CHAPTER II
LITERATURE REVIEW

I. Solid-state stability

The important factors which usually influence the stability of solids are, temperature, moisture and light. Solids can expose to these factors since in the preformulation stage through the production stage, distribution stage and storage. The principles of instability of solids are the pharmacological ineffectiveness and the adverse effects that occur.

A. Effect of Moisture

The physical and chemical properties of pharmaceutical solids are critically dependent on the presence of moisture. Some of the properties of pharmaceutical influenced by the presence of moisture are, for example, chemical stability, crystal structure, powder flow, compaction, lubricity, dissolution rate and polymer-film permeability. Moreover, some of unit operations, namely, wet granulation, extrusion, spheronization, tray drying, freeze drying, spray drying, fluid-bed drying, tabletting and aqueous film coating are obviously dependent on the amount and state of moisture present too (Carstensen, 1995).

1. Amount of moisture present

There are three types of amount of moisture present. First, bulk-moisture amount, is where the number of moisture moles is higher than that of drugs moles present and where the moisture acts as a stoichiometrically excessive solvent. Second, semi-bulk amount, where the number of moisture moles is

nearly the same as that of drugs, some moles of drugs will not contact with moisture. The last, moisture adsorbed in small amounts, where the moisture moles are very less than that of drugs moles. In case of semi-bulk amount and small amounts of moisture present, there would, in general, be insufficient moisture present to decompose all the drug substance present.

2. Stage of moisture present

The stage of moisture is as important as the amount present. Moisture present can be identified into three stages. The first stage is the moisture that dealt more or less exclusively with the amount of water present in pharmaceuticals, most of which are products of natural origin, with regard to issues of potency and commerce.

The second stage is the moisture that could affect the chemical and physical properties of drugs and dosage forms. This stage of moisture mostly called bound moisture, the moisture associated with a solid exhibiting a vapor pressure less than vapor pressure of moisture in the atmosphere and free moisture, moisture present in a solid exhibiting a vapor pressure greater than vapor pressure of moisture in the atmosphere. The free, or solvent-like, moisture is responsible for most of stability and production problems.

The third stage is the stage that even small amount of bound moisture could have a dramatic impact on properties and processes of pharmaceutical of interest.

3. Moisture characterization

There are several ways to characterize moisture associated with solids.

3.1. Thermal methods

Thermal gravimetric analysis (TGA) is the most widely used method for moisture content determination. The sensitivity and sophistication of TGA instruments ranges from the classical moisture balance (LOD) to specially designed microbalances enclosed in chambers that may be evacuated. Microprocessor control of the temperature increase has led to more reproducible and discriminating information.

Differential scanning calorimetry (DSC) is a thermal method that measures the energy change accompanying a nonadiabatic process. A small sample of the moist solid contained in a metal sample container is exposed to a controlled increase in temperature. Water dissociated from the sample is swept from the heating chamber by a nitrogen stream and the dynamic energy consumption (mcal/s) required to keep the sample at the same temperature as an empty sample container is recorded. When the temperature is increased at a constant rate, the area under the DSC curve reflects that energy, in the form of heat, associated with the phase change.

The principal advantage of the thermal methods is convenience. However, these analyses are not specific for water and exposure to high temperature may exert an unrealistic stress or alter the sample.

3.2. Karl Fisher titration

This is the specific titration of water utilizing a reagent developed by Karl Fisher, consisting of iodine, sulfur dioxide and pyridine in methanol. In its simplest form, the Karl Fisher titration is one-point determination of moisture content. Its principal advantage is specificity for water. It is a nonthermal method which is very sensitive and can be easily automated. The main disadvantage is that the solid must dissolve in the titration medium to be sure that the total amount of moisture is released.

3.3. Spectroscopic methods

The most useful spectral methods for the characterization of water in solids are Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR) and powder x-ray diffraction (XRD).

Hydrates normally form crystal structures that differ form the anhydrous form. This gives the different powder XRD pattern. In quantitative perspective, the relative areas of peaks may be used to establish the relative amounts of each form.

Infrared analysis of water associated with a solid centers on an assessment of the degree to which the environment influences the stretching frequency associated with the –OH group. The –OH stretching mode for free water in the gaseous state has characteristic energy of 3655 cm^{-1}. The frequency of this stretching is lowered when water is condensed and/of bound. By comparing the FTIR spectra of the anhydrous form with those of the sample with water, the –OH bands for the water can be identified.

Since the solid-state NMR spectra of the hydrous form is very different from that of the anhydrous form, this is a method which promises to increase the understanding of the state of water in solids and its specific influence on the chemicals of interest.

4. Moisture sorption isotherm

Sorption is the spontaneous acquisition of a component, water, from the atmosphere by a system, solid. The sorption isotherm demonstrates the relationship between sorbed water vapor and a solid. It is the most widely used expression to qualify a substance' s affinity for water. The relationship is at a constant temperature and pressure, as shown in Eq. (1)

$$N = f(x) \qquad (1)$$

Where *N*, the number of moles of water sorbed, is a function of *x*, the partial pressure, the vapor pressure of water in the atmosphere expressed as a fraction of the saturation vapor pressure of pure liquid water at the same temperature. of water in the atmosphere. This functional relationship may be stated in numerous ways. Often, the graphical presentation of sorption isotherms is a plot of the dependent variable moisture content versus humidity, with both expressed on a percentage basis.

