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FORMULATION DEVELOPMENT AND INVITRO EVALUATION OF VALSARTAN SUSTAINED RELEADSE TABLETS

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ABSTRACT

The Sustained released tablets containing Valsartan SR tablets were successfully prepared by wet granulation method. The optimized formulation contains the average thickness of 3.95±0.89, average hardness of 6.4±0.60, average weight of 302.4±0.54, friability of 0.37.The optimized formulation F8 which releases the valsartan in sustained manner in 1st hour it releases 8.51 % but the remaining drug release was sustained up to 12 hours.

KEY WORDS: Valsartan, wet granulation, sustained release tablets

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INTRODUCTION

Sustained Release Dosage Forms

To the date, for every disease or disorder state of the patient, proper medication is of prime importance to maintain the patient in good health. To achieve this, the medicine or drug is administered conventionally by one or more of several well defined and popular routes of drug administration including oral, parenteral, rectal, alveolar, ocular and topical. Among these above mentioned popular routes, oral conventional route of drug administration lies at the top of the hierarchy of the conventional routes. It is a reasonable assumption that drug concentration at the site of action is related to drug plasma level and that, in the great majority of cases, the intensity of effect is some function of drug concentration at the target site. The objective of the most therapeutic regimens is to rapidly raise the plasma concentration to the required level and then to hold it constant for the desired duration of treatment The extent to which this situation can be achieved depends on many factors, including the minimum effective concentration of the drug, the level at which side effects occur, the dose administered, the rate of drug release from the dosage form, the rate of elimination and the frequency of dosing. Provided that the dose size and frequency of administration are correct, therapeutic 'steady state' levels of the drug can be achieved rapidly and maintained by the repetitive administration of conventional oral dosage forms.

Traditionally patient only takes medication during the day time hours. Plasma levels can therefore fall to sub– therapeutic levels overnight. However, there are a number of major deficiencies of conventional dosage forms, few of which are listed here (1, 2).

• Inconvenience and /or difficult use of drugs with very short duration of action
or biological half-life.
• Need for frequent dosing
• Potential for "peak-valley" plasma levels, leading to toxicity and side effects
and incomplete therapy.
• Poor patient compliance, due to adverse effects, forgetfulness, and inconvenience
of dosage forms.
• Frequently needed for large systemic concentrations in order to achieve
Adequate concentration at target site or action.
• Potential variations in oral absorption due to variations in; GIT pH profile,
Presence and type of food and transit time in gut.

Like every failure that sets ahead the path of successes, these above mentioned major deficiencies of drug therapy based on repetitive administration of conventional single oral dosage form, have lead to the development of a more specialized group of oral dosage forms (modified release drug products). Thus, various modified drug products have been developed to release the active drug from the product at a controlled rate. The term controlled release drug products was previously used to describe various types of oral extended-release dosage forms, including sustained release, sustained action, prolonged action, slow release, long action, and retarded release. Many of these terms for controlled-release dosage forms were introduced by drug companies to reflect a special design for a controlled release drug product or for use as a marketing term. The United States Pharmacopoeia (USP) has adopted the term "extended release" whereas the British Pharmacopoeia (BP) has adopted the term "slow release". The Food and Drug Administration (FDA) of the United States has adopted the term "prolonged release". Both USP and FDA employ the term "delayed release" for enteric coated products (3-5).

Sustained- release dosage forms-It is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug." It provides prolonged but not uniform release of drug and reduces the need for repeated dosing. Once the maximum level is reached, the amount of drug in the body decrease slowly. So it will take longer to drop below the therapeutic range. In 1950's, the first modern oral sustained release product was introduced by Smith Kline and French (SKF) laboratories under the trade name "Spanule". This product consists of hundred of beads containing a drug and coated with varying thickness of natural wax such as bees wax & glycerylmonostearate. The prime goal of sustained release dosage form is to maintain the therapeutic blood or tissue level of the drug for an extended period. This system was used first to sustain the release of dextroamphetamine (Dexedrine). This is generally accomplished by attempting to obtain 'zero order' release from the dosage form.

The term "controlled drug delivery", came in to being to describe new concept of dosage form regimen in the mid to late 1960's. Controlled release dosage form is a class of pharmaceuticals or other biologically active product from which drug is released from the system in a planned, predictable and slower than the conventional manner (Fig-1).

