(REVIEW ARTICLE)

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Develop and evaluate novel drug delivery system of valsartan for treatment of Hypertension: A review

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Abstract

The sustained release tablets were formulated by using the combination of various release retardant polymers/excipient. The polymers used were hydroxypropyl methylcellulose, Micro Crystalline Cellulose and Sodium starch glycolate. The present investigation involves formulation and evaluation of sustained release tablets of Valsartan with a view to prolong the drug release in the gastrointestinal tract and consequently into the plasma. It showed good linearity and reproducibility which also indicated the analytical method used in the present study to be suitable for the estimation of the drug candidates in different dissolution media. Evaluation parameters such as thickness and diameter, weight variation and drug content uniformity test. The observation for all above evaluation parameters indicate that the values are within the IP specified limits. Thus, on the basis of our research findings it could be concluded that the performance of the developed sustained release tablets was found to be promising for the treatment of hypertension.

Keywords: Sustained; Hypertension; Cellulose; Linearity; Polymers; Valsartan

1. Introduction

High blood pressure (HBP) or hypertension means high pressure (tension) in the arteries. Arteries are vessels that carry blood from the pumping heart to all the tissues and organs of the body. Sustained-release dosage forms have been referred to as controlled-, delayed, extended- or modified-release dosage forms. These terms describe a dosage form that controls the drug absorption rate to achieve a desired plasma profile defined by steady-state pharmacology, for a particular compound after pre-determined lag times or intervals [1]. The basic rationale of controlled drug delivery system highlights the biopharmaceutical, pharmacokinetic, and pharmaco-dynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and increases therapeutic effect, in the shortest possible time by using smallest quantity of drug administered by the most suitable route. Most physiological, biochemical, and molecular processes in healthy organisms display robust, predictable changes on a 24 h schedule. Sustained release cardiac products can synchronize drug delivery with circadian rhythms in order to optimize efficacy and/or minimize side-effects. For diseases like hypertension, the cure may be dictated by the timing of drug administration. Hence the emergence of controlled delivery system coordination of medical treatment with biological rhythms is especially useful for disease states with known circadian patterns. By taking advantage of known biological patterns in disease manifestation, the goal of developing sustained release products to optimize the desired effects of a drug and minimize its undesired ones, can be achieved in certain disease states. There is a high incidence of disease symptoms and adverse

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events in the morning hours. So, ensuring that adequate plasma levels of a drug are present in the morning can be critical to effective treatment of many diseases, including hypertension and other cardiovascular diseases. With an aim of attaining therapeutic concentrations of the drugs at the time of its maximum requirement in the body, we intend to formulate drug delivery devices for better treatment of the diseases following a typical sustained release pattern. The kind of system will offer significant advantages over the currently available systems for the treatment of diseases following biological clock pattern of symptoms occurrence. The diseases targeted in this study are hypertension which is amongst the most prevalent ones following typical circadian rhythm. Overall, we intended to accomplish the goals to develop sustained drug delivery devices for the effective treatment of hypertension. Most CR formulations are dissolution-controlled, and drug release rate from the dosage form is the rate-limiting step. It is assumed that, once released, the drug is rapidly transferred from the gut lumen to blood. Therefore, efficient drug absorption from GI tract is a pre-requisite for a drug to be considered for use in oral CR dosage form. In general, the absorption rate for most drugs decreases as the dosage form moves beyond the jejunum. As long as the absorption rate remains above that of release rate, this change does not affect plasma levels. However, once past the ileocecal junction a variety of factors generally reduce the drug absorption rate to below acceptable value. This creates a time limit of about 6 to 9 h during which the drug can be delivered in a predictable manner. Valsartan formulation which provides sustained release of the drug over longer periods of time ex. to 24 hr. from administration [2]. Since the drug has to release predominantly in the terminal portions of the GI tract, it is prerequisite for the drug to have its absorption window in the small and large intestine. Drug candidates for the proposed formulations were selected on the basis of the above-mentioned property of having good absorption in the terminal portions of the GI tract [3].

2. Drug profile

Selected drug candidates and their profiles Valsartan as drug candidate was selected for the proposed formulations to be developed after carefully considering the above-mentioned points in selection of a suitable drug candidate [4]. Additionally, the pharmacokinetic data of the drugs (rapid and complete absorption, and low T max) makes these drug good candidates for being formulated as controlled delivery systems. In addition, the drug is having a good market potential if developed in the form of the proposed formulation. it gives the summary of the desirable characteristics on the basis of possession of which the drug candidates were selected.

