





## 1.1 SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM

Majority of new drug candidates have poor aqueous solubility. According to an FDA survey conducted between 1995 and 2001, only 9% of the new drug molecules belonged to BCS Class I category (1). The poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra- and inter subject variability, and lack of dose proportionality. To overcome these problems, various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, nanoparticles, solid dispersions, micronization, lipids, and permeation enhancers, liposome, nanosphere and parenteral emulsions. These drug delivery systems have following disadvantages: liposomes often have poor shelf stability and insufficient (for lipophilic drugs) loading; nanosphere have poor loading efficiency and the problem of elimination of residual solvent. Among these, emulsions may offer promising alternative as they provide good biocompatibility, longer shelf life, good solubilization of poorly watersoluble drugs, and high concentration of lipophilic drugs in aqueous media. Among the emulsification methods, the self-microemulsifying drug delivery systems (SMEDDS) are worthy of notice (2). Much attention is given to use of lipid microemulsion in drug delivery. Microemulsions are superior to simple solution or suspension or emulsion in terms of solubilization potential and thermodynamic stability, since they can be manufactured with little energy input (mixing) and have long shelf-life. The microemulsion definition provided by Danielsson and Lindman can be used as a point of reference (3). So microemulsion can be defined as “a system of water oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution”. The advantages of microemulsion over emulsion are that they may exhibit excellent kinetic stability. Another important difference concerns their appearance; emulsions are cloudy while microemulsions are clear or translucent. In addition, there are distinct differences in their method of preparation, since emulsion requires a large input of energy while microemulsions do not.

The definition suggests that self-microemulsifying drug delivery systems (SMEDDS) are not microemulsion, although they may be considered to be closely related systems. A SMEDDS typically comprises a mixture of surfactant, oil and drug (known as the concentrate) which when introduced into the body is rapidly dispersed

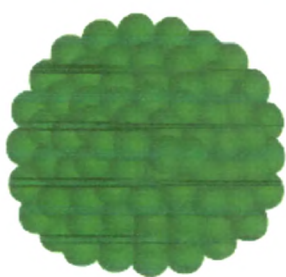
to form droplets of approximately the same size range as those observed in microemulsion systems. Once dispersed, such systems would be expected to behave *in vivo* much the same way as oil-in-water (o/w) microemulsions. Most researchers in the field agree however that for a microemulsion to be formed it is important that the system should contain some definite microstructure, in other words there is a definite boundary between the oil and water phases at which the surfactant is located. In order to gain an understanding for the reasons for microemulsion formation, it is useful to consider the properties of amphiphiles, such as surfactants, in solution. (4). Conventional surfactant molecules comprise a polar head group region and an apolar tail region. On dispersal in water, surfactants self-associate into a variety of equilibrium phases. This self-assembly of surfactant molecules, whether it happens in single solvent phase or in the presence of both oil and water, can lead to solidlike organized structure called “**liquid crystals**” which are nonstoichiometric (5). Hence before we discuss about microemulsion, it is appreciable to get the idea about liquid crystals.

### LIQUID CRYSTALS

As the name suggest, liquid crystals are materials which have properties intermediate to the solid and liquid states of matter. They are true fluids (i.e. they flow readily), but they retain *orientational order* on melting from the solid to the liquid crystal state. This is shown schematically in Figure 1.1 where a solid in the form of a hexagonal crystal lattice melts to form a liquid crystal before finally melting to the normal liquid state. One of the perquisites for a material to form a liquid crystalline state is that the molecules are *geometrically anisotropic*. As the crystal melts, there is a state where the molecules are free to move, but still retain some order- the **liquid crystal state**. In this case, they all point in the same direction and posses ORIENTATIONAL ORDER, but no positional order. It is an orientational order which is characteristic of the liquid crystal state. When the temperature increased further, the molecules eventually have sufficient energy to move completely randomly and no longer possess even orientational order- the liquid state (6).

