blending and Lubrication								
AerosIl SD 200	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Mg. stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Core tablet weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

API calculation (Moisture and Assay compensation): Drug: The quantity of API to be dispensed is done based on assay and moisture content by using following formula:

$$Potency = \frac{Dose \times 100 \times 100}{Assay\ on\ as\ is\ basis \times (100 - Loss\ on\ drying)}$$

In-vitro Dissolution test: This test provides evaluation of physiological availability of drug candidate. For FDA approval and bioequivalent product, it is important to compare the dissolution profile of product with the dissolution profile of reference-listed drug. Therefore similarity factor (f_2) is recommended by various regulatory committees that demonstrated the similarity in the percent (%) dissolution of test product with reference product. Dissolution profiles are considered similar if the calculated f_2 value is between 50 and 100. The similarity factor (f) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) difference of drug percent dissolved between the test and reference products.

Table.5.In vitro Dissolution Parameters of valsartan SR tablet

Drug Name	USP Apparatus	Speed (RPMs)	Medium	Volume(mL)	Recommended Sampling Times (hrs)
valsartan	II (paddle)	50	6.8phosphate buffer	1000ml	1,2,4,6,8,10 and 12hrs

Assay: This method is used to analyse or quantify a substance in a sample. Assay is an analytical process to determine not only the presence of substance and the amount of substance but also the biological and pharmacological potency of a drug

Stability study: In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

Objective of the study: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf- lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products. ICH specifies the length of study and storage conditions

ICH guidelines for stability study: It is up to the applicant to decide whether long-term stability study are performed at 25°C±2°C/60%RH±5%RH or 30°C±2°C/65%RH±5%RH. If 30°C±2°C/65%RH±5%RH is a long term condition there is no intermediate condition if significant changes occur at these stress conditions, then the formulation should be tested at an intermediate condition that is 30°C/75% RH. In the present work stability study was carried out for the optimized formulation for following condition and time period, at 40°C/75%RH for 6 month and 25°C±2°C/60%RH±5% up to 24 month.

Table.6.Time period of storage condition

Study	Storage Condition	Time Period
Long term	25°C±2°C/60%RH±5 RH	24 month
Accelerated	40°C±2°C/75%RH±5%RH	6 month

RESULTS AND DISCUSSION

FT-IR analysis by KBR pellets method: FT-IR is a great analytical technique can give the information regarding functional group absorptions of a molecule. The FT-IR analysis of Valsartan API and polymers performed by Bruker instrument and the results were discussed below. IR spectrum of Valsartan API shows characteristic functional group absorptions at different wavelengths. Analysis of Valsartan API -Ethyl cellulose and Valsartan API –Carbopol gives different IR spectrum as that of Valsartan API and some of the characteristic absorption frequencies of API were missing. So it may be concluded that the mixtures of Valsartan + Ethyl cellulose and Valsartan + carbpol are incompatible with the API. But, in case of the mixture of Valsartan API –HPMC shows similar IR spectrum as that of API, so HPMC can be used in Formulation of Valsartan formulation preparation.