Idealized moisture isotherms are for substances that sorb moisture in discrete stages such as, crystalline materials that are capable of forming hydrates and for substances that do not interact with water in discrete stages.

The sorption branch of the isotherm is obtained experimentally by measuring the equilibrium amount of water sorbed to a solid at known relative

pressure, beginning with a known mass of absolutely dry solid and then progressively increasing the relative pressure in the system (Brittain; 1996). Drying the solid sample under heat, possibly using vacuum to facilitate the removal of desorbed water vapor, is usually necessary to eliminate residual moisture. One must be aware, however, of the effects of such conditions on the chemical and physical stability of the solid. The desorption portion of the isotherm is obtained by progressively decreasing the relative pressure in the system from a relative pressure of approximately unity, again monitoring the equilibrium amount of moisture sorbed at each relative pressure. Generation of water sorption-desorption isotherms for a particular solid can lend considerable insight into the nature of the moisture-solid interaction, as well as the surface characteristics of the solid. For example, a material that exhibits sorption at lower relative humidities in much greater amounts than one might expect based on the specific surface area of the samples and that exhibits hysteresis over the complete range of relative humidities, is most likely absorbing water into its internal structure.

5. Control of relative humidity

Maintenance of constant relative humidity environments is essential for studying moisture-solid interactions. There are primarily four techniques that are frequently employed to maintain constant relative humidity, namely, saturated salt solutions, sulfuric acid solutions, temperature modification of an aqueous solution and mixing wet and dry air streams (Brittain, 1996). The saturated salt solutions establish relative humidity by reducing the vapor pressure above aqueous solutions.

At a controlled temperature, saturated salt solutions maintain a constant relative humidity as long as there is excess salt and bulk water present. As

water is added or removed from the solution, moisture from the headspace will condense/evaporate, with subsequent dissolution/precipitation of salt to maintain the equilibrium vapor pressure. Since the degree of vapor pressure depression is dependent on the number of species in solution and, further, since the solubility of most salts is somewhat dependent on temperature, the relative humidity generated is also temperature-dependent. Hence, use of the same salt at different temperatures can result in different relative humidities (Aso et al., 1995; Kesavan and Peck, 1996). And since the relative humidity is dependent on the number of dissolved species, it is essential that saturation be attained prior to beginning experimentation. In this regard, preparing the salt solutions several days before beginning a sorption study is recommended.

The saturated salt solutions were found to maintain the relative humidities within the limits in the desiccators for a period of up to five years. Examples of a series of saturated salt solutions at a controlled temperature for maintaining specified relative humidities in closed chambers are shown in Table 1.

6. Measurement of the critical relative humidity

The relative humidity at which a solid begins to deliquesce, RH_0, can be determined in two ways, directly and indirectly (Brittain; 1996). Directly is by measuring the relative humidity above a saturated solution of the substance. While indirectly is by measuring the steady state moisture uptake rate at relative humidities above RH_0 and then extrapolating to the relative humidity at which the moisture uptake rate is zero.

Table 1 Relative humidities of various saturated salt solutions (adapted from Lide, 1995)

Salt	%RH at 25 ^{O}C	Temperature range (^{O}C)	A	B
NaOH H_2O	6	15-60	5.48	27
$ZnBr_2$ $2H_2O$	8	5-30	1.69	455
KOH $2H_2O$	9	5-30	0.014	1924
LiCl H_2O	11	20-65	14.53	-75
$CaCl_2$ $6H_2O$	29	15-25	0.11	1653
$MgCl_2$ $6H_2O$	33	5-45	29.26	34
NaI $2H_2O$	38	5-45	3.62	702
$Mg(NO_3)_2$ $6H_2O$	53	5-35	25.28	220
NH_4NO_3	62	10-40	3.54	853
KI	69	5-30	29.35	254
$SrCl_2$ $6H_2O$	71	5-30	31.58	241
$NaNO_3$	74	10-40	26.94	302
NaCl	75	10-40	69.20	25
NH_4Cl	79	10-10	35.67	235
K_2SO_4	97	10-50	86.75	34

$RH = A \exp(B / T)$ where *RH* is the percent relative humidity at the valid temperature range

T is the temperature in Kelvin

A, B are constants

7. Measurement of equilibrium moisture sorption

Measurement of equilibrium moisture sorption can be carried out either gravimetrically or volumetrically (Brittain; 1996).

7.1. Gravimetric method

The principal of this method is to equilibrate dry sample at constant temperature and relative humidity. Then calculate an equilibrium weight of

sorbed water vapor is calculated by subtracting moist solid weight with that of at initial, dry solid.

This method can occur continuously or discontinuously. Continuous measurement usually involves placing a sample on a balance in a temperature and relative humidity-controlled environment. Discontinuous procedure is to store the samples in a constant relative humidity environment and require periodic sample removal for weightings. The advantages of continuous procedures are that it is obvious when equilibrium is attained and that improved accuracy and precision are possible since equilibrated samples do not have to be removed and subjected to ambient relative humidity, where subsequent sorption or desorption of water vapor can occur. However, only a single sample at one relative humidity can be run at a time while discontinuous techniques allow many samples to be equilibrated simultaneously in different chambers.

7.2. Volumetric method

In essence, volumetric method equilibrate a known headspace dosing volume at a measured water vapor pressure and then they expose the pre-equilibrated sample to this water vapor, with subsequent measurement of the water vapor pressure after equilibrium. The moles of water sorbed at the final pressure in the system, Δn, is obtained from the difference between the calculated water vapor pressure at equilibrium and the final measured water vapor pressure, ΔP.

$$\Delta n = \frac{\Delta P V}{R T} \qquad (2)$$

where R is the gas constant and T is absolute temperature.