Liquid crystals come in two basic classifications: *thermotropic* and *lyotropic*. The phase transition of thermotropic depends on temperature, while those of lyotropic liquid crystals depend concentration.

The molecules that make up *lyotropic* liquid crystals are surfactants which are one of components of microemulsion. Henceforth it is important to note that formation of microemulsion is depends on properties and behavior surfactants. When the concentration gets high enough, however, the molecules begin to arrange themselves in hollow spheres, rods and disks called *micelles*. Micelle come in varied sizes, but the smallest once have a diameter about twice as long as the length of hydrocarbon chain with all trans-bonds. As the concentration of amphiphile increases, the micelles become increasingly able to dissolve non polar substances. When these occur the micelles become large and swollen. If they reach a large enough size, the solution becomes cloudy and is called an *emulsion*. At lower concentrations, the swollen micelles are not large enough to interfere with light, but they are still extremely stable and exist in equilibrium. This phase is referred to as a **microemulsion**.

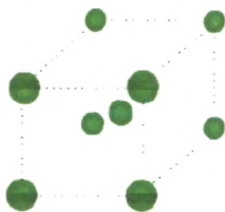


**Spherical micelle**

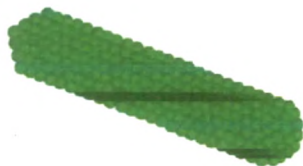


**Cross section**

As the concentration increases, the micelles begin to arrange themselves into loose patterns. At high surfactant concentration micelles are densely packed and are identified as cubic crystal lattice. Rod-shaped micelles often form into hexagonal arrays made out of six rods grouped around a central one for a total of seven, as illustrated in the picture below.



**Cubic liquid crystal**



**Hexagonal liquid crystal**

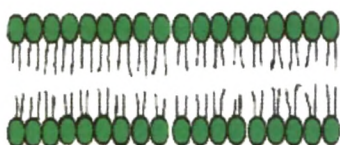


**Rod micelles close-up**

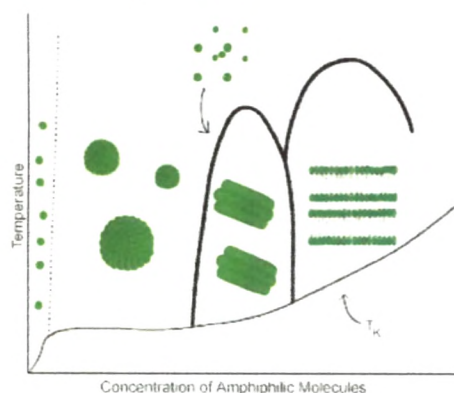




If water, a hydrocarbon, and a surfactant are mixed together, sometimes micelles form with opposite orientation of polar head and non polar tail which known as *reverse micelle*. These entrap water molecule inside oil droplet and form microemulsion known as a *ringing gel*. (7). Some ringing gels of cuboid liquid microstructure are available as cuboid liquid microstructure e.g. Contreheuma Gel Forte N, Trauma Dolgit Gel and Dolgit Microgel (ibuprofen based and introduced in 1996).



At even higher concentrations the molecules move into another liquid crystalline phase - the lyotropic liquid crystal *bilayer* or *lamellar phase*. Liquid crystal bilayers on the interface of emulsified droplets stabilize the emulsion and are capable of incorporating large amount of water. They are often preferable for parentral and dermatological emulsions.



The generic sort of phase diagram shows the changes in structure as concentration of amphiphilic molecules increases. The concentration, at which micelles form in solution called the **critical micelle concentration (CMC)**, is shown as a dotted line. The dark line below which few liquid crystals form represents a boundary

temperature, referred to as the Krafft temperature. Below the Krafft temperature, a few liquid crystals may be suspended in the solution, but for the most part the amphiphilic molecules stay widely distributed. Ultimately this orientation of amphiphile (surfactant) molecule serves to optimize the salvation requirement of surfactant and minimize the free energy of over all system. When surfactants are incorporated into immiscible mixture of oil and water, the surfactant molecule locate at oil/water interface which is thermodynamically favorable. This results in number of phases structured on microscopic or macroscopic scale which is an optically isometric microemulsion phase.

### SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS (SMEDDS)

SMEDDS is an isotropic mixture of oil and surfactant which gets emulsified in

aqueous media on gentle agitation. However third component is added as cosurfactant to this mixture to decrease emulsification time and droplet size achieved after self-emulsification. These differ from conventional emulsion as these are clear and thermodynamically stable systems.

Although formation of LC phase during self-emulsification is proved, the correlation between spontaneous emulsification and LC formations is still not definitely established. Self emulsification is very rapid and spontaneous process with LC phase formation and subsequent rupture taking place within seconds and often it is not possible to observe and study the intermediate LC phase under normal experimental conditions.

Self-emulsifying/ microemulsifying drug delivery systems (SED DS/SMEDDS) can be described as isotropic solutions of oil and surfactant, which form o/w (micro) emulsions on mild agitation in the presence of water. Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification (8, 9). SED DS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SED DS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles

### ***Mechanism(s) of Absorption Enhancement***

In case of lipophilic drug absorption from SMEDDS or o/w microemulsions improved drug dissolution appear to be predominant mechanism by which these systems improve oral absorption. One of the proposed mechanisms is based on enhancer (medium-chain glycerides)-induced structural and fluidity changes in the mucosal membrane thus resulting in significant permeability changes. Supporting to this, several in vitro studies have shown that medium-chain glycerides markedly affect the permeability of paracellular markers. The several factors, both physical and physiological, that may affect the drug absorption from this systems that include: 1) whether drug is formulated in an oil or emulsified form and in the later form how it is

distributed between the two phases, 2) the absorption pathway of the drug, 3) the nature and particle size of the *in vivo* emulsion, 4) the role of surfactants/enhancers 5) the metabolic pathway of oil and 6) the tendency of the formulation to slow gastric motility and to promote emptying of the gall bladder. The literature reports that the absorption of drugs from oral dosage forms containing oil(s)/lipid(s) is sometimes increased by the presence of a lipophilic solvent and sometimes remains unaffected or reduced if oil is non-digestible. So it can be predicted that effect of lipid(s) on drug absorption is dependent on the particular combination of drug and lipid involved. The nature of drug and that of lipid, as well as aqueous and lipid solubility of drug are crucial factors that control drug release/absorption from lipid-based dosage formulation.

For SMEDDS, it has been shown that the oil/water partition coefficient of the drug and droplet size can modulate drug release. The droplet size upon dilution with aqueous media is primarily controlled by the nature and concentration of the emulsifier, and phase diagrams of the oil/nonionic surfactant/ drug can be constructed to identify regions where maximum self-microemulsification occurs. The higher the concentration of emulsifier, the smaller the droplet sizes of the resulting emulsion and the faster the drug release. The combination of small droplets along with a low oil/water partition coefficient will allow for an optimum drug release from SMEDDS. Similarly, drug release from microemulsion (o/w and w/o), depends on a number of process parameters, such as oil/aqueous phase ratio, the droplet size, the distribution of drug in the phases of microemulsion system and its diffusion rate in both phases. It is observed that the higher the water/oil partition coefficient the higher the bioavailability. It is therefore not surprising that not all water soluble or insoluble drugs can be formulated in water-in-oil microemulsion with a concomitant improvement of their intestinal absorption. Though direct determination of drug distribution between the aqueous and oil phases of microemulsion is difficult water/oil partitioning studies using the aqueous and oil phases of the corresponding microemulsion should be conducted and correlated to the observed oral bioavailability and/or *in vitro* permeability (10).