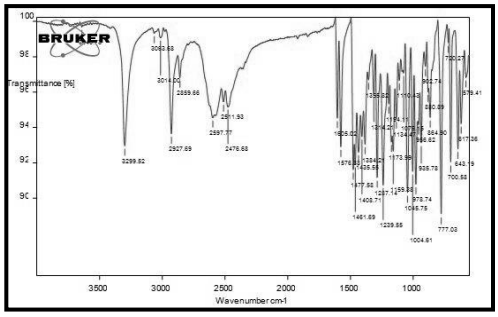

Figure.1.FTIR graph of Valsartan

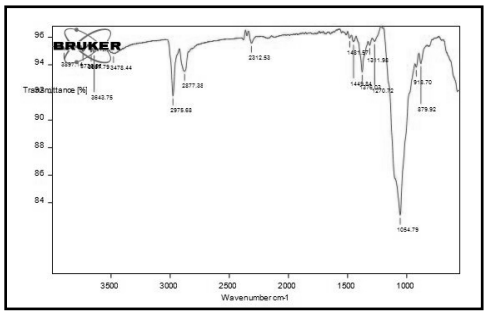

Figure.2.FTIR graph of Valsartan + Ethyl cellulose

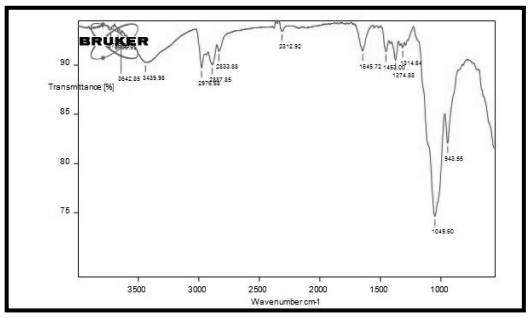

Figure.3.FTIR graph of Valsartan + carbapol

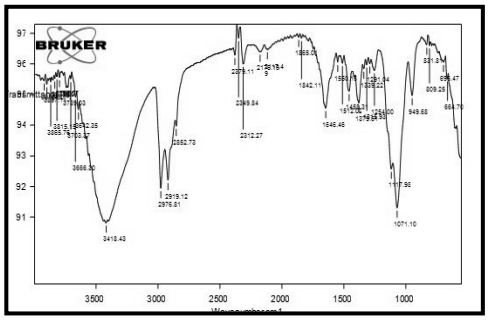

Figure.4.FTIR graph of Valsartan + HPMC

Table.7.Pre-compression parameters of Valsartan sustained release tablets F1-F20

F. Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's Index (%)
F1	0.461	0.654	1.41	29.23
F2	0.4375	0.5833	1.33	25.00
F3	0.4375	0.5526	1.26	20.833
F4	0.4199	0.5526	1.31	24.00
F5	0.3889	0.5250	1.35	25.95
F6	0.3620	0.5250	1.45	31.00
F7	0.3889	0.500	1.28	22.00
F8	0.4375	0.5833	1.33	25.00
F9	0.4375	0.500	1.28	22.22
F10	0.3750	0.477	1.27	21.42
F11	0.461	0.654	1.41	29.23
F12	0.3889	0.4772	1.22	18.51
F13	0.4375	0.5833	1.33	25.00
F14	0.4199	0.5526	1.31	24.00
F15	0.4375	0.5526	1.26	20.833
F16	0.3620	0.5250	1.45	31.00
F17	0.3889	0.500	1.28	22.00
F18	0.3889	0.4772	1.22	18.51
F19	0.4375	0.500	1.28	22.22
F20	0.3750	0.477	1.27	21.42

Swelling Index studies: The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 20 ml of phosphate buffer of pH 7.4. At the end of

specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The % weight gain by the tablet was calculated by formula:

$$\%\text{Swelling index} = \frac{M_t - M_0}{M_t} \times 100$$

Table 8: Compression parameters of valsartan sustained release tablets F1-F20

F. Code	Thickness (mm)	Hardness (N)	Friability (%)	Assay (%)
F1	5.25±0.10	126±10	0.05	98
F2	5.30±0.10	120±20	0.25	97
F3	5.35±0.10	115±10	0.38	98
F4	5.35±0.05	100±10	0.48	97
F5	5.25±0.05	110±10	0.08	99
F6	5.30±0.05	120±10	0.38	102
F7	5.35±0.05	115±10	0.10	101
F8	5.30±0.05	130±20	0.08	100
F9	5.30±0.05	120±10	0.05	98
F10	5.25±0.05	115±10	0.06	98
F11	5.25±0.10	115±15	0.05	98
F12	5.30±0.10	120±20	0.02	100
F13	5.35±0.10	126±10	0.38	98
F14	5.35±0.05	120±10	0.48	97
F15	5.25±0.05	115±10	0.08	99
F16	5.30±0.05	100±10	0.38	102
F17	5.35±0.05	110±10	0.10	101
F18	5.30±0.05	120±10	0.08	100
F19	5.30±0.05	115±15	0.05	98
F20	5.25±0.05	130±10	0.06	98

Table.9.Swelling Index studies of Valsartan SR tablets F1-F8

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	17.03%	15.28%	27.3%	22.8%	18.5%	22.6%	19.5%	15.4%
2	24.16%	35.6%	30.8%	41.2%	26%	39.8%	28.5%	22.15%
3	49.10%	52.4%	26.9%	49.5%	42.5%	52.9%	38.8%	38.12%
4	55.38%	60.2%	32.3%	63.7%	53.9%	60.5%	59.2%	47.4%
5	78.285%	66.7%	57.8%	72.6%	73.5%	64.9%	77.5%	64.7%
6	96.71%	76.1%	81.4%	85.4%	95.5%	82.9%	78.2%	68.3%

Table.10.Swelling Index studies of Valsartan SR tablets F9-F16

Time (hr)	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0
1	33.3%	17.5%	32.5%	26.7%	15.2%	11.01%	13.8%	19.21%
2	56.5%	28.9%	25.7%	39.8%	29.8%	19.8%	27.23%	23.20%
3	65.8%	41.3%	67.9%	48.2%	42.3%	21.88%	42.30%	38.09%
4	62.3%	60.5%	68.2%	57.1%	56.8%	52.61%	68.53%	56.21%
5	70.3%	61.5%	66.9%	61.4%	78.29%	80.10%	72.16%	68.13%
6	96.23%	82.5%	73.15%	72.5%	96.18%	91.29%	83.15%	80.06%