B. Effect of Light (Tonnesen and Greenhill, 1992)

Light can change the properties of different materials and products. The results of drug photodecomposition are loss of potency resulting therapeutically inactive and adverse effects. The drug substance can also cause light-induced side-effects after administration to the patient by interaction with endogenous substances.

The color displayed by drug substances or excipients is complementary to the light they absorb, for example, red powder is absorbing blue light (Sprowls, 1970). Most of therapeutic substances are white in appearance, meaning that they do not absorb light in the visible region, but they may absorb in the UV region.

1. Photodegradation mechanism

When drug absorbs radiation in the ultraviolet and/or visible region of the electromagnetic spectrum, it means that it is absorbing energy that is sufficient to break a bond in the molecule. The property of absorption is a first indication that the drug may be capable of participating in a photochemical process. The absorption spectrum of a compound is therefore an immediate way of determining the wavelength range to which the drug may be sensitive.

Photochemical damage to a substance is initiated by the absorption of energy by the compound itself or by a photosensitizer. The process begins with the excitation of drug molecules or sensitizers from their ground state to reactive excited states which chemical reaction is easily occurs, by absorption of photons of certain wavelengths. When absorption spectrum shows more than one absorption band, it indicates a corresponding number of excited state which can be reached by irradiation with the appropriate excitation wavelength.

2. Photodegradation type (Swarbrick and Boylan, 1995)

There are several types of chemical reaction involved in photodegradation as shown as follows:

1. Decarboxylation (e.g. naproxen, nalidixic acid, oxolinic acid and flurbiprofen)
2. N-Dealkylation (e.g. phenylalanine, tyrosine, chloroquine and methotrexate)
3. Dehalogenation (e.g. chlorpromazine, chloroquine and diclofenac)
4. Isomerization, Cyclization (e.g. adrenaline and diethylstilbestrol)
5. Oxidations (e.g. chlorpromazine, tetracycline, doxycycline and mercaptopurine)
6. Dehydrogenation (e.g. nifedipine, nitrendipine, nimodipine and nicardipine)
7. Photoreduction (e.g. pyrithione, nitrazepam and chloramphenicol)
8. Rearrangement (e.g. diphenyldramine, metronidazole and benzydamine)

3. Light source

There are number of electromagnetic radiation sources, ranging from direct sunlight, through filtered sunlight to a variety of artificial light conditions. The UV component of sunlight is the most potentially damaging, but there may be long exposures to fluorescent and incandescent lighting during the various stages of manufacture, storage and use, so it is important to consider their spectral distribution as well.

3.1. Direct sunlight

1. Ultraviolet radiation

1) *UV-C* UV-C band ranges from 200 nm to 290 nm and is often called short-wave or far-UV because the wavelengths in this region are the shortest UV radiation transmitted through air. Although most drugs and all cellular constituents absorb UV-C, sunlight at the earth' s surface contains no UV-C because of efficient absorption by molecular oxygen and ozone in the upper atmosphere. Despite its absence from natural sunlight at the earth' s surface, UV-C is present in artificial radiation sources such as germicidal lamps and can cause rapid photochemical degradation.

2) *UV-B* The UV-B spectral region is often defined as encompassing wavelengths from 280 to 320 nm. However, no solar radiation penetrates to the ground at wavelengths between 280 and 290 nm. Therefore it has been suggested that the interval from 290 to 320 nm be adopted as a practical definition of the UV-B. The UV-B intensity at a particular latitude varies greatly with time of day and the season of the year.

3) *UV-A* UV-A is the long wavelength UV region from 320 to 400 nm. It is also called near-UV because of its proximity to the visible spectrum. In total energy the amount of solar UV-A reaching the earth' s surface is enormously greater than that of UV-B.

2. *Visible region*

Visible region ranging from 400 to 800 nm which can be detected by human eyes. It is relevant when a colored substance is present in the formulation.

3. *Infrared region*

The only importance that infrared radiation, 800 to 3200 nm, can accrue in the context of photodegradation is that the sample can be heated, thereby activating thermal decomposition.

3.2. *Filtered sunlight*

Filtered sunlight is the sunlight radiated through filter, such as glasses and plastics. It has less UV radiation than direct sunlight depending on filter type and thickness.

3.3. *Artificial light*

Artificial light sources can have varying spectral characteristics depending on the particular construction. The advantage of this type of light source is consistency of intensity while that of sunlight varies according to the weather, the latitude, the time of day and the season of the year. To obtain the result most likely natural exposure, one needs to use an artificial light source which has an output with a spectral power distribution as near as possible to that of sunlight.

1. *Arc lamps*

1) *Mercury arc lamp* The low-pressure arc emits 90 per cent of its energy as a line at 254 nm, so is of no direct use in a sunlight-simulating experiment. The medium-pressure arc is also a line source, producing greater intensities at the other characteristic mercury emission wavelengths, 302, 313, 334, 366 and 405 nm. This arc lamp is moderate in cost, has a long life and gives a good representation of emission in the UV region, it has been widely used in drug photostability studies with a glass filter to shield the sample from the 254 nm radiation. The principal application is as an irradiation source to determine degradation pathways. The high-pressure mercury arc emits the same lines, as well as a continuous background radiation right across the solar UV and visible regions.

