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A Brief Review on Valsartan and Evaluation of Pharmacosomes

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ABSTRACT: Valsartan is an orally active Angiotensin II receptor type 1 antagonist which causes reduction in blood pressure and is used in treatment of hypertension. Angiotensin II Receptor type 1 antagonists have been widely used in treatment of diseases like hypertension, myocardial infarction and heart failure. Their beneficial effects are related to inhibition of Angiotensin II by blockade of AT1 receptor. It was first developed by Novartis and has a wide market in the developed and the developing countries. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. It is also available in combination with other antihypertensive drugs. This review evaluates the detail profile of Valsartan like physicochemical properties, pharmacokinetics, indications and contraindication storage, etc. and the preparation methods of pharmacosomes and its detailed evaluation. The main objective of this study is to review that the formulation of pharmacosomes is a better approach for enhancement of bioavailability of valsartan.

KEYWORDS: Valsartan, Hypertension, Pharmacosomes, Bioavailability, etc.

I. INTRODUCTION:

Valsartan is a potent, orally active non-peptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type-I which causes reduction in blood pressure and is used in treatment of hypertension. It was first developed by Novartis and has a wide market in the developed and the developing countries. It is also available in combination with other antihypertensive drugs. It is a lipophilic drug and possesses moderate onset of action than other drugs of the same category. It is soluble in the neutral pH range. Valsartan is soluble in acetonitrile and methanol. It belongs to the BCS class III drug classified as low permeability and high solubility drug. The drug is rapidly absorbed orally and has limited volume of distribution and is extensively bound to plasma proteins. Valsartan is not extensively metabolized and is mainly excreted by non-renal routes. Valsartan is effective in treatment of paediatric, adolescents and the elderly patients with mild to moderate hypertension. [1, 2]

II. HISTORY:

Valsartan was first developed by Novartis and was sold under the brand name DIOVAN and it currently holds the largest market share for the drug of its kind in the market.[1]

III. DRUG PROFILE OF VALSARTAN:

3.1 PHYSICOCHEMICAL PROPERTIES OF VALSARTAN:

Valsartan is (2S)-3-Methyl-2-(pentanoyl {[2'-(1H-tetrazol-5-yl)-4-biphenylyl] methyl} amino)butanoic acidwith empirical formula $C_{24}H_{29}N_5O_3$. Its molecular weight is 435.519g/mol. [3]

Valsartan is a white coloured crystalline powder that is freely soluble in ethanol, methanol, and acetonitrile and sparingly soluble in water. Valsartan appears in the melting range of 105-110˚C. The partition coefficient of Valsartan is 0.033 (log P=1.499), suggesting that the compound is hydrophilic at physiological pH. The compound is stable under storage in dry conditions. As valsartan has pH dependent solubility it belongs to a special case in a proposed general classification system that categorises drugs with respect to their biopharmaceutical and absorption properties.In the biopharmaceutical classification system, valsartan has been classified as Class III drug with low permeability, poor metabolism and high solubility. Valsartan has bioavailability of about 25% due to its acidic nature. Being acidic in nature it is poorly soluble in the acidic environment of GIT and is absorbed from the upper part of GIT that is acidic in nature and where its solubility is low.Valsartan is 0.18 g/L soluble in water at 25˚C.In a buffered solution a dianion salt is formed due to which its

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solubility is increased. In phosphate buffer (pH 8.0), valsartan is 16.8 g/L soluble at 25˚C. [1, 4]

3.2 CHEMICAL CLASS OF VALSARTAN:

Chemically valsartan belong to category of "tetrazole" derivative. The structure of valsartan is shown in Fig. 1 [5]

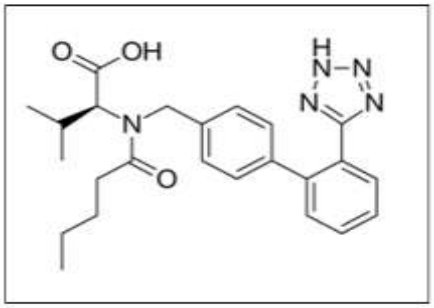

Fig 1. Structure of Valsartan

3.3 MECHANISM OF ACTION OF VALSARTAN:

Valsartan blocks the actions of angiotensin II, which include constricting blood vessels and activating aldosterone, to reduce blood pressure. The drug binds to angiotensin type I receptors (AT1), working as an antagonist. This mechanism of action is different than that of the ACE inhibitor drugs, which block the conversion of angiotensin I to angiotensin II. As valsartan acts at the receptor, it can provide more complete angiotensin II antagonism since angiotensin II is generated by other enzymes as well as ACE. Also, valsartan does not affect the metabolism of bradykinin like ACE inhibitors do.[5, 6]

3.3 PHARMACOKINETIC PROFILE OF VALSARTAN:

Absorption

Valsartan is rapidly absorbed orally. After oral administration of Valsartan 80mg capsule and solution formulation in 12 healthy volunteers, maximum plasma concentrations (C_{max}) of Valsartan (1.64mg/l and 3.25 mg/l) were respectively reached in ~ 1-2 h.[1]

