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Optimization and Evaluation of Modified Dosage form of Antihypertensive Drug

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Abstract
The goal of the current study is to produce a modified dose form of the hypertension drug Valsartan. Without any issues, sustained release tablets were compressed, and the formulation's excipient ratio was left unchanged. We seek to develop drug delivery systems with a typical sustained release pattern in order to achieve therapeutic concentrations of the medications at the point of their maximum necessity in the body. Wet granulation technology was used in this research project to create sustained release matrix tablets employing a variety of polymers and excipients. The bulk density, compressibility index, total porosity, angle of repose, and drug content of the granules of various formulations were all assessed. All formulations' weighed amounts of granules contained a consistent amount of medication. The formulations for Valsartan sustained release fit Higuchi's model of drug release well, and batch F6 of the formulations which is based on weight variation, drug content, hardness, friability, in-vitro drug released profiles, and stability studies was the best of all the batches. Although F6 had a decent release rate during the research, the release occurred earlier than planned. It was discovered that formulation F6's in-vitro drug release was 94.74 2.11 for up to 24 hours. This leads us to the conclusion that, as compared to the current systems for the treatment of disease, modified dose forms of antihypertensive agents will offer considerable advantages.

Keywords: Antihypertensive agent, Valsartan, Sustain release tablet

Introduction

Antihypertensive are a class of medications used to treat high blood pressure (high blood pressure). The goal of antihypertensive medication is to avert high blood pressure-related consequences like myocardial infarction and stroke. According to the evidence, lowering blood pressure by 5 mmHg can lower the risk of stroke by 34%, ischemic heart disease by 21%, dementia, heart failure, and cardiovascular disease mortality. Antihypertensive come in a variety of classes and work to reduce blood pressure in various ways. Thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers are some of the most significant and popular medicines. [1]

Antihypertensive medications fall under a number of chemical classes and are used to treat, regulate, or prevent hypertension. Antihypertensive medication types differ from one another both structurally and therapeutically. They are crucial in the practice of anaesthesia because they are frequently prescribed to the general public. In the UK, the overall prevalence of hypertension is 31%; NICE defines it as a measurement of 140/90 mm Hg or higher in a clinic,

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followed by a subsequent ambulatory or home measurement of 135/85 mm Hg or higher. Antihypertensive medications are frequently prescribed for unrelated illnesses, such as anxiety and thyrotoxicosis, or heart failure. Examples of such medications are -blockers and ACEIs. As a result, the medicine and its indication both have an impact on how anaesthesia is administered. [2]

Angiotensin Converting Enzyme Inhibitors, Beta Blockers, Angiotensin Receptor Blockers, Calcium Channel Blockers, Diuretics, Alpha Adrenergic Blockers, and Central Sympatholytics are just a few examples of the numerous antihypertensive medications that are available. To lower practise variability, expense, and promote rational pharmacotherapy, treatment guidelines for drug selection are available from a variety of expert groups. It has been demonstrated that following these recommendations can improve the standard of antihypertensive therapy. [3]

Classification of Anti Hypertensive Drugs

Angiotensin Converting Enzyme (ACE) Inhibitors

Mechanism of Action

These medications competetively suppress the activity of ACE (also known as kininase II) to stop the production of the inactive decapeptide angiotensin I into the active octapeptide angiotensin II (Doolittle RF, 1983). The blood and tissues affected by this include the kidney, heart, blood arteries, adrenal gland, and brain. A powerful vasoconstrictor, angiotensin II also facilitates sympathetic activity, stimulates the release of aldosterone, and has other possible negative effects on the cardiovascular system. When the renin-angiotensin system is stimulated (such as after diuretic therapy or in renal artery stenosis), the reduction in blood pressure secondary to vasodilatation following ACE inhibition is greatest, but ACE inhibitors also lower blood pressure when there is normal or low activity of the renin-angiotensin system. However, Afro-Caribbeans and older people, who frequently have low renin hypertension, respond less well to ACE inhibitor monotherapy. Bradykinin, a kinin that enhances vasodilator action and may help explain why ACE inhibitors are generally successful, accumulates as a result of ACE (kininase II) inhibition.[4]

Diuretics

Mechanism of Action

Diuretics reduce blood pressure by encouraging the body to urinate out extra water and sodium. Diuretics may be used with other blood pressure drugs if they don't work as well on their own. Diuretic medications may raise blood sugar levels in diabetics. In most circumstances, this can be fixed by altering the dosage of a medication, diet, insulin, or oral diabetes medication. Most of the time, the rate of blood sugar increase doesn't alter much, but some of these medications may cause your body to store less potassium. Consuming foods high in potassium may assist to significantly reduce potassium loss. If your doctor advises it, you can avoid potassium loss by taking a potassium-containing beverage or tablet along with the diuretic. [5]

