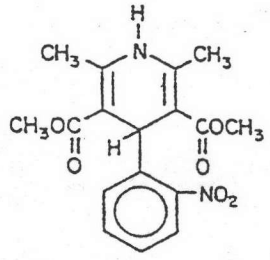
CHAPTER II

REVIEW OF LITERATURE

Nifedipine

A. Physicochemistry

Chemical structure of nifedipine (Scheme 1)



Scheme 1

Empirical formula : $C_{17}H_{18}N_2O_6$

Molecular weight : 346.34

Chemical name : 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester.

: Dimethyl 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate (The United States Pharmacopoeial, Inc., 1990)

Description : A yellow crystalline powder. Melting

point 171°C to 175°C (Moffat et al, eds., 1986).

Solubility : Easily soluble in acetone, chloroform; less soluble in ethanol. Practically insoluble in water. Very light sensitive in solution. (Windholz et al., ed., 1983).

B. Pharmacology

Nifedipine has pharmacologic actions similar to those of other calcium-channel blocking agents. The principle physiologic action of nifedipine is to inhibit the transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells, without changing serum calcium concentrations (McEvoy, ed., 1989).

C. Pharmacokinetics

Absorption : Approximately 90% of an oral dose of nifedipine is rapidly absorbed from the GI tract following oral administration. Only about 65-75% of an oral dose reaches systemic circulation as unchanged drug since nifedipine is metabolized on first pass through the liver. Peak serum concentrations are usually reached within 0.5-2 hours after oral administration.

Distribution : Binding of nifedipine to plasma proteins is concentration dependent and ranges from 92-98%.

Elimination : Plasma half-life of nifedipine is 2-5 hours. The drug is rapidly and completely metabolized in the liver to inactive metabolites. Approximately 70-80% and 15% of an oral dose of nifedipine are excreted as metabolites in urine and feces, respectively (McEvoy, ed., 1989).

D. Uses and administration

Nifedipine is used in the treatment and prophylaxis of angina pectoris and in the treatment of mild to moderate hypertension. The usual oral dose is 10 mg three times daily. It may also be administered sublingually or buccally by directing the patient to bite the capsule for a more rapid effect. Nifedipine may be given as a sustained-release tablet in a dose of 10 to 40 mg twice daily in hypertension. Nifedipine may be administered by injection via coronary catheter for the treatment of coronary spasm during coronary angiography and balloon angioplasty (Reynolds, ed., 1989).

E. Adverse effects

The most common adverse effects of nifedipine are associated with the vasodilatory action, such as dizziness, flushing, headache, hypotension, and peripheral edema.

F. Dosage forms

Capsule 5, 10 mg of nifedipine (Adalat$^{(R)}$).

Injection 100 μg/ml of nifedipine (Adalat IC$^{(R)}$).

Tablet, sustained release 10 mg of nifedipine (Adalat Retard$^{(R)}$) (Reynolds, ed., 1989).

Photolysis

Consideration of the decomposition of pharmaceutical compounds resulting from the absorption of radiant energy in the form of light has become more important in recent years because of the complex chemical structure of many new drugs (Lachman, Lieberman and Kanig, eds., 1986).

Mechanism of photolysis

Two major mechanisms can be identified (Conners, Amidon and Stella, eds., 1986; Lin and Lachman, 1969; Stewart and Tucker, 1985):

(a) primary photochemical decomposition;

(b) photosensitiser or secondary photochemical decomposition.

Primary photochemical reactions occur when the drug molecule (A) itself absorbs energy from the radiation source, then an unstable exited state species (A^*) is produced (Eq.1). The absorbed energy can be lost either by a radiative mechanism in which the energy is given off in several ways :

(a) as thermal energy producing an increase in temperature in the surrounding medium (Eq.2);

(b) as fluorescence or phosphorescence where the absorbed energy is re-emitted as longer wavelength radiant energy (Eq. 3); or

(c) as chemical energy initiating chemical decomposition (Eq. 4).

The whole process can be defined by Equations 1-4.

$$A \xrightarrow{h\nu} A^* \qquad \text{(Eq. 1)}$$

$$A^* \xrightarrow{k_1} A + \text{heat} \qquad \text{(Eq. 2)}$$

$$A^* \xrightarrow{k_2} A + h\nu' \qquad \text{(Eq. 3)}$$

$$A^* \xrightarrow{k_3} \text{product(s)} \qquad \text{(Eq. 4)}$$

The potential for decomposition of a drug will be greater at lower wavelengths since the energy of radiation is related to wavelength by :

$$E = h\nu \qquad \text{(Eq. 5)}$$

$$\nu = c/\lambda \qquad \text{(Eq. 6)}$$

where E = energy absorbed,

h = Planck's constant (6.625×10^{-27} erg-s),

ν = frequency of the radiation in Hz (s^{-1}),

c = velocity of light,

λ = wavelength.