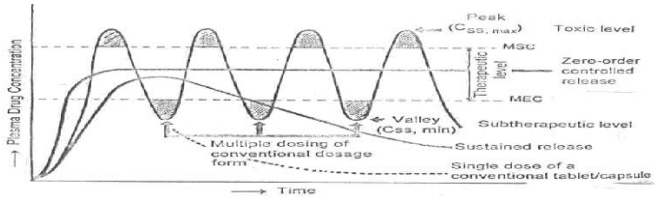

Fig-1 A hypothetical plasma concentration – time profile from conventional Multiple and single doses of sustained and controlled delivery formulations (6)

Developing country is a self explanatory term that is used to describe most countries with low level of standard living. According to report from International Monetary Fund (IMF) in 2010, Ghana is among the emerging and developing countries economically. It is considered as a country which has not achieved a lot with relation to industrialization. Factors as rate of literacy, general life expectancy, population growth compared to the general standard of living of the population. Ghana has over the year's

economy remained essentially agricultural even though the industry is better developed in Ghana than the rest of the continent. The country achieved a 6.4% growth rate in 2007. This is evident as the setting of the research is characterized with main occupations as Agriculture, Private businesses, Production, Transport and Equipment work, Professional and Technical work and other services. According to WHO (2009), deaths as a result to non communicable diseases as hypertension will increase by 17% over the next decade, with the greatest increase in the African region (27%). However, primary prevention has been proposed as the 13 most cost effective approach to the emerging epidemic. (Maher et al. 2010.) In 2003,a cross-sectional study by Amoah et al. (2003) conducted in Ghana concluded that high prevalence in women (29.5%) compared to male (27.6%) and low level of awareness. However, focus has been on communicable diseases in developing countries until recently as that similar study conducted in 2006 still showed a high prevalence with 32.3% of participants not having knowledge of the disease More than 500,000 women between the ages of 19 and 49 have been estimated to have died in developing countries each year due to hypertensive-related causes. Research reveals that women with pre-existing or chronic high blood pressure are more likely to have complications during pregnancy than those with normal blood pressure. Previous studies have showed hypertension as one of the major causes of maternal death in Ghana (Ghana Maternal Health Survey 2007). However, to a considerable extent, the growth and effectiveness of reducing maternal death by means of prevention and treatment of hypertension has not been effective even though it can be prevented. In addition, a research conducted in Uganda concluded that approximately one in every three adult aged 20 years or older was hypertensive. Prevalence of 30.5% and female more hypertensive than males in this study suggested that advancing in ageing was a risk factor due to exposure to lifestyle risk factors of hypertension. A recent research showed the huge gab on the statistics of industrialized countries, developed countries and the least developed. It is extremely important to investigate on the knowledge and attitude of this target group about the preventive measures of hypertension. Significant reduction in maternal mortality can thus be achieved.

Valsartan is an angiotensin-receptor blocker (ARB) that may be used to treat a variety of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Valsartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS); it competes with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II. Unlike angiotensin-converting enzyme (ACE) inhibitors, ARBs do not have the adverse effect of dry cough. Valsartan may be used to treat hypertension, isolated systolic hypertension, left ventricular hypertrophy and diabetic nephropathy. It may also be used as an alternative agent for the treatment of heart failure, systolic dysfunction, myocardial infarction and coronary artery disease. 94 - 97% bound to serum proteins, primarily serum albumin. Valsartan is excreted largely as unchanged drug (80%) and is minimally metabolized in humans. The primary circulating metabolite, 4-OH-valsartan, is pharmacologically inactive and produced CYP2C9. 4-OH-valsartan accounts for approximately 9% of the circulating dose of valsartan. Although valsartan is metabolized by CYP2C9, CYP-mediated drug-drug interactions between valsartan and other drugs is unlikely. 83% of absorbed valsartan is excreted in feces and 13% is excreted in urine, primarily as unchanged drug.

The aim of the present study was to fabricate and evaluate sustained release tablets Valsartan, using different natural polymers like Guar gum and Xanthum gum which is suitable for delivering the drug for sufficient long time and reduce frequency of dose.

MATERIALS AND METHODS

Pre-Formulation Studies

Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It is the first

step in rational development of drug dosage forms of a drug substance. It provides the information required to define the nature of the drug and a framework for the drug combination with pharmaceutical excipients in dosage form. Hence, pre-formulation studies were performed on the obtained sample of drug for identification and compatibility studies.

IR Spectroscopy

The FT-IR spectrum of the obtained drug sample was compared with the standard FT-IR spectra of the pure drug.