Beta Blockers

Mechanism of Action

Cardiovascular and noncardiac diseases are treated with beta blockers. Beta blockers inhibit the production of epinephrine, or adrenalin, by blocking the B1 and B2 adrenergic receptors. When concentrations are high, epinephrine can constrict blood vessels. The heart doesn't have to work as hard because of beta blockers' ability to make the heart beat more slowly and with less force. [6]

Calcium Channel Blockers

Mechanism of Action

Reduce the amount of calcium available for muscular contraction by blocking the flow of calcium via the voltage-gated L-type (for Large/Long-lasting current) calcium channel on vascular smooth muscle cells and cardiac myocytes. Be aware that MIBEFRADIL, an inhibitor of the cardiac calcium T-type (Transient current) channel, has just been discontinued due to undesirable medication interactions.[7,8]

Angiotensin-2 Receptor Antagonist

Mechanism of Action

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Angiotensin II is a highly potent chemical end product that dramatically narrows blood arteries by causing the muscles around them to contract. High blood pressure results from this constriction increasing the pressure inside artery arteries (hypertension). Drugs called angiotensin receptor blockers (ARBs) stop the effects of angiotensin II. As a result, blood pressure drops and arterial vessels widen, making it simpler for the heart to pump blood. ARBs can therefore be used to treat hypertension and heart failure. Additionally, they halt the course of renal damage brought on by diabetes or high blood pressure.

A brand-new family of hypertension medications is called angiotensin receptor antagonists. They work by inhibiting the angiotensin (AT1 type) receptor, which regulates the physiological effects of angiotensin on blood pressure, salt and water balance, as well as cardiovascular structure and function. The effects of the renin-angiotensin system on the cardiovascular and cardiorenal systems are specifically blocked by this class of drugs.[9]

Signs and Symptoms

The patient with primary hypertension may generally show no symptoms or may have serious risk factors for cardiovascular disease. The American Heart Association may mention cardiovascular risk factors linked to age, gender, heredity, smoking, high lipid profiles, obesity and overweight, and diabetes mellitus. Adult patients having two or more prior readings of high blood pressure on average.[10]

Valsartan

Valsartan is offered as an immediate release tablet formulation comprising 40 mg, 80 mg, 160 mg, or 320 mg. It is a nonpeptide, orally active, and selective angiotensin II antagonist operating on the AT1 receptor subtype. It may be used alone or in combination with other antihypertensive drug types.

Valsartan is used as an instant release in India. A once daily sustained-release version of valsartan is used to lessen administration frequency and boost patient compliance. Valsartan is not available on the market in continuous release form, and research into this topic is still continuing.

ARBs have been shown to reduce cardiac hypertrophy, renal function, cardiovascular and cerebrovascular morbidity and mortality in hypertensive patients with or without diabetes mellitus. Numerous large, long-term studies are currently being conducted

to evaluate the effectiveness of these medications in treating heart failure, acute myocardial infarction, and diabetic nephropathy.

Materials and Method

Chemicals such as Valsartan USP, Potassium dihydrogen orthophosphate, Disodium hydrogen phosphate, Methanol, Ethanol, Hydrochloric acid, Micro Crystalline Cellulose (MCC), Magnesium Stearate, Aerosil, and Glacial acetic acid are offered by Dr. SSK Labs Pvt Ltd, Pune.

Formulation Development

Preparation of SR Formulation Using Wet Granulation Method

Table No. 1.Valsartan Sustained Release Formulation

Ingredients	Required quantity (mg/tablets)					
	F1	F2	F3	F4	F5	F6
Valsartan	160	160	160	160	160	160
Dicalcium phosphate	36.75	36.75	36.75	36.75	36.75	36.75
Microcrystalline cellulose	35	25	15	-	-	-
Hydroxypropyl methylcellulose	-	-	-	35	25	15
Aerosil	1.25	1.25	1.25	1.25	1.25	1.25

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Magnesium stearate	17	27	37	17	27	37
Total wt in mg	250	250	250	250	250	250

Determination of Mechanism of In Vitro Drug Release

The in vitro dissolution data was fitted to the Higuchi release model, the Korsmeyer and Peppas model, the Zero order, the First order, the Zero order, and the Higuchi Release model. Table contains the equations for the mentioned models.

S.I. = {(Wt-W0) / W0} ×100

Where-

W0 = initial weight,

Wt=final weight

Table No.2 .Models for Analysis of In Vitro Dissolution Data

Sr. No	Model	Equation
1.	Zero order	F=kxt (where F is the fraction of drug release ,k is the release constant and t is the time)
2	First order	In F=kxt, (where F is the fraction of drug release ,k is the release constant and t is the time)
3	Higuchi	F =k √t
4	Korsmeyer and Peppas model*	F=ktn If , n< 0.5 fickian diffusion n> 0.5 non fickian diffusion

Accelerated Stability Studies

Accelerated Stability Study (WHO Guidelines)

Studies on stability were conducted to ascertain the impact of the polymer and additives on the drug's stability as well as the formulation's physical stability under accelerated storage settings for temperature and humidity. To determine stability and shelf life, a three-month accelerated stability research was conducted at 40 °C, 50 °C, and 60 °C with 65 5% RH. A sufficient number of duplicates of the improved tablet were packaged in 1g sealed 30 ml HDPE bottles (desiccant).