2) *Xenon arc lamp* It has the best resemblance to sunlight and it has a relatively smooth continuous output spectrum with some line emission superimposed in the region 450 - 500 nm. The principle disadvantages are its comparatively short life span ,1500 to 2000 hours, high initial cost and small area of irradiation.

3) *Metal-halide lamp* This irradiation source has very similar properties as xenon arc lamp but lesser life span, approximately 750 hours.

2. *Fluorescent lamps*

Fluorescent lamps have been used in photostability testing by a number of laboratories (Lachman, Swartz and Cooper, 1960; Anderson et al., 1991). The operating principle of fluorescent lamps is based on mercury vapor discharge at

very low pressure, producing the 254 nm emission which is converted to higher wavelengths by the phosphor coating on the inside surface of the tube.

There are three subtypes of fluorescent lamp, as daylight fluorescent lamp which gives both visible and UV region, white fluorescent lamp which irradiates visible region and black light lamp which irradiates UV-A region.

The main advantages of this lamp are low cost, long life span, low heat output and large irradiation area. However, it is not possible to achieve a sunlight-simulating spectrum with just one type of fluorescent lamp, a combination must be used to get the appropriate amounts of UV-A, UV-B and visible component.

3. *Incandescent lamps*

Incandescent lamps or filament lamps have a spectral output with relatively high infrared and low ultraviolet components compared with sunlight, therefore they are not frequently used in photostability test (Everhard and Goodhart, 1963).

4. Measurement of light intensity

The measurement of the light incident upon a sample can be expressed in term of the number of photons of a particular wavelength crossing a unit area in a unit time. Using the Planck equation,

$$E = h\nu = hc / \lambda \qquad (3)$$

Where E is the energy absorbed, h the planck' s constant, c the velosity of light, λ the wavelength and ν the radiation frequency.

4.1. Physical instrument

Radiometers are devices based on various types of photocells which generate a current when light falls upon them. Lux meter is simply a radiometer which has a spectral responsiveness that closely matches the visual response of the human eyes, thus measuring incident radiant power in the visible region of the electromagnetic spectrum. The unit of measurement is in lux and is calibrated against a specific tungsten lamp.

4.2. Chemical actinometry

While physical instrumentation is more convenient, the lack of an integrated output and the need for regular calibration are hindrances to its widespread application to measure the number of photons absorbed by a sample. The alternative is the use of a chemical actinometer system in which a photochemical reaction of known characteristics is monitored when it is subjected to the same irradiation condition as the test sample.

While quinine hydrochloride actinometer is specific to only ultraviolet region (Yoshioka et al., 1994), ferrioxalate actinometer is the most widely used actinometer (Akimoto et al., 1988; Morimura et al., 1995) since it gives a response over broad wavelength range. This system is based on potassium ferrioxalate which prepared by reaction of ferric chloride with potassium oxalate.

5. Factors influencing photodegradation

5.1. Drugs properties

Structural formula of drugs results wavelength range to which the drug may be sensitive. Liquid or solution states give the greatest degradation rate while crystalline state give the least, since the importance of molecular mobility (Guo, Byrn and Zografi, 2000).

5.2. Spectral distribution from light source

The degradation will occur only if spectral radiated from light source is the same region of that drug absorb. Therefore, it is not dependent on which type of light source. In some reported drug photostability studies, different lamps were used as light sources (Asker and Habib, 1991; Vandenbossche et al., 1993; Nunez-Vergara, Sunkel and Squella, 1994; Tiefenbacher et al., 1994; Zhan, Yin and Liu, 1995). Morimura (1995) found that orbifloxacin degraded more rapid when the light source was only 110 lux of near UV lamp than 1500 lux of fluorescent lamp. This was because orbifloxacin absorbs radiation in near UV region much more than in visible region. Therefore, data from different lamps cannot be compared with each other meaningfully.

5.3. Light intensity

The more light intensity gives the more photodegradation. Light intensity depends on type of light source, number of light source and distance between the light source and samples (Majeed et al., 1987; Matsuura, Imaizumi, and Sugiyama, 1990).

5.4. Area of exposure

When a drug in the solid state is irradiated by light, usually the photodegradation occurs on the surface much more rapidly than inside the solid (Carstensen, 1974; Zhang, Yin and Liu, 1995).

5.5. Other factors

Other factors such as, type of solvent, photosensitizer, buffer, pH , ionic strength, temperature (Graham, Biehl and Kenner, 1977; Kaminski et al., 1979; Moore, 1990; Asker and Habib, 1991; Asker and Islam, 1994; Okamoto, Mori and Nishihata, 1994; Chinnian and Asker, 1996; Ferdous and Asker, 1996; Fokkens and Gorissen, 1996; Ogata et al., 1998; Skiba et al., 2000) and type of container (Narurkar et al., 1986; Yu, Portmann and Simmons, 1995; Oustric-Mendes et al., 1997; Brigas et al., 1998; Ho and Wong, 1998) can also influence photodegradation rate.