Compatibility Studies of Drug & Polymers

Prior to the development of the dosage forms the pre-formulation study was carried out. Hence infrared spectra of pure drug and the physical mixture of drug and polymers were taken. Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 150 cm^{-1} in a shimadzu FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks (7-10).

Preparation of the Standard Calibration Curves of Valsartan

Standard calibration linearity curve of Valsartan in pH 6.8 Phosphate buffer

Valsartan (100mg) was dissolved in 10ml of methanol and volume was made up to 100 ml in volumetric flask using Phosphate buffer pH 6.8. From this stock solution 10 ml was withdrawn and is diluted to 100ml in volumetric flask which gives the concentration of 100 µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give concentrations 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml. Absorbance of each solution was measured at 250 nm using Shimadzu UV- 1700 UV-Vis double beam spectrophotometer with Phosphate buffer pH 6.8 as a reference standard.

Standard calibration linearity curve of Valsartan in 0.1N HCL

Valsartan (100mg) was dissolved in 10ml of methanol and volume was made up to 100 ml in volumetric flask using 0.1N HCL. From this stock solution 10 ml was withdrawn and is diluted to 100ml in volumetric flask which gives the concentration of 100 µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give concentrations 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml. Absorbance of each solution was measured at 250 nm using Shimadzu UV- 1700 UV-Vis double beam spectrophotometer with 0.1N HCL as a reference standard.

Formulation Development

The pharmaceutical development studies have to be carried out with the purpose of selecting right dosage form and a stable formulation. These studies give detailed description of all the steps involved in the process of formulation development. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product (11-13).

Formulation of SR tablets

This sustained release tablets was prepared by wet granulation method. Sieving- The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve. Dry mixing- Valsartan, Micro Crystalline Cellulose and natural polymers were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug. Preparation of binder solution-Weigh PVP K-30 accurately and it is mixed with IPA to form a solution is used as binder solution and kept separately. Then the granulation, drying and sieving were followed by lubrication for final compression. Magnesium stearate and talc were weighed and they were passed through sieve#20.Then mixed with dried granules of Valsartan in a polybag for 5minutes to get a uniform blend. Then the lubricated granules of Valsartan were weighed accurately and fed into the die of single punch machinery and compressed. For this 9mm round punch was used for compression (Table-1).

Table-1 formulation table for sustained release tablets

Formulation	F_1	F_2	F_3	F_4	F_5	F_6
Valsartan	80	80	80	80	80	80
Xanthum gum	80	120	160	-	-	-
Guar gum	-	-	-	80	120	160
MCC	110	70	30	110	70	30
PVP K-30	20	20	20	20	20	20
IPA	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2	2	2	2	2	2
Talc	8	8	8	8	8	8
Total weight	300	300	300	300	300	300

Formulation of Sustained release tablets

Development of sustained release tablets of Valsartan was carried out. Sustained release tablets were prepared using formulae given below. Sustained release tablet was prepared on 16 station tablet compression machine by wet granulation. The tablets of different formulations were punched with 9mm round punch on compression machine.

RESULTS AND DISCUSION

Compatability studies

The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of valsartan mentioned in Table-2 were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the excipients.

Table-2 Interpretation data of valsartan with optimized formulation

Functional groups	valsartan	Optimized formulation
	Observed peak	Observed peak
N-H stretch	3445	3405.47
-OH	2962	2938.66
-C=O	1105.98	1073

Pre-compression parameters results shows clear evidence that granules have excellent flow properties (Table-3).

Table-3 Pre-compression parameters for SR tablets

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio	RESULT
F1	25^0 73'	0.318	0.352	9.659091	1.106918	Excellent
F2	25^0 16'	0.315	0.342	7.894737	1.085714	Excellent
F3	26^0 68'	0.323	0.354	8.757062	1.095975	Excellent
F4	27^0 58'	0.314	0.338	7.100592	1.076433	Excellent
F5	28^0 38'	0.312	0.335	6.865672	1.073718	Excellent
F6	26^0 42'	0.315	0.332	5.120482	1.053968	Excellent

***In-vitro* dissolution test**

The results of *in-vitro* drug release studies in 0.1N HCl (for first two hours) and 6.8 phosphate buffers (from 3 to 12 hours) are presented in table-4 and fig-2. Initially our aim was to select optimum concentration of individual polymers of different concentration for SR tablets. Hence the tablets containing, SR tablets of drug (valsartan) were prepared by altering the concentration of different natural polymers.