3. Drug profile

Valsartan belongs to a family of medications known as angiotensin II receptor blockers. These medications are used to lower mild-to-moderate high blood pressure. Valsartan is also be used to treat chronic heart failure or to reduce the risk of death after a heart attack in people who cannot use another type of medication called angiotensin-converting enzyme inhibitor. Valsartan is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of valsartan is about 25% (10- 35%). This relatively low bioavailability of valsartan is primarily due to its poor solubility in the acid milieu of the gastrointestinal tract. Valsartan is an acid, and therefore, has good solubility at pH>5 and low solubility in acidic conditions of the gastrointestinal (Gl) milieu. There is, therefore, considerable interest in providing a valsartan formulation which provides sustained release of the drug over longer periods of time e.g., to 24 hr. from administration. There also exists a need for valsartan formulation which results in one or more of reduce inter – subject variability, reduce intra – subject variability [5].

3.1. Structural formula
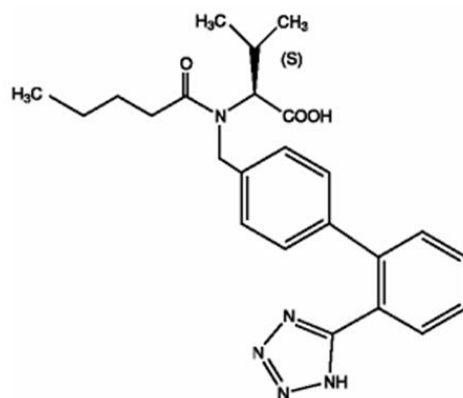
3.1.1. Chemical name

N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5yl) [1,1′-biphenyl]-4-yl] methyl]-L-Valine.

3.1.2. Category

Cardiovascular Agent

3.1.3. Sub Category

Angiotensin II Receptor Antagonist

3.1.4. Molecular Formula

C24H29N5O3

3.1.5. Molecular weight

435.5

3.1.6. Proprietary Name

Diovan; Tareg

3.2. Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin angiotensin system (RAS), with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium [6]. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis [7].

3.3. Selection of polymers/excipients

All excipients used in this study are Generally Regarded as Safe (GRAS) listed, and appear in the Food and Drug Administration Inactive Ingredients Guide for inclusion in oral formulations.

The common excipients used in the present novel formulation includes a diluent, binder, lubricant, glidants, and a hydrophilic matrix forming polymer which provides sustained release profile of drug delivery.

4. Methods

4.1. Preparation of Standard Plots/Calibration Curves

The standard plots of valsartan were prepared (n=3) in the following media: methanol, 0.1N HCl (pH 1.2), Acetate Buffer (pH 4.5) and Phosphate Buffer (pH 6.8).

4.2. UV spectral analysis

The λmax of the drug solution in methanol was found out to be 249.7 nm which was very close to the reported λmax value of 250 nm for valsartan (Simons and Simons, 2005). Additionally, the λmax value was found to be at 249 nm confirms the drug when the solution was made with phosphate buffer.

4.3. 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 [8, 9].

4.4. Evaluation

4.4.1. Sustained release tablets study

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 1, HPMC is used to form hydrophilic matrix drug delivery system. Parallel trials were taken in study 1 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 four batches (F1- F4) were taken initially to optimize the concentration of the polymer. In study 1, formulations F1 – F4 were granulated with HPMC 15 cps in concentration of 35, 25, 15 and 10 mg respectively. 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.

5. Conclusion

The present investigation involves formulation and evaluation of sustained release tablets of Valsartan with a view to prolong the drug release in the gastrointestinal tract and consequently into the plasma [10]. The validated UV analytical methodology for the drug in methanol, 0.1 HCl. Acetate buffer and phosphate buffer, the R^2 (0.9997, 0.999, 0.9984 and 0.997 respectively over a concentration range of 1 µg/ml to 10 µg/ml) (λ_{max} = 249 nm) with RSD values < 2% showed good linearity and reproducibility which also indicated the analytical method used in the present study to be suitable for the estimation of the drug candidates in different dissolution media [11]. The tablets were subjected to various evaluation parameters such as thickness and diameter, weight variation and drug content uniformity test. The observation for all above evaluation parameters indicate that the values are within the IP specified limits [12]. Thus, on the basis of our research findings it could be concluded that the performance of the developed sustained release tablets were found to be promising for the treatment of hypertension.

Compliance with ethical standards

Acknowledgments

Disclosure of conflict of interest

No conflict of interest.

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