Thus the shorter the wavelength (λ) or the higher the frequency (ν), the greater is the energy absorbed. Consequently, drug degradation is more likely to occur when radiation is absorbed in the ultraviolet and lower visible regions of the spectrum. The chemical reactions occurring are complex but include oxidation-reduction, ring rearrangement and modification, and polymerisation.

In photosensitiser or secondary photochemical reactions, the energy is absorbed by non-drug molecules (B) which impart their increased energy to the drug molecules (A) with subsequent degradation (Eqs. 7,8). The molecules absorbed radiant energy are called photosensitisers and act as catalyst for drug decomposition.

$$B \xrightarrow{h\nu} B^* \qquad \text{(Eq. 7)}$$

$$B^* + A \longrightarrow A^* + B \qquad \text{(Eq. 8)}$$

The kinetics of photochemical reactions is more complicated than the kinetics of thermal reactions (Lachman, Lieberman and Kanig, eds., 1986). This is due to (1) the complex nature of most photochemical reactions (Lin and Lachman, 1969); (2) various factors which include formulation factors (nature of solute, solvent, pH, buffer type, concentration and excipients) and storage factors (radiation sources, time and intensity of irradiation, temperature and packaging) (Stewart and Tucker, 1985) and (3) the photochemical reaction may be enhanced by, inhibited by, or independent of simultaneous thermal reactions (Lin and Lachman, 1969).

As a result of the complexity of photolytic reactions, zero-order, first-order and second-order are possible in photodegradative reactions (Lachman, Lieberman and Kanig, eds., 1986). Photolysis reactions are usually associated with oxidation because the latter class of reaction is often initiated by light (Banker and Rhodes, eds., 1990; Mollica, Ahuja and Cohen, 1978).

Prevention of photolytic reactions

For drugs degraded by photolysis, the use of appropriate light resistant containers offers the best form of protection against decomposition. Generally amber bottles will restrict the incident energy below 470 nm (Lachman, Swartz and Cooper, 1960). In addition, depending on the type of chemical reaction caused by light absorption, the formulation can be manipulated to stabilize the drug (Stewart and Tucker, 1985).

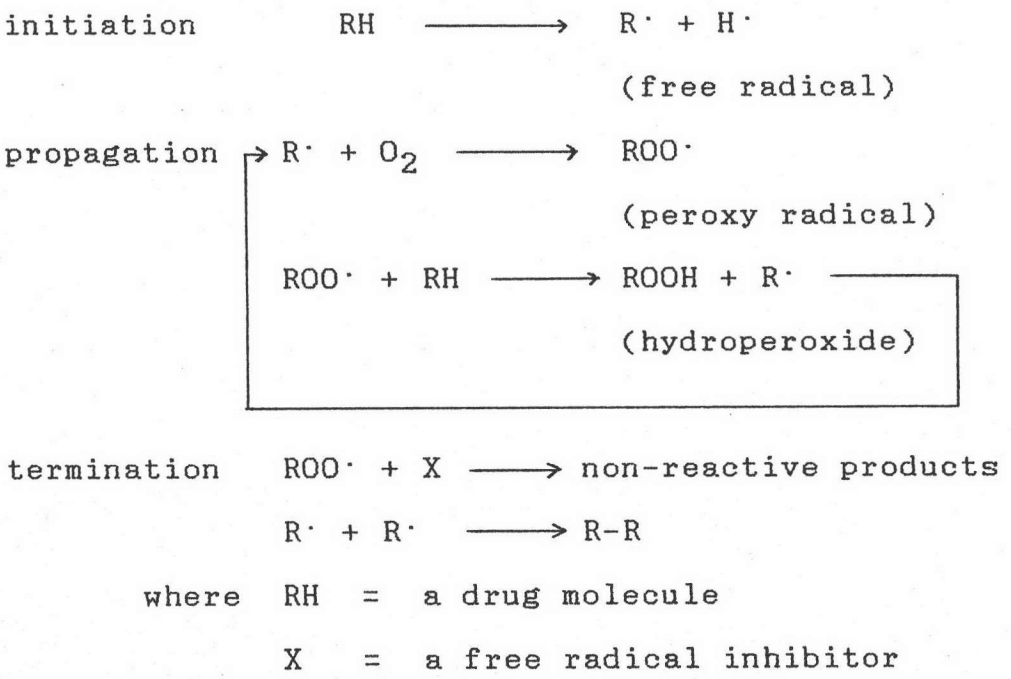
Oxidation

Oxidation is one of the major causes of drug instability. Two basic mechanisms of oxidation exist :

(a) autoxidation which involves reaction with molecular oxygen, chain reactions and free radical formation; and

(b) the reversible loss of electrons without the addition of oxygen.