II. Degradation kinetics

The rate, velocity, or speed of a reaction is given by the expression, dc/dt, where dc is the decrease of concentration over an infinitesimal time interval, dt. According to the law of mass action, the rate of a chemical reaction is proportional to the product of the molar concentration of the reactants each raised to a power usually equal to the number of molecules, a and b, of the substances A and B undergoing reaction. In the reaction

$$a\,A + b\,B + \ldots = \text{Products}$$

$$\text{Rate} = -\frac{1}{a}\frac{d(A)}{dt} = -\frac{1}{b}\frac{d(B)}{dt} \quad (4)$$

$$\text{Rate} = k\,(A)^{a}\,(B)^{b} \quad (5)$$

where *k* is the rate constant

The chemical stability of the drug was determined by analysis of the drug remaining during storage and the degradation rate constant was evaluated. The degradation rate constant was calculated referring to zero-order, first-order, second-order, or third-order kinetics. The mathematical equations of these kinetics are shown as follows.

Zero-order $$C = C_0 - k_0 t \quad (6)$$

First-order $$\ln C = \ln C_0 - k_1 t \quad (7)$$

Second-order $$\frac{1}{C} = \frac{1}{C_0} + k_2 t \quad (8)$$

Third-order $$\frac{1}{C^2} = \frac{1}{C_0^2} + 2 k_3 t \quad (9)$$

where C_0 = the initial concentration of drug,

C = the concentration of drug at time t,

k_0, k_1, k_2, k_3 = the degradation rate constant of zero-order, first-order, second-order and third-order, respectively.

The order of a reaction may be determined by several methods as follows:

A. Substitution method

The data accumulated in a kinetic study may be substituted in the integrated form of the equations that describe the various orders. When the equation is found in which the calculated *k* values remain constant within the limits of experimental variation, the reaction is considered to be of that order.

B. Graphic method

A plot of the data in the form of a graph may also be used to ascertain the-order. If a straight line results when concentration is plotted against t, the reaction is zero-order. The reaction is first-order if log concentration versus t yields a straight line. It is second-order if 1/concentration versus t gives a straight line. And when a plot of 1/concentration^2 against t produces a straight line, the reaction is third-order.

C. Half-life method

In a zero-order reaction, the half-life, $t_{1/2}$, is proportional to the initial concentration, C_O. The half-life of a first-order reaction is independent of C_O, half-life for a second-order reaction, is proportional to 1/ C_O. In a third-order reaction, it is proportional to 1/ C_O^2 as follows.

Zero-order	$t_{1/2}$	=	$C_0 / (2\ k)$	(10)
First-order	$t_{1/2}$	=	$0.693 / k$	(11)
Second-order	$t_{1/2}$	=	$1 / (C_0\ k)$	(12)
Third-order	$t_{1/2}$	=	$3 / (2\ C_0^{\ 2}\ k)$	(13)

III. Controlled release delivery system (Martin, Bustamante and Chun, 1993)

The rationale for the controlled delivery of drugs is to promote therapeutic benefits while at the same minimizing toxic effects. Normal drug dosing may follow a sawtooth kinetic profile, in which the dose first greatly exceeds the desired therapeutic level, then falls to a subclinical level and on subsequent dosing rises to dangerously high values, falling again to ineffective concentration, in continuous cycles of excessive-ineffective levels. Controlled, sustained drug delivery can reduce the undesirable fluctuation of drug levels, enhancing therapeutic action and elimination dangerous side effects.

There are several delivery systems used in drug release control, such as prodrugs, liposomes, microcapsules, microparticles, nanocapsules and nanoparticles. Microparticles or microspheres consist of a solid rate-controlling polymer matrix throughout which the drug is distributed. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 100 μm. Several pharmaceutical techniques have been applied to prepare microspheres including spray drying.

Release mechanisms of controlled release delivery system

1. *Zero-order release mechanism*

It is an ideally controlled release mechanism, which can deliver the drug at a constant rate until the device is exhausted of active agent. The release rate is given as

$$M_{,} = M_{0} - K_{0} t \qquad (14)$$

Where K_0 is a zero-order rate constant, t is time and M_0 is the mass of active agent release at $t = 0$.

2. *First-order release mechanism*

In the first-order mechanism, the release rate dependent on the drug concentration remaining in the device and approached the release rate of zero as the device approached exhaustion.

$$\ln M = \ln M_{0} - K_{1} t \qquad (15)$$

Where K_1 is a first-order rate constant, t is time and M is the mass of active agent release at time t.

3. *Second-order release mechanism*

The second-order release kinetics is not a common type of the release mechanism.

$$1/M = 1/M_0 - K_2 t \qquad (16)$$

Where K_2 is a second-order rate constant, t is time and M is the mass of active agent release at time t.

4. *Square root time release mechanism*

The second common type of the release mechanism is the square root time or Higuchi model. In contrast to first-order release, the release rate here remained finite as the device approached exhaustion. The amount of drug released is proportional to the square root of time.

$$Q = \frac{[\, D \varepsilon (2A - \varepsilon C_S) C_S t \,]^{1/2}}{\tau} \qquad (17)$$

$$\log Q = \log k_H + \tfrac{1}{2} \log t \qquad (18)$$

Where Q is the weight in grams of drug release per unit surface area

k_H is Higuchi rate constant

A is the concentration of drug in the tablet

D is the diffusion coefficient of the drug in the matrix

C_S is the solubility of drug in polymeric matrix

ε is the porosity of the matrix

τ is the tortuosity of matrix

t is the time.

IV. Spray Drying (Swarbrick and Boylan, 1996)

The production of microspheres by means of spray drying offers many advantages. Such particles can be manufactured with a fixed configuration, composition and size. Thus spray drying can avoid uniformity problems and enhance dissolution, while making the most of selected raw material properties. Particles produced by spray drying are usually spherically or regularly shaped with a tight-size distribution and content uniformity. By combining various spray techniques and drying parameters a wide range of physical properties can be obtained for a given substance.