Table.11.Swelling Index studies of Valsartan SR tablets F17-F20

Time(hr)	F17	F18	F19	F20
0	0	0	0	0
1	9.26%	11.13%	19.06%	10.96%
2	15.12%	17.26%	21.26%	29.21%
3	26.28%	33.28%	30.09%	40.19%
4	43.96%	52.8%	48.21%	53.16%
5	56.61%	66.21%	58.26%	49.23%
6	73.28%	71.09%	68.89%	60.02%

Table.12.In-vitro dissolution studies of valsartan SR tablet F1-F10

Time	Valsartan SR tablet Formulation F1- F10									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	38.07	37.34	35.82	33.06	33.06	31.34	30.28	26.68	29.64	24.07
2	62.07	60.87	57.02	52.43	46.43	43.65	41.67	37.73	37.33	33.01
4	80.43	80.26	81.3	77.87	67.87	64.26	60.93	59.47	51.74	46.87
6	97.05	95.87	93.08	90.21	89.76	87.36	83.44	81.76	67.83	65.23
8	100.5	101.7	100.9	103.2	97.21	94.57	90.78	97.21	89.21	84.85
10	-	-	-	-	102.2	102.4	103.6	100.8	100.72	99.7
12	-	-	-	-	-	-	-	-	101.64	100.65

Table.13.In-vitro dissolution studies of valsartan SR tablet F11-F20

Time	Valsartan SR tablet Formulation F11-F20									
0	0	0	0	0	0	0	0	0	0	0
1	18.05	15.82	27.81	25.76	20.12	7.82	10.1	8.03	7.12	6.82
2	32.3	24.93	42.54	40.65	39.34	24.73	16.04	14.65	15.36	14.73
4	43.07	38.01	61.68	57.02	51.07	32.01	21.48	21.09	25.78	23.17
6	62.49	58.66	73.76	70.23	64.78	49.66	41.08	35.93	34.78	34.66
8	73.85	72.83	88.32	87.85	79.85	70.73	62.84	60.85	60.33	59.89
10	90.52	88.32	100.65	98.78	86.52	76.42	84.81	84.98	76.59	76.42
12	101.22	100.08	102.3	100.32	99.98	91.08	96.06	95.63	91.92	91.87

Tab 14: Stability studies at 40^{o}C and 75% RH

Test	Standard	Initial	1 Month	2 Months	3 Months
Appearance and colour	White powder	Complies	Complies	Complies	Complies
Loss on drying	NMT 0.5%	0.29%	0.22%	0.19%	0.17%
Assay (on dried basis)	99 to 101%	100.11%	100.32%	100.45%	99.57%

SUMMARY

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraint and flexibility in the design of the dosage form. Cellulose derivatives are widely used in the design of sustained release drug formulations. Valsartan, widely used in the treatment of anti-hypertensive to reduce in vascular resistance and blood pressure and biological half-life is approximately 6 hrs and dosage frequency more than one per day makes Valsartan an ideal candidate for sustained release. Drug, polymers and reagents were procured from different sources. Methodology on formulation and evaluation of matrix tablets was adopted from reported methods. Formulation variables include nature and concentration of polymers with different physico-chemical properties. Matrix tablets are characterized for physico-chemical properties, *in-vitro* release and stability experiments were conducted in triplicate. The discussion on results obtained during the present study is given in chapter 6. Pre-formulation studies on Valsartan were in agreement with reported literature. The method adopted in the preparation yielded tablets with uniform weight, thickness, hardness; friability and drug content was found with prescribed limits. Modulation of drug release was effected by nature and concentration of polymers used. Among all the formulations tablet F-12, F-15 containing (1:1.5), (1:1) ratio of polymer blend of HPMC and carbapol showed better controlled drug release over a period of 12 hrs. All the prepared matrix tablets follow Non-fickian controlled drug release. Matrix tablets were found to be stable with respective drug content, friability, hardness and weight variation during the stability study period.

CONCLUSION

The compatibility of the drug and the polymer such as HPMC, EC and carbopol was found to be compatible with each other. The pre formulation studies showed that all parameter were within the limit. The present study conclusively proved that matrix tablets can be efficiently prepared by using HPMC, carbapol, and ethyl cellulose for sustained release of valsartan. The prepared tablets gave promising results in controlling the release of a sparingly water soluble drug

Valsartan. Vancouver style was followed to write the reference quoted in the study and is listed in the chapter of bibliography.

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