#### **SELECTION OF ESSENTIAL COMPONENTS FOR SMEDDS**

SMEDDS are easily manufactured and physically stable isotropic mixture of oil,

surfactant, cosurfactant and drug substances that are suitable for oral delivery in soft and hard gelatin capsules. Self-emulsifying formulations are easily dispersed in the GI tract, where the motility of the stomach and small intestine provides the agitation necessary for emulsification. SMEDDS forms transparent microemulsion with a size of less than 100 nm (9). Small lipid droplet size and associated greater lipid surface are produced by SMEDDS formulation facilitates lipid digestion resulting in more rapid incorporation of the drug into the bile salt mixed micelles. The ultimate result is an increase in the degree and uniformity of drug absorption relative to that associated with simple lipid solution of drug (11). The improve drug absorption provided by SMEDDS is depending upon maintenance of drug in solubilized state until it is absorbed from GIT (12). In intense where lipid vehicle hydrolysis rate exceeds that of drug absorption, luminal drug precipitation can occur resulting in suboptimal and more variable drug absorption (13).

Self-emulsification has been shown to be specific to the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; and the temperature at which self-emulsification occurs. In support of these facts, it has also been demonstrated that only very specific pharmaceutical excipient combinations could lead to efficient self-emulsifying systems (14, 15, 16).

#### *Oils*

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride (17). Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Furthermore, edible oils which could represent the logical and preferred lipid excipients choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties (10). They offer



formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semi synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SEOFs (18).

#### *Surfactant*

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, the most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolized glycerides and polyoxyethylene 20 oleate (Tween 80). Safety is a major determining factor in choosing a surfactant (10, 19, 20). Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. The surfactant involved in the formulation of SEDDS should have a relatively high HLB and hydrophilicity so that immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media (good self-emulsifying performance) can be achieved (9, 21). Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS (10, 18). The formulation of w/o microemulsions for use as SEDDS or SMEDDS has been investigated using blends of low and high HLB surfactants, which were commercially available and pharmaceutically acceptable, typically sorbitan esters and Tween 80. The oil phase comprised long or medium chain length glycerides (22).

#### *Co-solvents*

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as, ethanol, propylene glycol (PG), and polyethylene glycol (PEG) are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in microemulsion systems. On the other hand, alcohols and other volatile co-solvents

have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatin capsules in conventional SEDDS leading to drug precipitation. Thus, alcohol-free formulations have been designed (10), but their lipophilic drug dissolution ability may be limited.

#### ***Mechanism of self-emulsification***

The mechanism by which self-emulsification occurs is not yet well understood. Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion (23). Emulsification occurs spontaneously with SEDDS because the free energy required to form the emulsion should be low and either positive or negative (10). It is necessary for the interfacial structure to show no resistance against surface shearing in order for emulsification to take place (24). The ease of emulsification was suggested to be related to the ease of water penetration into the various LC or gel phases formed on the surface of the droplet (25). The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. This is followed by the solubilization of water within the oil phase as a result of aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interphase. Further aqueous penetration will lead to the formation of the dispersed liquid crystal (LC) phase. In the end, everything that is in close proximity with the interface will be LC, the actual amount of which depends on the surfactant concentration in the binary mixture. Thus, following gentle agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruption and droplet formation. As a consequence of the LC interface formation surrounding the oil droplets, SEDDS become very stable to coalescence (25, 26).