(a) Autoxidation occurs in three phases :- initiation, propagation and termination, as in scheme II (Stewart and Tucker, 1985).



Scheme II

Initiation process is catalyzed by heat and light (Mollica, Ahuja and Cohen, 1978). In addition, autoxidation is catalyzed by hydrogen ion concentration, trace metals or peroxides and presence of oxygen (Akers, 1982; Stewart and Tucker, 1985).

(b) Oxidation occurs by the reversible loss of electrons without the addition of oxygen. This process of oxidation involves the transfer of electrons and protons. A chemical oxidation-reduction half-reaction can be expressed by :

reduced form $\rightleftharpoons$ oxidized form + n electrons (Eq.9)

The Nernst equation is used to compute standard oxidation potential (E^o) (Akers, 1982). The greater the standard oxidation potential of the cell, i.e., the greater the difference between the oxidation and reduction half-cell potentials, the more readily will oxidation occur (Stewart and Tucker, 1985).

Antioxidants

Antioxidants are added to pharmaceutical formulations as stabilizer against oxidation of the drug. Mechanisms of antioxidation include (Akers, 1982) :

(a) preferentially undergoing oxidative degradation in place of the drug because of the higher standard oxidation potential (E^o) of the antioxidant; e.g., water-soluble antioxidants like ascorbic acid and sulfurous acid salts,

(b) serving as an acceptor of the free radical and inhibiting the free radical chain reaction process; e.g., water-insoluble antioxidants like propyl gallate and butylated hydroxy toluene,

(c) retarding the formation of free radicals; e.g., metal sequestering agents.

In addition, antioxidants can be classified as (a) primary antioxidants, (b) reducing agents, and (c)

antioxidant synergists (Akers, 1982; Stewart and Tucker, 1985).

(a) Primary antioxidants interfere with the propagation step of autoxidation reactions. Thus, primary antioxidants are only useful to protect drugs degraded by autoxidation, e.g., propyl gallate, etc.

(b) Reducing agents are effective against both autoxidation and oxidation due to reversible loss of electrons, e.g., ascorbic acid and sulfurous acid salts.

(c) Antioxidant synergists possess little inherent antioxidant activity but they can be used to assist drug stabilization in conjunction with antioxidants, e.g., ethylenediaminetetra acetic acid (EDTA).

Light Stability Testing of Pharmaceuticals

A. Sources of light

Natural daylight (sunlight) provides radiations of a continuous spectrum. The solar radiation has been confined mostly to the infrared and visible regions of the spectrum. Only a part of the ultraviolet light adjacent to the visible region has been observed. This is because the earth's atmostphere absorbs the shorter ultraviolet radiations and thereby the spectrum of the

sun terminates quite sharply at about 300 nm (Lin and Lachman, 1969). Sunlight is varied not only from day to day, but hour to hour. Because of this problem, a few sunlight stability test are studied (Bundgaard, Norgaard and Nielsen, 1988; DeMerre and Seibold, 1951).

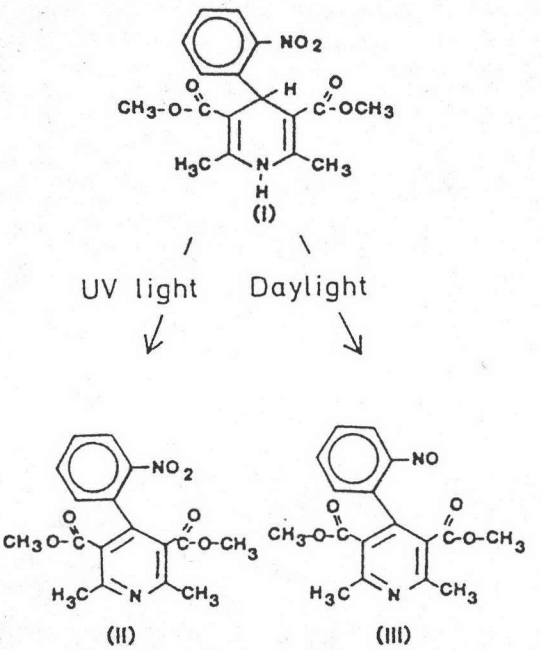
In order to control, diminish or eliminate the effect of variables, various artificial light sources have been developed with a spectral energy distribution intended to simulate that of sunlight. Sources such as carbon arc lamps (Narurkar et al., 1986), mercury vapor lamps (Akimoto, Nakagawa and Sugimoto, 1985; Matsuda, Itooka and Mitsuhashi, 1980), tungsten lamps (Kostenbauder, DeLuca and Kowarski, 1965), xenon lamps (Thoma and Klimek, 1985 b) and fluorescent lamps (Hung et al., 1988; Lachman, Swartz and Cooper, 1960). and monochromatic light sources have been used (DeMerre and Seibold, 1951).