Distribution

Valsartan has only limited distribution outside the plasma compartment and is extensively bound to the plasma proteins (94- 97%) and hence is only limited distributed outside plasma compartment. [1]

Metabolism

Valsartan does not require any metabolism in the body to become active. After the oral administration of 80 mg of [^{14}C] - radiolabelled valsartan only one pharmacologically inactive metabolite was found in plasma nearly about 11%. The primary metabolite was identified as valeryl 4-hydroxy Valsartan (M1) accounted for about 9% of the dose and is inactive in hypertension. M1 has about 200 fold lower affinity for the AT1 receptor than valsartan. [7]

Excretion

Valsartan is mainly excreted in faeces via biliary excretion and hence it is not recommended for patients with hepatic dysfunction and biliary cirrhosis. After the administration of an i.v dose in healthy volunteers, plasma clearance of Valsartan was found to be ~2 l/h. [8, 9]

3.4 DOSAGE:

Valsartan is available in the dose range of 10, 20, 40, 80, 160, and 320 mg. All doses of Valsartan have been found to be safe and tolerable.[10]

3.5 CONTRAINDICATIONS:

Valsartan is contraindicated in patients with severe hepatic impairment, liver cirrhosis, and biliary obstruction. In a study conducted it was seen that liver function tests (LFTs), bilirubin levels were found to be raised after the valsartan administration in patients.[11]

IV. PHARMACOSOMES:

Pharmacosomes are amphiphilic, colloidal dispersions of drugs covalently bound to lipids, and may exists as ultra-fine vesicular, micellar, or hexagonal aggregates, depending on the chemical structure of the drug lipid complex. These are the lipid based drug delivery systems that are appropriately elaborated as the colloidal dispersions of drugs having a covalent, electrostatic or hydrogen bonding with lipid. They are rightly termed as "pharmacosomes"due to the linking of a drug (pharmakon) to a carrier (soma). The structure of pharmacosomes is given in Fig. 2 Pharmacosomes are amphiphilic lipid vesicular systems that have shown their potential in improving the bioavailability of poorly water soluble as well as poorly lipophilic drugs. [12]

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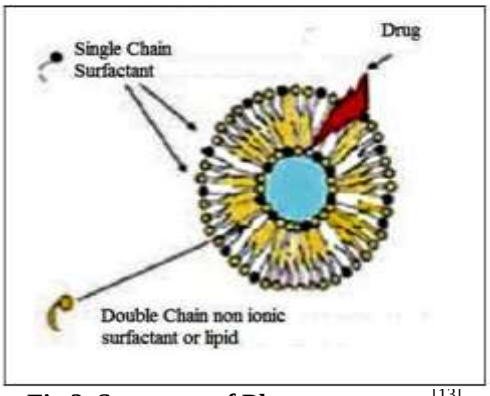

Fig 2. Structure of Pharmacosomes [13]

4.1 Components of Pharmacosomes:

There are three components are drugs, solvent and carriers (lipid).

A. Drugs :

Any drug having an active hydrogen atom (-COOH, - OH,-NH2 etc.) can be esterified to the lipid, with or without spacer chain resulting into amphiphilic complexes. These synthesized amphiphilic complexes (pharmacosomes), facilitate membrane, tissue, or cell wall transfer, in the organism.[14]

B. Lipids:

Phospholipids are principal molecular building block of cell membranes. Two type of phospholipids generally used are phosphoglycerides and spingolipids. The most common phospholipid is phosphotidyl choline molecule.[15]

C. Solvent:

Organic solvent of analytical grade and intermediate polarity is used in development of pharmacosomes. It must be of high purity and volatile in nature. The phospholipids and the drug must be dissolved in the selected solvent. The selection of solvent depends on polarity of the drug and the lipid.[16]

4.2 ADVANTAGES OF PHARMACOSOMES: [17, 18]

Pharmacosomes have certain advantages such as-

1. They are suitable for hydrophilic as well as lipophilic drugs.
2. Entrapment efficiency is high and not affected by encaptured volume and drug-bilayer interactions.
3. No problem is associated with drug incorporation.
4. The physicochemical stability of the pharmacosomes depends upon the physicochemical properties of the drug- lipid complex.
5. Drug can be delivered directly to the site of action.
6. It improves bioavailability especially in case of poorly soluble drugs.
7. No need of removing the free unentrapped drug from the formulation as needed in case of liposomes.
8. There is reduction in adverse effects and toxicity.
9. There is reduction cost of therapy.

4.3 DISADVANTAGES OF PHARMACOSOMES: [19, 20]

Pharmacosomes have certain disadvantages such as-

1. Synthesis of a compound depends upon its amphiphilic nature.
2. Require surface and bulk interaction of lipids with drugs.
3. Require covalent bonding to protect the leakage of drugs and on storage, undergo fusion and aggregation, as well chemical hydrolysis.
4. Pharmacosomes can only encapsulate the water insoluble drugs in relatively small hydrobic regions within membrane bilayer rather than relatively large surface.

