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R E V I E W A R T I C L E

Formulation and Evaluation of Sustained Release Tablets of Valsartan

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A B S T R A C T

The present study was aimed to formulate and evaluate sustained release tablets of valsartan, which comes under BCS class iii, using HPMC as a polymer in different proportion by "Wet granulation method". Compatibility among the formulation components was assessed by DSC analysis. These prepared tablets were evaluated for various parameters like weight variation, hardness and friability, drug content, stability, swelling index and other parameters.

Keywords: Valsartan, sustained release, HPMC.

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1. Introduction

Sustained release dosage form is defined as "Any drug or dosage form modification that prolongs the therapeutic activity of the drug for an extended period of time." This delivery system is increasingly being used in the treatment of acute and chronic disease as they maintain the concentration of the drug in plasma above the minimum effective concentration to and below the minimum toxic level for the extended period of time. [1] 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, avoiding multiple dosing , increase the plasma drug concentration , avoid side effects and overcome problems associated with conventional system. Valsartan is an angiotensin II receptor antagonist that is used for the treatment of hypertension. It treat the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin I receptor in many tissues. The selection of natural polymers than synthetic polymers as matrix system for sustained drug delivery is to obtain desired drug release, patient compliance, cost effectiveness and to enhance compatibility with the drug. Hence in the present study an attempt has been made to develop

sustained release matrix tablet of Valsartan using natural polymers. Matrix materials such as Guargum and Pectin are used in the formulation. The goal of designing sustained release drug delivery system of valsartan tablets is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing controlled drug delivery [2]. Valsartan belongs to BCS class III [3].

Chemical Structure of Valsartan

Valsartan, N-valeryl-N-[[2-(1H-tetrazole-5-yl) biphenyl-4-yl] methyl] -valine has an empirical formula of $C_{24}H_{29}N_5O_3$ and molecular weight of 435.5 g/mol. It is available as a white microcrystalline power with a melting range of 105-110C.The structure contains two acidic functions and one asymmetric centre. The compound is a S enantiomer. Valsartan is soluble in water at 25C. In a buffer solution the solubility is increased because the dianionsalt is formed. Valsartan is an orally active specific angiotensin II receptor blockers effective in lowering blood pressure in hypertensive patients [4].

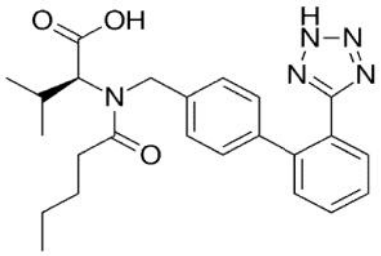

Fig1: Chemical structure of valsartan

2. Mechanism of action

- Angiotensin II is formed from angiotensin I in a reaction catalysed by angiotensin converting enzyme(ACE, kinase II)
- Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of syntheses of aldosterone, cardiac stimulation, and renal reabsorption of sodium.
- Valsartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II by selectively blocking the binding of angiotensin II AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.
- The increased plasma levels of angiotensin are following AT1, receptor blockade with Valsartan may stimulate unblocked ATP receptor.
- Blockade of the regin angiotensin system with ACE inhibitors which inhibit the biosysthesis of angiotensin II from angiotensin I which is widely used in treatment of hypertension. It also inhibits the degradation of bradykinin, a reaction also catalysed by ACE.
- Blockade of angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on rennin secretion, but the resulting increased plasma rennin activity and angiotensin II circulating level do not overcome the effect of Valsartan on blood pressure
- Its action is therefore independent of the pathways for angiotensin II synthesis[4].

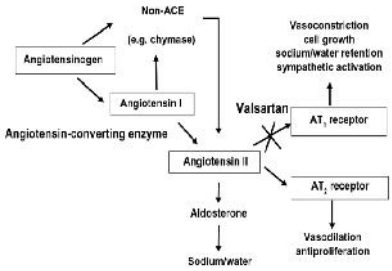

Fig 2: Mechanism of valsartan

Advantages:

- Sustained release formulations have many advantages over traditional, immediate release products.
- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients[5].

USES:

- Patient compliance.
- Avoid multiple dosing.
- Increasing the plasma drug concentration.
- Avoid side effects.
- Overcome the problems associated with conventional system[6].

Formulation

Materials-

- Valsartan
- HPMC
- Lactose
- Magnesium stearate
- Talc

Methods

Drug excipients compatibility of the drug with excipients was determined by differential scanning calorimeter. This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients.

Preparation: Valsartan tablets with different concentration of polymer were prepared by the wet granulation technique. All ingredients in required quantities were weighed individually. All these ingredients were first sieved and mixed for 5 min. Isopropyl alcohol was granulated through sieve 8# and prepared granules were dried at 60 c for 1h.

The dried granules were passed through sieve 10# and fractions of granules retained on the sieve were discarded then blended with talc and magnesium stearate for lubrication of granules which were then compressed on single punch tablet machine using circular 4mm punch. The compression of the tablets was done by using tablet compression machine [7].

3. Evaluation

Weight variation:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness and Friability:

For each formulation, the hardness and friability of 6 tablets were determined using the hardness tester (lab Tech, India) and the friabilator (vergo friabilator, India) respectively[8].

Drug content:

Three tablets were selected randomly from each batch, powdered separately and then taken into 3 volumetric flasks of 100ml. In each flask 100ml of phosphate buffer pH 7.4 was poured and kept for 24 hrs. After filtering the solution and making suitable dilution, the absorbance of the filtrate was measured at 251nm using UV-VIS double beam spectrophotometry (thermo scientific, India).From absorbance, drug content was determined according to the following formula.

Drug content = (actual drug content / theoretical drug content) 100

Stability study:

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. The selected formulation were packed in yellow colour PVDC/ALU, blister. They were then stored at 40 c / 75% RH for three months and evaluated [9].

Swelling index:

Measurement of the swelling index was carried out to gain an insight into the phenomenon of polymer hydration and to evaluate the extent of media penetration within the tablets. The swelling index was determined by equilibrium weight gain method the study was carried out in the USP dissolution apparatus type - 1. The tablets were accurately weighed, placed in dissolution basket matrix system was withdrawn from the dissolution vessel, lightly bottled with the tissue paper to remove excess test liquid and re weighed. The swelling index (S1) of each tablet was calculated according to the following equation

$SI = \{(Wt - Wo)/ Wo\} 100$

Where,

SI = Swelling index

Wt = Final weight

Wo = Initial weight

Release kinetics:

In order to examine the release mechanism of drug sample from the prepared matrix tablets of the optimized formulation , the results of the dissolution study was examined in accordance to the kinetic models such as zero order, first order , Higuchi equation , Korsemoyer- pappas equation and Hixson – crowell equation[10].

In-vitro disintegration time: The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specification[11].

4. Conclusion

In this study, concluded about the formulation and evaluation of valsartan tablets as sustained release dosage form and the materials involved in this method. The evaluation tests were studied based on the tablet dosage form, we can study about various evaluation testes like hardness and friability, weight variation, drug content, swelling index, stability test, release kinetics and in-vitro drug release studies.

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