Accelerated Stability Testing According to ICH Q1A (R2) Guidelines

These were put in a stability chamber with a 40 0.5 °C and 75 5% RH control. At 30, 60, and 90 days, samples were removed. The samples' drug content and release characteristics were assessed.

Result and Discussion

The following section covers in detail the results obtained from the formulation and evaluation of Valsartan sustained release tablets.

Physiochemical Characterization Study

Physical Description

Valsartan was observed to be an off-white fine powder with no discernible flavor or odour.

pH Determination of Valsartan

The pH of the drug solution at 5% w/v in DM water was discovered to be 5.5, which was within the acceptable range when compared to the norm.

Solubility

Chloroform	:	sparingly soluble
Methanol	:	very soluble
Ethanol	:	very soluble
Water	:	practically insoluble

Solubility of the drug in different media was observed and tabulated in Table 3.

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Table No.3.Valsartan Solubility in Different pH Media at 37°C (n=3)

Sr. No.	Media	Mean Solubility (mg/ml) ± SD
1	0.1N HCl (pH 1.2)	0.084 ± 0.155
2	Acetate buffer (pH 4.5)	14.6 ± 0.029
3	Phosphate Buffer (pH 6.8)	16.8 ± 0.063
4	DM water (pH 7.2)	0.18 ± 0.091

In a buffered solution, the solubility is increased because the di anion salt is formed. As Valsartan has pH dependent solubility it belongs to a special case in a proposed general classification system those categories drugs with respect to their biopharmaceutical and absorption properties. In the biopharmaceutical classification system Valsartan is an acid, and therefore, has good solubility at pH>5 and low solubility in acidic conditions. Valsartan is absorbed from the small intestine where its solubility is low.

Melting Point

Valsartan samples were discovered to have melting points of 113ºC. Valsartan reported melting point was between 116 and 117ºC. As a result, there was good agreement between experimental and official results, indicating the study's medication powder was pure.

Flow and Consolidation Properties

The methodology involved measuring the variables for evaluating the flow and consolidation properties of Valsartan, including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The gathered information is summarized in (Table 4). The substance had passable to bad flow qualities, according to the flow and consolidation data, which indicated the addition of 0.5–1.0% glidant. However, a poorly flowing drug may not be causing serious formulation-related problems because the drug's dose ranges from 80 to 160 mg and the recommended level of excipients in the formulation is significantly higher than the drug itself.

UV Spectral Analysis

The λ_{max} of the drug solution in 0.1N HCl was found out to be 249.7 nm which was very close to the reported λ_{max} value of 250 nm for Valsartan. Additionally, the λ_{max} value was found to be at 249 nm confirms the drug when the solution was made with phosphate buffer.

Table 4.Flow and Consolidation Properties for Valsartan

Parameter	Mean (± SD)
Angle of repose (º)	16.46 ± 0.8
Bulk density (g/cc)	0.41 ± 0.063
Tapped density (g/cc)	0.5578 ± 0.081
Compressibility index	42.36
Hausner’s ratio	1.73

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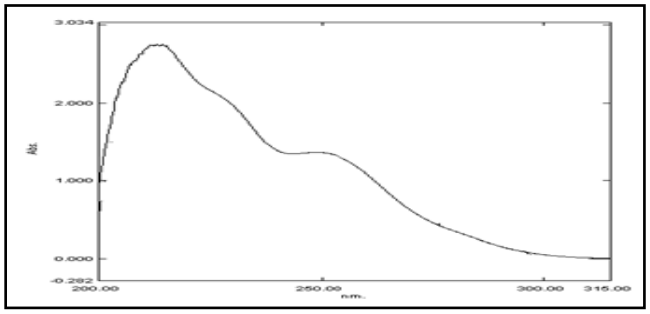

Figure No.1. UV Spectrum of Valsartan in 0.1N HCl

Method of Analysis (UV spectrophotometry)

Valsartan was analyzed in various physiological pH media ranging from pH 1.2-6.8 and the spectra were recorded and are shown in Fig 7.2– 7.3. The spectra in each media gave a fairly constant λ_{max} value in between 248- 249.7 against the reported value of 249nm.