B. Light model systems

Different light model systems have been used to simulate the light degradation of drug substances such as (a) light stability cabinet which fabricated by Lachman and Cooper (Lachman and Cooper, 1959), (b) Fade-ometer (Eble and Garrett, 1954; Narurkar et al., 1986), (c) Rayonet Photochemical Reactor (Gu, Chiang and Johnson, 1988), and (d) "HPUV(R)" light stability cabinet (Habib and Asker, 1989).

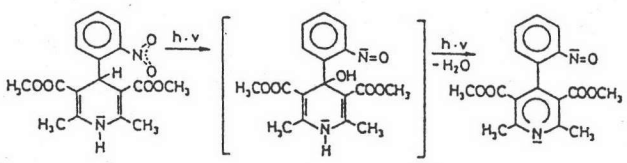
Stability Studies of Nifedipine

Nifedipine is a dihydropyridine derivative (I) (Iwanami et al.,1979). It undergoes facile photochemical oxidation when exposed to light. Depending on the source of irradiation, two photo-oxidation products of nifedipine have been reported (Jacobsen, Pedersen and Mikkelsen, 1979; Majeed et al., 1987; Pietta, Rava and Biondi, 1981). One is the 4-(2′-nitrophenyl)-pyridine homologue (II) elicited by ultraviolet light, and the other is the 4-(2′-nitrosophenyl)-pyridine homologue (III) caused by daylight irradiation (scheme III).



Scheme III

The mechanism of photo-oxidation of nifedipine was proposed to be an intramolecular redox reaction (Al-Turk et al., 1988; Thoma and Klimek, 1985 a). The nitro group on the aromatic ring is considered to absorb light energy to afford its n-π^* excited state, which has radical-like activity (scheme IV).



Nifedipine excited state Oxidation product

Scheme IV

Al-Turk et al. (1988) have concluded that the nitro group is required for the photo-oxidation of nifedipine and the structural requirement for the nitro group of the nitrophenyl-1,4-dihydropyridine to be in the ortho position.

After exposure to fluorescent light, UV spectrum of oxidized form is different from which of the reduced form and the reduced form is deduced to be the non-aromatic nitrophenyl-dihydropyridine compound and the oxidized form is the compound resulting from conversion to the fully aromatic nitrosophenyl-pyridine derivative (Al-Turk et al., 1988).

The photo-oxidation of nifedipine is influenced by several factors : concentration of solution and solvent effects, where as temperature (at about 50°C) and ionic strength have no influence on stability (Thoma and Klimek, 1985 b). Nifedipine crystals are more stable than its solution (Al-Turk et al., 1988; Thoma and Klimek, 1985 b). Al-Turk et al. (1988) have found that photo-oxidation of nifedipine is influenced by pH of solution.

Nifedipine solution is affected by light of wavelength below 450 nm (Thoma and Klimek, 1985a), and also, nifedipine tablet is sensitive to light over the range of 340-420 nm (Sugimoto et al., 1983). The photo-degradation rates under different light sources were found to differ from one another because of the difference in energy distribution (Akimoto et al., 1988; Thoma and Klimek, 1985 b). Majeed et al. (1987) have concluded that the maximum rate of the photo-oxidation was at the highest light intensity.

Tucker, Minty and MacGregor (1985) have found that the red blood cells seem to be acting as a light filter. The rate of drug breakdown is less than 2% per hour compared to 25% per hour in plasma. However, plasma has a small light protective effect as the rate of decomposition in plasma is significantly lower than that in water.

The photo-degradation of nifedipine tablets was studied (Sugimoto et al., 1983). Photolysis of nifedipine without film or covered with transparent polyethylene film containing UV absorber was rapid. The polyethylene colored films or opaque gelatin films prevented the decomposition of nifedipine slightly.

Film coating of nifedipine by combining both titanium dioxide and tartrazine in a film formulation was concluded that it could sufficiently assure the photostability of nifedipine in the ordinary range of film thickness (50-100 μm) being applied to commercial dosage forms (Teraoka, Matsuda and Sugimoto, 1988).

In addition, the effect of an antioxidant : sodium bisulfite was studied on photostability of nifedipine solution (Al-Turk et al., 1988).

Analysis of Nifedipine

The analytical procedures for determination of nifedipine and its oxidized degradation products were reported using high performance liquid chromatography (Pietta, Rava and Biondi, 1981), gas chromatography (Jacobsen, Pedersen and Mikkelsen, 1979), gas liquid chromatography (Dokladalova et al., 1981; Tucker, Minty

and MacGregor, 1985). In addition, a direct and simple spectrophotometric method for simultaneous determination of both nifedipine and its oxidized degradation product was proposed by Al-Turk et al. (1989).