#### **FORMULATION CONSIDERATION OF SMEDDS**

##### ***Drug incorporation into SMEDDS***

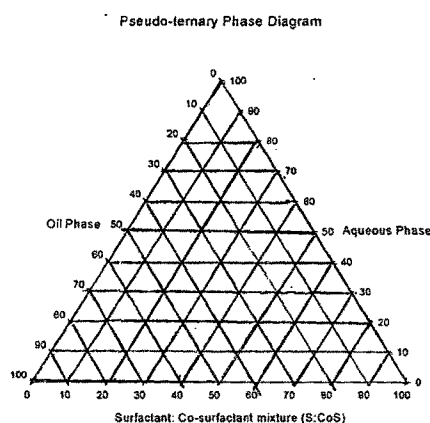
The efficiency of drug incorporation into a SMEDDS is generally specific to each case depending on the physicochemical compatibility of the drug/system. In most cases, there is an interference of the drug with the self-emulsification process up to a certain extent leading to a change in the optimal oil/surfactant ratio (27, 28). The interference of the drug compound with the self-emulsification process may result in a

change in droplet size distribution that can vary as a function of drug concentration. It should be pointed out that emulsions with smaller oil droplets in more complex formulations are more prone to changes caused by addition of the drug compound (29). Hence, the design of an optimal SMEDDS requires pre-formulation solubility and phase diagram studies to be conducted.

#### ***Solubility of Drug in excipients***

The primary consideration in selecting excipients for SMEDD lies in identifying excipients combination which will solubilize the entire dose of drug in volume acceptable for unit oral administration. Drug must be physically and chemically stable with the excipients. Drug release characteristic must be constant with the age of formulation. To form SMEDDS lipophilic surfactants (HLB <12), are employed when grater drug solubilizing capacity is desired inn formulation. Such surfactants facile more self-microemulsification and smaller droplet size but these increase risk of drug precipitation as hydrophilic components may separates from oil phase during dispersion in the GIT leading to a loss of drug solubilizing capacity. (30)

#### ***Phse Diagram Study***



Excipients combinations yielding SMEDDS formulations are identified by construction of pseudo-ternary phase diagram. Pseudo-ternary phase diagram can be represented in a triangular format (triangle) which has three coordinates. Each coordinate represents one component of microemulsion system. A typical pseudo-ternary phase diagram illustrating the different phases on respective coordinates is shown in figure above. Each coordinate is representing one phase present in the microemulsion system viz. (1) Oil phase (O component), (2) Surfactant: Cosurfactant

phase S: CoS component), and (3) Aqueous phase A component). Each coordinate also represents 0 to 100% concentration of each of the phases in the increment of 10%. In case where four or more components are investigated to formulate microemulsion system, pseudo-ternary phase diagram is used wherein each corner typically represents binary mixture of two components such as surfactant/cosurfactant, water/drug, or oil/drug. Phase diagram is an imperative tool to comprehensively study the microemulsion system and its phase behavior although construction phase diagram is highly time consuming exercise. In addition to that, phase diagram represents 36 ME points hence, for each ratio or a microemulsion system, a number of experiments including excipients and drug are required to expansively study the phase behavior (31). However, as a conservative approach, it is a traditional scientific practice to appropriately blend titration technique with phase diagram approach together in order to save time and to make it commercially viable option. In this investigation, an approach derived on the basis of titration technique followed by construction of phase diagram was used. The experiments conducted are represented either in form of two-dimensional phase diagram or three-dimensional phase diagram. Microemulsion has four basic components; oil phase (O component), surfactant (S component), Co-surfactant (CoS component) and aqueous phase (A component). ME is represented by a four dimensional point.

As a practical example, mixtures consisting of different amounts of the selected excipients are evaluated for their self-emulsifying properties by addition for pharmaceutically relevant amount of formulation 250 mL of water or biorelevant, stimulated physiological fluid. The resulting dispersion is examined by direct visualization and by dynamic light scattering to accurately determine the lipid droplet size.