Development and Validation of UV Spectrophotometric Method in 0.1N HCl pH 1.2

Calibration curves of the drug were prepared in each of the above mentioned physiological pH media (n=3). At 249 nm, the absorbance of the prepared standard solutions (1–10 g/ml) was calculated. A mean absorbance of 0.031 to 0.176 was discovered. The concentration versus absorbance graph Beer-rule Lambert's was followed by Fig. 7.2 at the higher concentration range, with a regression coefficient of 0.997. The calibration curve data for Valsartan in 0.1N HCl pH 1.2 are shown in Table 5.

Table No.5.Absorbance Data of Standard Solutions of Valsartan in 0.1N HCl pH 1.2

S. No.	Concentration (µg/ml)	Absorbance
1	1	0.031
2	2	0.060
3	3	0.089
4	4	0.119
5	5	0.148
6	6	0.176

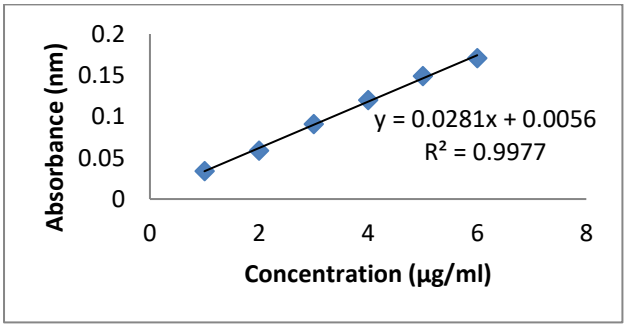

Figure No.2.Standard Curve of Valsartan in 0.1N HCl pH 1.2

Development and Validation of UV Spectrophotometric Method in 0.067 M phosphate buffer pH 6.8[15]

At 249 nm, the absorbance of the made-up standard solutions (1–10 g/ ml) was calculated. The average absorbance ranged from 0.037 to 0.202. The concentration versus absorbance graph Beer-rule Lambert's was followed by Fig.3 at the higher

concentration range, with a regression coefficient of 0.994. The calibration curve data for Valsartan in 0.067 M phosphate buffer pH 6.8 are shown in Table 6.

Fourier Transform Infrared spectroscopy

Valsartan FTIR spectroscopy was compared to a reference spectrum, and peaks were identified in accordance with the functional groups it contains.

Table No.6.Absorbance Data of Standard Solutions of Valsartan in 0.067 M Phosphate Buffer pH 6.8

S. No.	Concentration (µg/ml)	Absorbance
1	1	0.037
2	2	0.070
3	3	0.103
4	4	0.146
5	5	0.1695
6	6	0.202

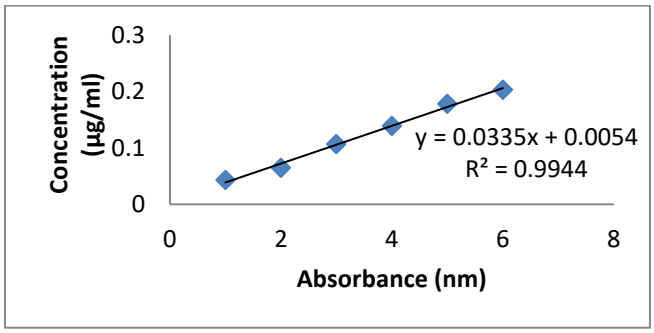

Figure No.3.Standard Curve of Valsartan in 0.067 M Phosphate Buffer pH 6.8

Table No.7.FTIR Peak of Pure Sample of Valsartan

Sample	Major peaks(wave numbers, cm-1)	Chemical moiety
VAL	2966.52	C-H str., -CH3
	1734.01	C=O str.,Carboxyl
	1604.77	C=O str., amide

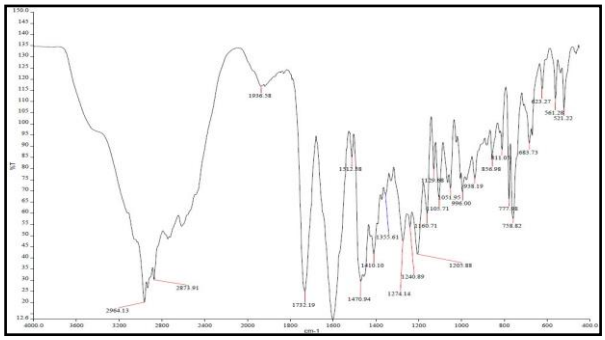

Figure No.4.FTIR Spectrum of the Valsartan Excipient Compatibility with Drug

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Table No.8.FTIR Peak of Drug Excipient Compatibility Study

Sample	Major peaks(wave numbers, cm-1)	Chemical moiety
VAL	2952.13	C-H str., -CH3
	1620.55	C=Ostr.,Carboxyl
	1400.01	C=O str., amide