A. Steps in spray drying technique

1. Formation of slurry to be sprayed. This slurry may be a simple concentrated solution or a dispersion of an insoluble material in a vehicle or medium.
2. The liquid is atomized into droplets. This action is critical as the droplet size and spray pattern dictate the equipment size as well as the final product size.
3. The droplet is exposed to a heated gas flow, normally air. Inert gases may be used to prevent oxidation. The heated gas supplies the energy required to vaporize the solvent.
4. The dry free-flowing powder or encapsulated liquid or solid is collected.

B. Equipments in spray drying technique

1. Atomizers

There are four types of atomization devices as, air (high velocity), airless, disk (or rotary) spray and ultrasonic. The type of spray method used is the

principal factor in the design of the dryer itself. Airless and air spray dryers tend to be tall and narrow, whereas disk dryers are short and wide. Air atomization or the two fluid nozzle process produces the smallest particles of any spray device and the smallest particles at a given pressure and capacity. However, they are strongly influenced by parameters such as viscosity and pressure differences. This type of atomizer is used for particle sizes below 100 μm.

2. *Dryers*

The size and configuration of a spray dryer are dictated by the atomization device chosen. Disk atomizers primarily require dryers that are wide. This makes them an excellent choice where overhead space is a problem. Disk spray dryers are widely used in portable units because their short, wide design facilitates moving. Air and airless atomizing requires drying chambers that are taller than those of comparable disk units.

Within the design of the drying chamber, three types of air flow are possible, along with single- or multiproduct discharge. Different discharge arrangements can be used for particle size classifications, which eliminate a subsequent unit operation for separation. These can result in three types of air flow relative to the product as, cocurrent, countercurrent and mixed flow. The type of air flow can have a marked impact on the physical properties of the final product.

C. Production parameters

A number of the physical properties of the product have a direct influence on the spray drying process. If these properties are clearly understood and optimized in formulating a solution, dispersion, or slurry spray, efficiencies can be greatly increased. The following primary properties should be considered.

1. *Viscosity*

Since the formation of a spherical drop is promoted by the ability of the drop medium to move, high viscosity hinders correct drop formation. In general, the viscosity is the primary product characteristic affecting the formation of droplets in a spray. As the viscosity is lowered, less energy or pressure is required to form a particular spray pattern. As the viscosity is raised, the system' s capacity as well as the spray angle decrease.

Increasing the feed solids concentration in the dispersion does not directly affect viscosity. The maximum of undissolved solids is limited by the ability to maintain uniformity in the dispersion and to feed it to a nozzle. Care must be taken with high solid loading, above 30%, to maintain proper atomization to ensure correct droplet formation. High solid loading, as well as high viscosity, increase the wear factor on spray equipment.

2. *Surface tension*

Formulations or media with low surface tension require less energy to form a droplet. Additional of a small amount of surfactants, such as polysorbate, sorbitan monooleate, or monolaurate, can significantly lower the surface tension. This can result in a wider spray pattern, smaller droplet size and higher drop velocity. However, care must be exercised as the permeability of the final product can be greatly affected by an excess of ingredients, which lower surface tension.

3. *Specific gravity*

Specific gravity does not have a direct effect on the spray. If the specific gravity of a product differs from 1.0, the capacity should be calculated with great care.

4. *Temperature*

The temperature of a given product solution or dispersion being dried should be optimized for processing efficiency. As the temperature of a solution to be sprayed is increased, that solution is easier to dry as it brings more energy to the system. Increases in temperature usually affect viscosity and surface tension, aiding in the formation of droplets.

5. *Heat capacity and latent heat*

Heat capacity is the amount of heat needed to raise the product temperature by 1 ^{o}C. Latent heat refers to the energy required for evaporation. A medium with a low heat capacity and latent heat offers advantage. Less energy is required to raise the droplet temperature and cause solvent evaporation.

6. *Volatility of a solvent or medium*

This is a measure of the rate of evaporation. A high volatility is desirable in any drying process. Organic solvents often require sophisticated safety and environmental equipment in order to meet local effluent regulations.

D. Instrument settings

1. *Inlet / Outlet air temperature*

The inlet air temperature is defined as the temperature of the drying air, which flows through the instrument with the aid of the aspirator. Instead of air, another gas can naturally be used, provided this is necessary for the work in question. When a solution, emulsion or dispersion is spray dried, the main aim is to remove a solvent, i.e. a liquid, by evaporation. In order that the solvent

evaporates during the short contact time with the stream of air when the product is spray dried, the temperature of the air stream must lie a good bit above the boiling point of the solvent. This does not mean, however, that the end product is also exposed to this temperature. This is because the droplets sprayed into the hot stream of air immediately form a steam coating which protects the core of the droplet, i.e. the product from thermal influences.

The outlet air temperature is defined as the temperature of the air stream containing the solid particles before it enters the cyclone. This temperature is also not necessarily identical to the temperature of the product. The outlet air temperature results out of a combination of the inlet air temperature, the aspirator setting, the pump setting as well as the concentration of the substance being spray dried. In addition, it also depends on the heat of evaporation of the solvent.

For an end product with very low residual moisture content, the inlet air temperature must be as high as possible and the temperature drop between the inlet and outlet air as small as possible.