4.4 METHOD OF PREPARATION OF PHARMACOSOMES:

In general methods are employed to prepare the pharmacosomes are as follows-

1. Solvent evaporation method / Handshaking method: Firstly a mixture of drug and lipid are dissolved in a volatile organic solvent such as dichloromethane .Thereafter solvent is evaporate using rotatory evaporator in round bottom flask which leaves a thin film of solid mixture deposited on the walls of flask. Then dried film hydrated with aqueous medium & readily gives a vesicular suspension. [21]

2. Ether injection method: In this method solution containing drug-lipid complex is mixed properly and is slowly injected into a hot aqueous medium through gauze needle and vesicles form readily. [22]

3. Anhydrous co-solvent lyophilization method: First of all drug and phospholipids are dissolved in solution of dimethyl sulfoxide containing glacial acetic acid. Then mixture is agitated to get clear liquid and then freeze-dried overnight at condenser

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temperature. The resultant complex is flushed with nitrogen and stored at 4°C. [23]

4. Super critical fluid process: Two different techniques of super critical fluid process are used. Gas anti solvent (GAS) and solution enhanced dispersion by the supercritical fluid (SEDS). Drug and lipid complex are dissolved in a supercritical fluid of CO_2 mixed into the nozzle mixing chamber [24]

4.5 EVALUATION PARAMETERS OF PHARMACOSOMES:

A. Complex Determination:

The formation of complex and conjugate can be determined by the correlation spectrum observed in complex sample with that of discrete constituents and also with their mixture with the help of FTIR spectrum. [25]

B. X-ray power diffraction (XRPD):

It is performed to determine the degree of crystallanity by using the relative integrated intensity of reflection peaks. The integrated intensity is given by the area under curves of the XRPD patterns and it represents the specimen characteristics.[26]

C. Dissolution studies:

Dissolution studies, in vitro are done using various models available for the purpose. The results are assessed on the basis of apprehended activity of the active constituent's therapeutically. In vitro dissolution studies of drug-PC complex as well as plain drug were performed in triplicate in a USP six station dissolution test apparatus, type II at 100 rpm and at 37°C. An accurately weighed amount of the complex equivalent to 100 mg of drug acid was put into 900 mL of pH 6.8 phosphate buffer. Samples (3 ml each) of dissolution fluid were withdrawn at different intervals and replaced with an equal volume of fresh medium to maintain sink conditions. Withdrawn samples were filtered (through a 0.45-mm membrane filter), diluted suitably and then analysed spectrophotometrically. [27, 28]

D. Drug content:

To determine the drug content in drug – pc complex, complex equivalent to drug weighed and added into volumetric flask with suitable solvent. The solution is mixed by means of magnetic stirrer. After 24 hrs suitable dilution drug content is determined UV spectrophotometrically. [29]

E. in- vitro release:

In the bulk, equilibrium reverse dialysis bag technique described here, emulsion is introduced inside the dialysis bag and the continuous (receiver) phase is placed outside. Dialysis bags containing the continuous phase (receiver phase) alone are suspended in a vessel containing the donor phase (diluted emulsion) and the system is stirred. At predetermined time intervals, each dialysis bag is removed and the contents are analysed for released drug. An advantage of this technique is the increase in the membrane surface area available for transport from the donor to the receiver phases. Another advantage of this method is the increased efficiency in terms of staffing as a consequence of the reduction in the number of steps. [24]

F. Scanning Electron Microscopy/Transmission Electron Microscopy:

These techniques can be utilized for studying the surface order of pharmacosomes. The purity grades of the lipid being used and few variables observed during operation (method of preparation, vacuum assigned and rotational speed) alter the shape and size of pharmacosomes. Pharmacosomes are formed of greasy nature if prepared using lower purity grades of lipids resulting in large aggregate formation and those fabricated using lipids of more than90% purity grade show susceptibility to degradation due to oxidation, which affects complex stability. So, 80% purity grade is the commonly used phospholipid grade. [30]

G. Solubility:

The modification in solubility caused by complexation can be evaluated using shake-flask technique. In this technique, the organic phase, that is, 1-octanol and aqueous phase, that is, buffer solution at appropriate pH consisting of drug phospholipid conjugate are consorted, and after constant shaking, equilibrium is maintained at a temperature of 37 °C for 1 day. The aqueous phase is separated and then concentration is determined using UV or HPLC technique. [30]

V. CONCLUSION:

Valsartan is a white coloured crystalline powder that is freely soluble in ethanol, methanol, and acetonitrile and sparingly soluble in water. Valsartan appears in the melting range of 105-110°C. The partition coefficient of Valsartan is 0.033 (log P=1.499), suggesting that the compound is hydrophilic at physiological pH. Valsartan has

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bioavailability of about 25% due to its acidic nature. Valsartan is an effective antihypertensive agent in patients with mild to moderate hypertension. Pharmacosomes are the novel vesicular drug delivery system.Pharmacosomes play an important role in the selective targeting and the controlled delivery of various drugs. From the above review we studiedPharmacosomes its components and various methods of preparation and evaluation parameters of pharmacosomes& conclude that the formulation of pharmacosomes is a better approach for enhancement of bioavailability of valsartan.

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