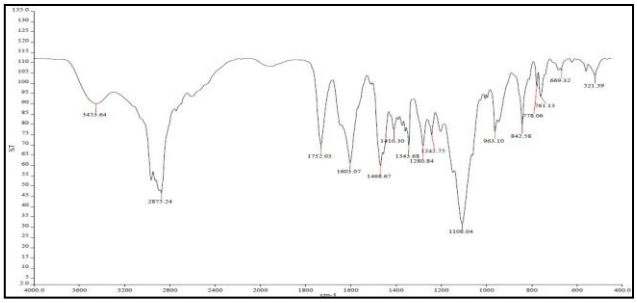

Figure No.5 FTIR of Drug Excipient Compatibility Study

Partition Coefficient:-

Knowledge of the partition co-efficient of a drug is useful as it provides an indication of how a particular drug may be distributed through the body; provide insight into the potential for absorption in addition to drug action at non-specific sites in the human body.

The partition co-efficient of a drug is a measure of the lipophilicity of that compound and is expressed as the ratio of solute distribution between a lipophilic and hydrophilic phase. The partition coefficient of the drug sample at 37^{o} C was found to be 3.86. Reported value is 4.5.

Table No.9.Partition Coefficient of Valsartan in Octanol/IPB (pH 6.8).

Amount of drug in Octanol (mg) (n = 3)	Amount of drug in buffer phase (C_a)(mg) (n = 3)	Partition coefficient (C_t-C_a)/C_a	(±SD)
19.8945	0.00226	3.86	± 0.05

Formulation Development

Preparation of SR Formulation Using Wet Granulation Method

The total dose of Valsartan per day sustained-release formulation was calculated by the following equation using available pharmacokinetic data.

D_t = Dose (1 + 0.693 × t/$t_{1/2}$) + overage

Where, D_t = total dose of drug;

Dose = conventional dose (40mg);

t = time (hrs) during which the sustained release is desired (24 hrs);

$t_{1/2}$ = half-life of the drug (6 hrs).

D_t = 40(1+ (0.693 × 24)/6) = 150.8 +6% ≅160 mg

Physical Evaluation of Granules[14,13]

The granules of different formulations were evaluated for angle of repose, bulk density, compressibility index, total porosity and drug content.

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Table No.10.Evaluation of Pre-Compressed of Valsartan Sustained Release Granules

Tablets	Angle of repose	Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Compressibility Index (%)	Total porosity (%)	Hausner's ratio	Drug content (%)
F1	24.86±0.03	0.514±0.05	0.582±0.03	13.76±0.03	38.04±0.04	1.17	99.48±0.35
F2	24.12±0.04	0.510±0.03	0.583±0.05	12.96±0.04	37.61±0.03	1.18	98.99±0.52
F3	24.12±0.04	0.507±0.03	0.583±0.04	12.96±0.04	37.61±0.04	1.16	99.55±0.17
F4	21.23±0.03	0.494±0.04	0.556±0.04	12.26±0.04	26.98±0.03	1.20	98.33±0.59
F5	22.69±0.04	0.495±0.05	0.356±0.03	13.08±0.04	31.25±0.02	1.18	98.67±0.97
F6	23.43±0.03	0.307±0.05	0.353±0.03	13.45±0.03	31.97±0.03	1.15	99.70±0.15

The results of angle of repose and compressibility index (%) ranged from 21.23 ± 0.03 to 24.12 ± 0.04, and 12.26 ± 0.04 to 13.76 ± 0.03, respectively. The results of LBD and TBD ranged from 0.307±0.05 to 0.514 ± 0.05 and 0.356±0.03 to 0.583 ± 0.05, respectively. The results of percentage porosity of the granules ranged from 26.98 ± 0.03 to 38.04 ± 0.04. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

The results of angle of repose (<30) indicate good flow properties of the granules. This was further supported by lower compressibility index values Table 10. Generally, compressibility index values up to 15% result in good to excellent flow properties. Bulk densities of granules prepared by using water alone as a granulating agent (F-1 to F-6) were found to be quite higher than those of other granules. This may be due to the presence of more fines in the granules, as water alone could not provide sufficient binding to the granules. Granule density, porosity and hardness are often interrelated properties. In addition, granule density may influence compressibility, tablet porosity, dissolution and other properties. The percentage porosity values of the granules ranged from 26.98 ± 0.03 to 38.04 ± 0.04. %, indicating that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26% shows that the particles in the powders are of greatly different sizes and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates. The drug content in the weighed amount of granules of all formulations was found to be uniform. All these results indicate that the granules possessed satisfactory flow properties.

Chemical Evaluation of Granules[12]

Content Uniformity

The prepared wet granules of formulations (F1-F6) were assayed for content uniformity and the results obtained are shown in Table 11.