2. *Aspirator*

The aspirator sucks the drying air through the instrument and at the same time produces a partial vacuum. A very fine product, with a low specific weight may require a lower aspirator performance. Undesirable turbulence in the dryer can usually be eliminated by increasing the aspirator performance.

3. *Pump performance*

The function of the built-in pump is to feed the solution to be spray dried into the apparatus. The setting of the feed pump influences mainly the

temperature drop between the inlet and outlet air temperatures. If more or less liquid is sprayed into the chamber, more or less heat is also removed due to the evaporation. The pump performance is dependent on various factors, such as viscosity of the solution to be spray dried, diameter of the tubing used, etc. An increased pump performance increases the temperature drop between the inlet and outlet temperatures.

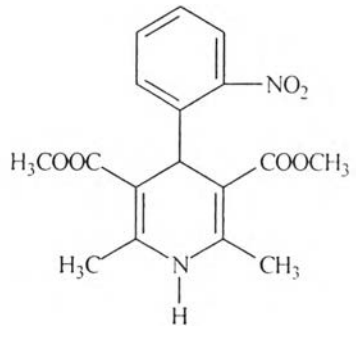
4. Spray flow

The spray flow is defined as the necessary quantity of pressurized air for the spraying of the solution, emulsion or dispersion. Instead of pressurized air, another gas can naturally also be used. The particle size of the end product can be influenced by spray flow. The larger the spray flow, the smaller the particle size of the end product.

V. Nifedipine

A. Pharmaceutical properties (Windholz, 1983)

Chemical structure



Empirical formula	$C_{17}H_{18}N_2O_6$
Chemical name	3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester. Dimethyl1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridinedicarboxylate
Molecular weight	346.34
Melting range	between 171 and 175 ^{o}C
Solubility	easily soluble in acetone, chloroform, less soluble in ethanol, practically insoluble in water

Nifedipine, an oral calcium-blocking agent, is a dihydropyridine derivative with potent coronary and peripheral arterial vasodilator properties and used in the treatment of angina pectoris and hypertension.

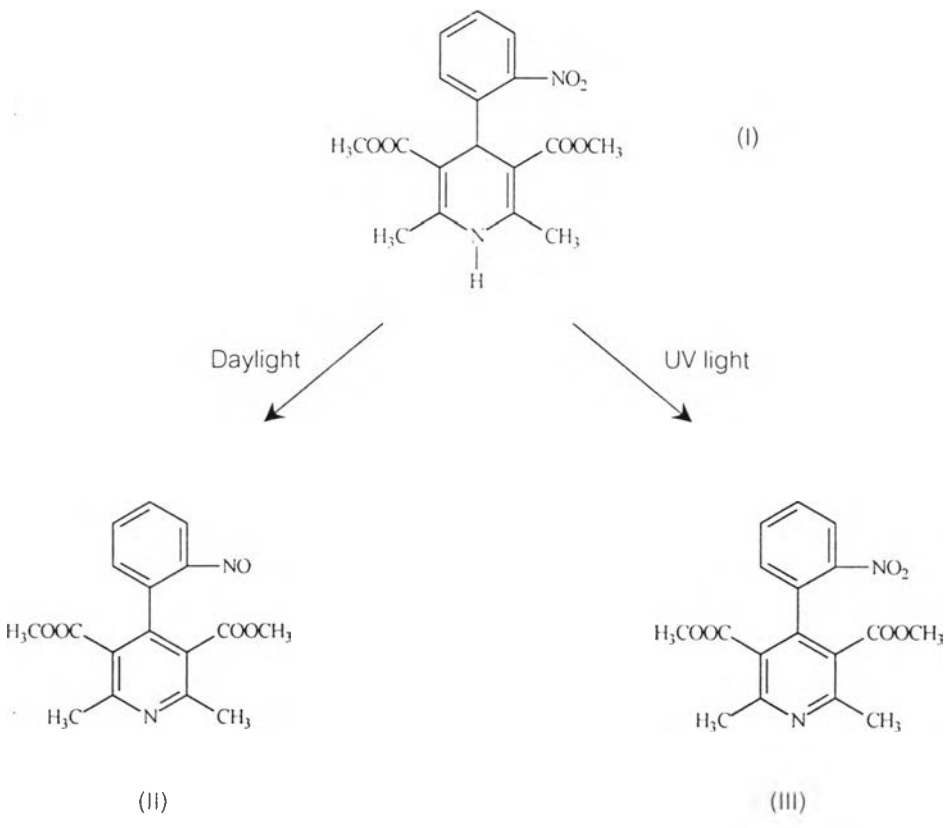
It is absorbed rapidly and almost completely after oral administration. The rate of resorption depends upon the type of formulation administered. Nifedipine undergoes metabolism in the liver to inactive acid or lactone derivatives which show a pH-dependent equilibrium in aqueous solutions. Only trace of unchanged nifedipine are eliminated through renal pathway (Florey, 1989).

B. Photodecomposition of Nifedipine

Like most 4-(2-nitrophenyl)-1,4-dihydropyridine derivatives, nifedipine (I) undergoes photo-oxidation when exposed to light. It is more sensitive to light when in solution than in the crystalline form. Depending on the light source, two major degradation products of nifedipine have been reported. By sunlight, nifedipine is converted mainly into nitrosopyridine (II). Exposure to UV light leads to the formation of a nitropyridine (III) derivative. Both are biologically

inactive compounds (Matsuda, Teraoka and Sugimoto, 1989; Sadana and Ghogare, 1991; Hayase et al., 1994). Additionally, there were few reports on other minor photodegradation products, i.e., cis-azoxy derivative, trans-azoxy derivative, N,N'-diioxide derivative and lactam derivative (Matsuda, Teraoka and Sugimoto. 1989; Hayase et al., 1993).