## FORMULATION EVALUATION

Gross visual evaluation of the resulting emulsions has proven to be a reliable means of estimating the oil droplet size. Transparent to slightly bluish, opalescent dispersion possess oil droplet size between 20 nm and 40nm and are thus classified as microemulsion (30). The efficiency of self-emulsification could be estimated by determining the rate of emulsification and droplet size distribution. Turbidity measurements can be carried out to determine the rapid equilibrium reached by the

dispersion and the reproducibility of this process (32). The droplet size determines the rate and extent of drug release as well as absorption. Photon correlation spectroscopy (PCS) is a useful method for determination of emulsion droplet size (33) especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method. Pseudo-ternary phase diagrams, in which the ratio of two or more of the components is kept constant while typically three other excipients concentrations are varied, can be constructed to describe such systems. Normally, the oil, surfactant and co-surfactant or co-solvent ratios are changed in an attempt to identify the self-emulsifying regions and/or other types of dispersions (34, 35). Finally, appropriate experimental conditions (optimum excipient concentrations) are established by means of ternary diagram studies allowing formulation of the required SEDDS and/or SMEDDS. The characterization of SMEDDS can be made utilizing dye solubilization, dilutability by the dispersed phase excess and conductance measurements (10). The charge of the oil droplets of SEDDS is another property that should be assessed. The charge of the oil droplets in conventional SEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1–3%, will yield SMEDDS with a positive  $\xi$ -potential value of about 35–45 mV (36, 37).

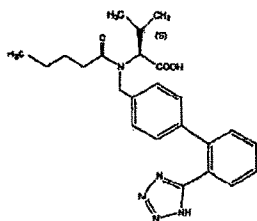
#### **IN VIVO STUDIES WITH SMEDDS**

Bioavailability study is efficiency measurement tool for SMEDDS. Low particle size and effect of triglycerides increase the drug bioavailability form SMEDDS formulation ranged form 1.5-fold to approximately 7-fold is reported. (38, 39) The results of these studies suggest that the physiological properties of the drug, as well as the excipients selected for the formulation, appear to determine the bioavailability enhancing potential of particular formulation for a given drug substance.



## 1.2 DRUG PROFILE

### 1.2.1 VALSARTAN



Valsartan is a nonpeptide, orally active and specific angiotensin II antagonist acting on the AT<sub>1</sub> receptor subtype. Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'- biphenyl]-4-yl]methyl]-*L*-valine. Its empirical formula is C<sub>24</sub>H<sub>29</sub>N<sub>5</sub>O<sub>3</sub>, its molecular weight is

435.5, and its structural formula is shown to left side. Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

#### ***Physiochemical Properties*** (40)

State: solid

Melting Point: 116-117°C

Predicted water solubility: 2.34e-02 mg/mL

Log P/Hydrophobicity: 5.8

Pka: 4.73 and 3.9 (weak acid)

#### ***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, with effects that include vasoconstriction, stimulation of synthesis and release 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 to the AT<sub>1</sub> 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. There is also an AT<sub>2</sub> receptor found in many tissues, but AT<sub>2</sub> is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. The increased plasma levels of angiotensin II following AT<sub>1</sub> receptor blockade with valsartan may stimulate the unblocked AT<sub>2</sub> receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of

hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Since valsartan does not inhibit ACE (kininase II) it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

### ***Pharmacokinetics***

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for valsartan is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration ( $C_{\max}$ ) by about 50%. AUC and  $C_{\max}$  values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

### ***Metabolism and Elimination***

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

### ***Distribution***

The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin (41).

### ***Side Effects***

Along with its needed effects, a medicine may cause some unwanted effects.

## CHAPTER I

### INTRODUCTION

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Although not all of these side effects may occur, if they do occur they may need medical attention.

#### **Less common**

Bloody urine; cold sweats; confusion; decreased frequency/amount of urine; difficult breathing; dizziness, faintness, or lightheadedness when getting up from lying position; fainting; increased blood pressure; increased thirst; irregular heartbeat; loss of appetite; lower back/side pain; nausea; nervousness; numbness or tingling in hands, feet or lips; shortness of breath; swelling of face, fingers, lower legs; troubled breathing; unusual tiredness or weakness; vomiting; weakness or heaviness of legs; weight gain.