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Table No.11.Quality Control Data for SR Content Uniformity

Formulations Number	Recovered drug concentration (in mg)
1	159.94
2	160.03
3	160.02
4	160.03
5	160.05
6	160.09

Physical Evaluation of Compressed Tablets

Valsartan SR tablet evaluation parameters such as thickness, average weight, hardness, friability, and disintegration time are listed below.

Table No.12.Evaluation of Valsartan Sustained Release Tablet Characterization

Formulation	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)	Drug Content (%)
F-1	249.0±1.53	3.44 ± 0.01	0.1 ± 0.02	18.2 ± 0.21	99.84±0.15
F-2	250.3±1.76	3.47 ± 0.03	0.53 ± 0.05	15.0 ± 0.15	98.83±0.80
F-3	249.5±1.56	3.35 ± 0.01	0.52± 0.06	11.0 ± 0.24	98.69±0.90
F-4	251.3±1.67	3.38 ± 0.02	0.56 ± 0.03	9.4 ± 0.3	99.46±0.10
F-5	250.2±1.21	3.42 ± 0.01	0.49 ± 0.05	14.8 ± 0.17	99.21±0.41
F-6	250.0±1.62	3.47± 0.02	0.18 ± 0.04	10.0 ± 0.17	100.3±0.15

The tablets of different formulations were subjected to various evaluation tests, such as thickness, diameter and uniformity of weight, drug content, hardness, friability and in vitro dissolution.

The thickness of the tablets ranged from 3.35 ± 0.01 to 3.47 ± 0.02. The hardness and percentage friability of the tablets of all batches ranged from 9.4 ± 0.3 to18.2 ± 0.21 and 0.1 ± 0.02 to 0.56 ± 0.03, respectively.

The average percentage deviation of 20 tablets of each formula was less than ± 5%. Drug content was found to be uniform among different batches of the tablets and ranged from 98.69 ± 0.60 to 100.3 ± 0.15.

All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets of more than 250 mg ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 98%. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable physicochemical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

Surface Morphology Studies Using Scanning Electron Microscope (SEM)

The morphology of a cross section of optimized sustained release tablets (study) were observed under a scanning electron microscope (model LEO -435 VP).

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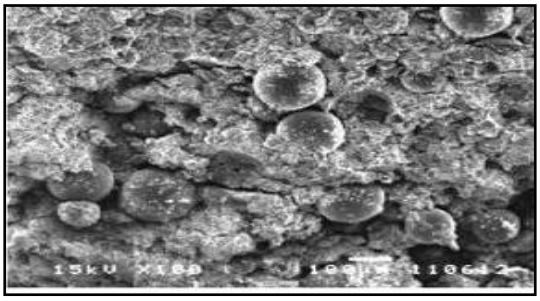

Figure No.6. SEM Photographs of Sustained Release Matrix Tablet

In photomicrograph obtained from SEM it was clearly observed that: Matrix tablet (F6), was observed to be having more porous surface due to the binding of HPMC with water. Swelling increases and tablet looses interfacial strength between the particles, showed highly porous tablet surface. Usually SSG are added to formulation to facilitate the break-up or disintegration of tablet into smaller particles but here the intension behind was to push the required amount of drug that is dumped in between the matrix to get the desired release at appropriate time.

Chemical Evaluation of Compressed Tablets

Assay

The concentration of Valsartan in all formulations was found to be 99.88 ± 1.8% - 101.05 ± 0.96 %. The recovery values for all formulations are within the limits recommended by the United States pharmacopeia (98 % - 102%).

In Vitro Dissolution Studies

In Vitro Studies of Sustained Release Tablet in Phosphate Buffer pH 6.8

Sustained release tablets of Valsartan were developed at the strength of 160 mg so as to increase the bioavailability and to reduce the dose frequency.

In the present study, HPMC is used to form hydrophilic matrix drug delivery system. Parallel trials were taken in study by varying the concentration of HPMC 15 cps to achieve the desired release profile of Valsartan for 24 hrs. Normal wet granulation method was employed and six batches (F1- F6) were taken initially to optimize the concentration of the polymer. Dissolution studies were performed with 0.067 M phosphate buffer with 0.2 % of sodium lauryl sulphate, pH 6.8 as the drug was very likely to release in intestinal medium.[1]

Table No.13.In Vitro Release Profile of Valsartan Sustained Release in Different Amount of HPMC in study