Table-4 cumulative percentage drug release from sustained release tablets

Time	F1	F2	F3	F4	F5	F6
Dissolution medium 0.1N HCL						
1	10.8	10.2	7.8	10.3	8.51	8.51
2	15	12	12.6	18	14.1	13.3
6.8pH phosphate buffer						
3	31	28.6	26.5	38.4	35.2	33
4	39	38.2	38	45.4	45.0	45.8
5	58	55.4	52	58.6	58.9	60
6	70.4	68.2	58	65.3	70.5	74.5
8	80.15	75.8	66.3	78.6	79.6	79.3
10	--	81.6	79.4	84.1	81.2	80.8
12	--	--	83.8	--	82.7	86.8

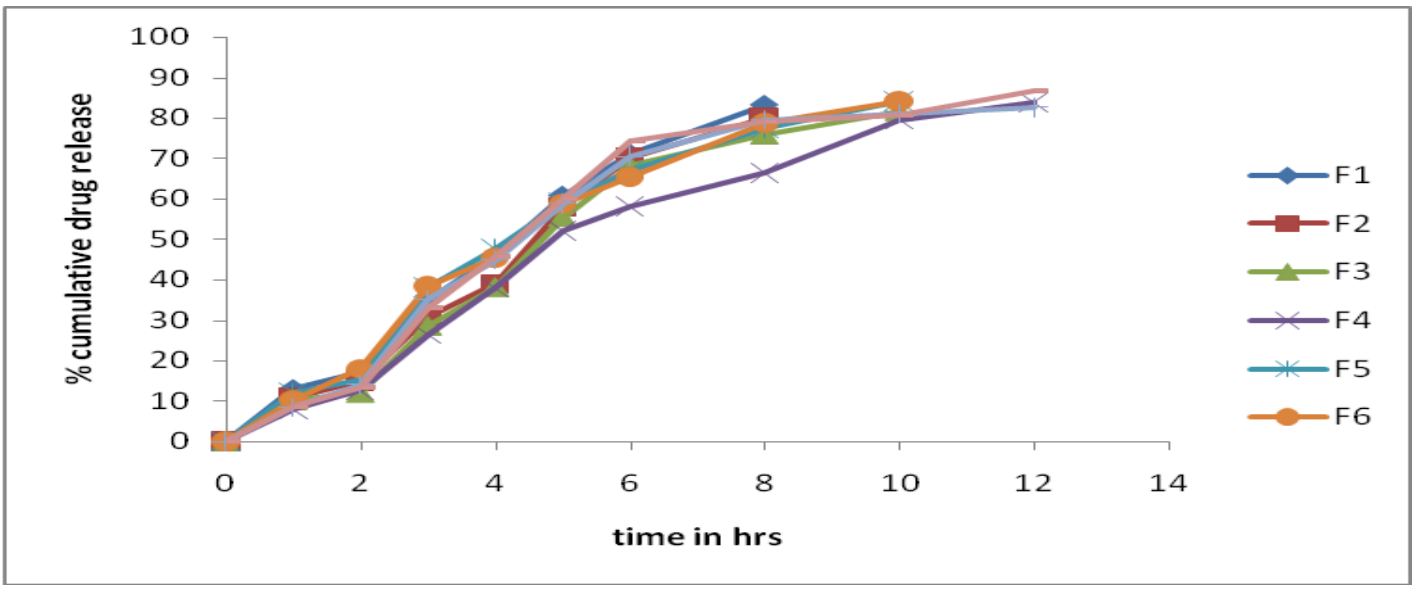

Figure- 2 dissolution graph for sustained release formulations

In-vitro **release of valsartan sustained release tablets**

From the above results, it was confirmed that the F8 formulation SR tablets fulfill the sustained release theory, In that the Guar gum was used separately in the formulations, but increasing the polymer concentration, it was clearly identified that the drug release was retarded. And also from the table, it was also confirmed that the formulation made with guar gum (F4 and F8) showed sustained drug release compared to the formulations made with XANTHUM GUM (F1 to F4).

CONCLUSION

The Sustained released tablets containing Valsartan SR tablets were successfully prepared by wet granulation method. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index .The prepared granules were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation contains the average thickness of 3.95±0.89, average hardness of 6.4±0.60, average weight of 302.4±0.54, friability of 0.37.The optimized formulation F8 which releases the valsartan in sustained manner in 1st hour it releases 8.51 % but the remaning drug release was sustained up to 12 hours. "Hence it may be summarized that the F8 tablets prepared by wet granulation method for sustained release tablets might be a perfect and effective formulation to treat the hypertension".

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