#### **Rare**

Chills, fever, or sore throat; swelling of face, mouth, hands, or feet; trouble in swallowing or breathing (sudden).

### ***Dosage and Administration***

#### **Hypertension**

##### **Adults**

PO Initial dosage: 80 or 160 mg once daily. Maintenance dosage: 80 to 320 mg once daily.

##### **Children 6 to 16 yr of age**

PO Initial dosage: 1.3 mg/kg (up to 40 mg) once daily. Adjust dose based on BP response. Dosages higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in children.

#### **Heart Failure**

##### **Adults**

PO Initial dosage: 40 mg twice daily; titration to 80 and 160 mg twice daily should be done to the highest dose, as tolerated by the patient (max dose, 320 mg/day).

#### **Post-myocardial infarction**

##### **Adults**

PO Initiate 12 h after MI at 20 mg twice daily. Titrate within 7 days to 40 mg twice daily with additional titrations to a target maintenance dosage of 160 mg twice daily, as tolerated by the patient.

### Hepatic/Renal Function Impairment

Exercise care with dosing in patients with hepatic or severe renal function impairment.

#### General Advice

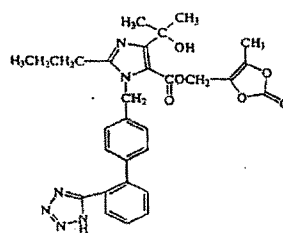
Valsartan may be administered with or without food (42).

### 1.2.1 OLMESARTAN

Olmesartan medoxomil is a prodrug and hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT<sub>1</sub> subtype angiotensin II receptor antagonist. Olmesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Olmesartan medoxomil is described chemically as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is C<sub>29</sub>H<sub>30</sub>N<sub>6</sub>O<sub>6</sub> and its structural formula is:

Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol.



#### Physiochemical Properties (40)

State: solid

Melting Point: 175-180°C

Predicted water solubility: 7.75e-03 mg/mL

Log P/Hydrophobicity: 5.9

pKa: 8.6

#### 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, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT<sub>2</sub> receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Similar to valsartan, olmesartan medoxomil does not inhibit ACE (kininase II) it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

### ***Pharmacokinetics***

#### ***General***

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (C<sub>max</sub>) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

#### ***Metabolism and Excretion***

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile.

#### ***Distribution***

The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly



## CHAPTER I

### INTRODUCTION

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bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses. In rats, olmesartan crossed the blood-brain barrier poorly, if at all. Olmesartan passed across the placental barrier in rats and was distributed to the fetus. Olmesartan was distributed to milk at low levels in rats.

#### ***Pharmacodynamic***

Olmesartan medoxomil doses of 2.5 to 40 mg inhibit the pressor effects of angiotensin I infusion. The duration of the inhibitory effect was related to dose. Plasma concentrations of angiotensin I and angiotensin II and plasma renin activity (PRA) increase after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. (41).

#### ***Side Effects***

##### **Cardiovascular**

Tachycardia.

##### **CNS**

Dizziness; fatigue; vertigo; insomnia.

##### **Dermatologic**

Rash.

##### **Gastro-Intestinal**

Abdominal pain; dyspepsia; gastroenteritis; nausea.

##### **Genitourinary**

Urinary Tract Infection.

##### **Metabolic**

Hypercholesterolemia; hyperlipemia; hyperuricemia.

##### **Miscellaneous**

Chest pain; pain; peripheral edema; arthritis; myalgia; skeletal pain

#### ***Dosage and Administration***

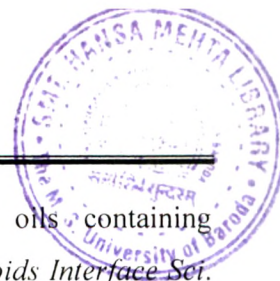
##### **Adults**

*PO Start with 20 mg once daily; after 2 wk, dosage may be increased to 40 mg/day if further reduction in BP is needed (42).*

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