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	**0**
1	11.19 ± 1.65	11.53 ± 1.77	12.08 ± 1.98	15.91±1.12	15.11± 1.45	16.29 ±1.17
2	21.19 ± 2.11	21.84 ± 2.56	22.88 ± 2.17	30.13 ± 2.73	25.05 ± 2.97	27.01 ± 1.99
4	28.75 ± 3.33	29.63 ± 3.67	31.05 ± 2.81	40.88 ± 2.89	32.16 ± 3.54	34.68 ± 3.56
6	35.7 ± 4.42	36.79 ± 2.99	38.56 ± 3.49	50.76 ± 3.66	38.7 ± 3.21	41.73 ± 2.11
8	40.57 ± 4.84	41.81 ± 3.11	43.81± 5.13	57.69 ± 3.71	43.74 ± 3.65	57.17 ± 3.61
12	47.32 ± 5.87	48.77 ± 3.67	51.11± 4.90	67.29 ± 5.21	51.6 ± 4.45	65.64 ± 3.33
16	55.96 ± 3.84	57.67 ± 4.32	60.44 ± 3.97	79.57 ± 6.27	59.03 ± 3.82	73.65 ± 4.87
20	63.86 ± 3.42	65.81± 3.45	68.97 ± 3.11	90.81 ± 2.44	66.93 ± 3.61	82.17 ± 3.98
24	69.6 ± 2.71	71.73 ± 2.73	75.17 ± 2.63	92.97 ± 3.21	75.8 ± 1.79	94.74 ± 2.11

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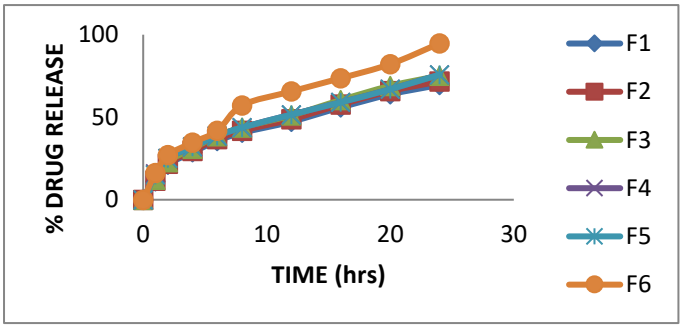

Figure No.7. In Vitro Release Profile of Valsartan Sustained Release Tablet

Kinetics Release

In order to examine the release mechanism of drug sample from the prepared tablets, the results of the dissolution study was examined in accordance to the kinetic models such as zero-order, first order, Higuchi equation and Korsemeyer–Pappas equation.

1. Zero Order Kinetics

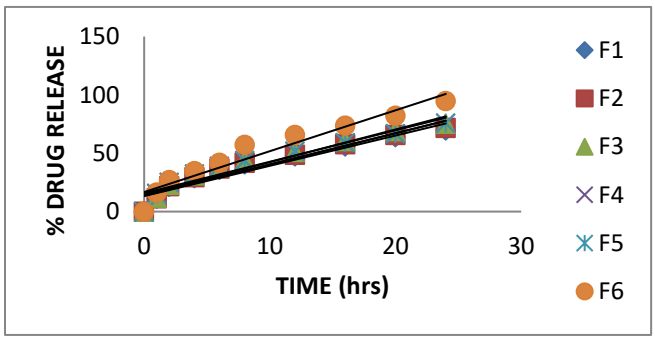

Figure No.8.Zero Order Kinetics of Valsartan

2. First Order Kinetics

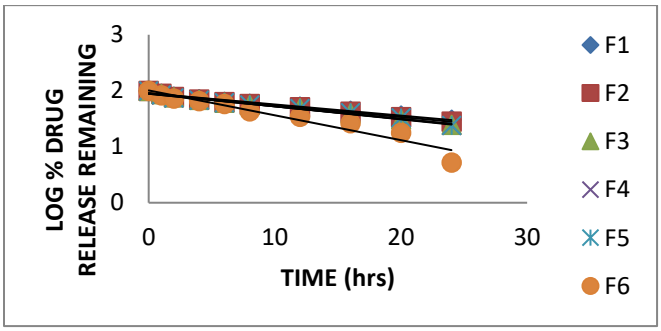

Figure No.9. First Order Kinetics of Valsartan Sustained Release Tablet

3. Higuchi's Model

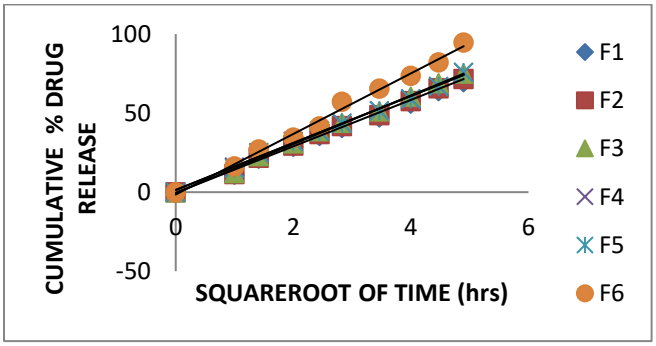

Figure No.10. Higuchi's Model Kinetics of Valsartan Sustained Release Tablet

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4. Korsemeyer Peppas Model

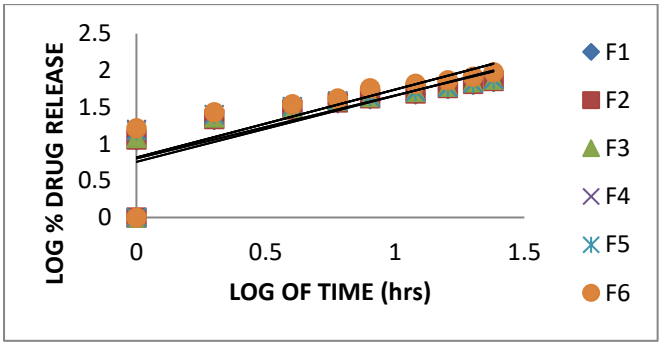

Figure No.11.Korsemeyer Peppas Model Kinetics of Valsartan Sustained Release Tablet

Table no.14.Release Kinetics of Valsartan Sustained Release in Different Amount of HPMC

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer R^2
F1	0.920	0.982	0.996	0.696
F2	0.920	0.984	0.996	0.693
F3	0.920	0.986	0.996	0.688
F4	0.913	0.979	0.996	0.634
F5	0.913	0.979	0.995	0.642
F6	0.928	0.931	0.993	0.668

From the data and graphical representations, the Valsartan Sustained Release Formulations were showed well fitted Higuchi's model kinetics and formulation F6 was showed best among the formulations were prepared based on Physical and Chemical evaluation of compressed tablets and in-vitro drug released profiles and also well fitted the Higuchi's model kinetics**.**

Accelerated Stability Studies of Optimized Valsartan SR Tablets

Stability studies of valsartan tablets were carried out to determine its nature in the presence of polymers and other formulation additives under conditions of storage. Stability testing was carried for the estimation of drug content in valsartan SR tablets, using UV spectroscopy.

Accelerated Stability Study (WHO Guidelines)

Prepared tablets (30 X 1) were packed tightly in an HDPE container and stored at 40 °C ± 5 °C, 50 °C ± 5 °C, and 60 °C ± 5 °C for 90 days (Table 7.14). Samples were withdrawn at 0, 30, 60 and 90 days and were analyzed for their drug content by UV spectroscopy using the standard curve. The log of the drug remaining was plotted against time (in days) (Figure 11) Slope of each line was obtained and degradation rate constant were calculated by the formula.

Slope = -K /2.303.

Where K is the degradation constant

$t_{0.9} = 0.1052 / K_{25}$

Where, $t_{0.9}$ is the time required for 10 % degradation of the drug and is referred to as shelf life.

The amount of drug remaining in the optimized valsartan (SR) tablet at each time interval is shown in Table 15. It can be seen from the table that the amount of drug remaining in the formulation at the end of 90 days was 99.80625%, 97.05875% and 98.06257% at 40 ± 5 ºC, 50 ± 5 ºC and 60 ± 5 ºC respectively.

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Table No.15.Degradation of Valsartan (SR) According to WHO Guidelines

Sr. No	Time (days)	Temperature (°C)	Mean conc. of drug remaining (± SD, N=3) µg/ml	% drug remaining	Log % drug remaining
1	0	40 °C and 65 % RH	159.86 ± 0.04	98.90625	1.9952
2	30		159.32 ± 0.05	97.56875	1.9906
3	60		158.39 ±0.05	99.99188	1.9999
4	90		158.10± 0.07	99.80625	1.9991
5	0	50 °C and 65 % RH	159.86± 0.03	98.90625	1.9952
6	30		158.24± 0.05	99.89375	1.9995
7	60		157.60± 0.05	99.69375	1.9986
8	90		156.93± 0.06	97.05875	1.9870
9	0	60 °C and 65 % RH	159.86 ± 0.02	96.90625	1.9863
10	30		157.55 ± 0.03	99.46253	1.9976
11	60		156.84 ± 0.03	98.90187	1.9952
12	90		156.34± 0.05	98.06257	1.9915

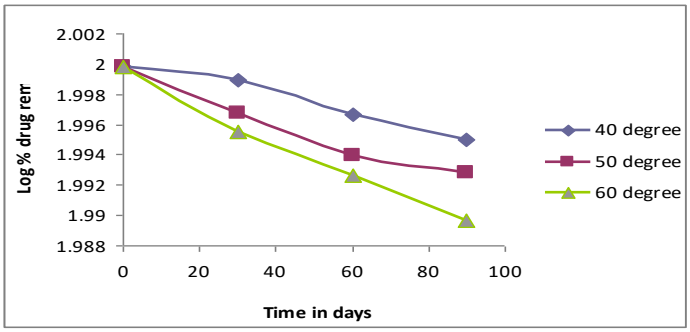

Figure No.12.Kinetics of Valsartan Degradation from Optimized SR Table

Aknowlegement

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