The spectra of nifedipine solution in 95% ethanol showed absorbance maxima at 237 and 360 nm. After decomposed, the absorbance showed a decrease in the absorbance maxima at 237 and 360 nm and the appearance of a new maximum at 280 nm (Al-Turk et al., 1989; Majeed et al., 1987).



C. Factors influencing nifedipine photodegradation

The photostability of nifedipine is influenced by several parameters such as wavelength and intensity of light. Temperature and ionic strength have an influence on the stability (Florey, 1989).

1. *State of nifedipine* It was reported that nifedipine is sensitive to light in solid-state and extremely sensitive to light in dissolved state in solution (Florey, 1989). This is accounted for the inability of a deeper penetration of light.

2. *Nifedipine concentration* The degradation process of nifedipine in solid state followed first-order kinetics, however, in solution form, it followed zero-order kinetics at concentrations higher than 4×10^{-4} M and followed first-order kinetics at lower concentrations (Majeed et al., 1987). Therefore, at the low concentration, degradation rate of nifedipine solution depends on nifedipine remaining concentration.

3. *Spectral distribution of light source* The degradation profiles were irrespective of kinds of light sources. However, the photodegradation was influenced by the wavelength to absorption of nifedipine. Thoma and Klimek (1991) found that nifedipine solution did not show absorption spectrum at wavelength about 475 nm and higher. Therefore, the photodegradation began at 450 nm and increases considerably up to about 400 nm.

4. *Light intensity* It was found that degradation rate increased when light intensity increased (Majeed et al., 1987; Matsuda, Teraoka and Sugimoto, 1989).

5. *pH of the solution* Degradation rate constant also depend on the pH. Majeed et al. (1987) found that in solution pH 2, the degradation rate reached a maximum.

And when the pH was increased to 5, the minimum rate was found. It was suggested that, this may be due to the formation of an ionized pyridine ring at pH 2.

D. Photostabilization of Nifedipine

The usual approach utilized to protect light-sensitive drugs is to use a light-resistant package. However, there are some other ways that give obvious and more effective means. Based on the principle of photoprotection by spectral overlapping, photoprotection of a light-sensitive drug can be achieved by finding suitable stabilizers whose absorption spectra overlap that of the light-sensitive drug.

Ali and Sharma (1992) found that curcumin can decrease photodegradation rate of nifedipine both in solution and solid state. Since curcumin in methanol showed absorption maximum at 422 nm while nifedipine was reported to be sensitive to light over the range of the wavelengths between 340 and 700 nm, it is likely that curcumin absorbs the UV radiation and thereby minimizes the radiation effect on the nifedipine molecules. Moreover, Thoma and Klimek (1991) suggested that by using curcumin, the relevant long-wavelength region of nifedipine' s spectrum between 300 and 450 nm is well covered. Addition of curcumin in roughly equimolar of that nifedipine solution leads to remarkably good photostabilization by a factor of 60, relative to the half-life in daylight. Furthermore, other yellow food colorants, fast yellow and tartrazine, can be used to produce similar stabilizing effects.

Since synthetic iron oxides are strong absorbers of radiation wavelength below 400 nm, it was also used in photostabilization of nifedipine (Desai et al., 1994). The photostability was studied on uncoated tablets of nifedipine with

yellow, red, or black iron oxide. Tablets containing iron oxide were found to be more light stable than those without it. Furthermore, inclusion of a combination of yellow and red iron oxides gave more stability than the inclusion of either yellow or red iron oxide alone.

Film coating with colorants also used to protect nifedipine from photodegradation. Teraoka, Matsuda and Sugimoto (1989) prepared nifedipine tablets coated with tartrazine and/or titanium dioxide film. Degradation rate constant of nifedipine was decreased as both colorant concentration and film thickness increased. The titanium dioxide system exhibited superior light protection properties to the tartrazine system at all additive concentrations. However, combination of both colorants gave much better light protection than did the colorants separately. Similarly, Bechard, Quaraishi and Kwong (1992) also used film coating in order to prevent photodegradation of nifedipine. The film consists of hydroxypropyl methylcellulose (HPMC) and titanium dioxide. After exposed to 4.4 klux fluorescent light, the results showed that the film thickness was a key variable, however, the potential effect of such a high level of coating on the dissolution, bioavailability of a drug would have to be determined before such an approach be envisaged.

There are only few reports about the effect of antioxidants to the photostability of nifedipine. Al-Turk et al. (1988) found that the concentration of 6×10^{-5} to 500×10^{-5} M of sodium bisulfite did not show significant changes in degradation rate of nifedipine solution.

E. Modification of nifedipine release

Since nifedipine is practically insoluble in water, there have been many investigatious focusing on the drug dissolution enhancement. Save and

Venkitachalam (1992) prepared nifedipine-polyethylene glycol solid dispersion by melting or fusion method in order to improve nifedipine solubility in the aqueous body fluids. The dissolution rate of the drug was markedly increased in these solid dispersion systems. The increase in dissolution was function of the ratio of drug to polyethylene glycol used and the molar weight of polyethylene glycol.

Since nifedipine has a relatively short elimination half-life, 3.4 hours, in the human body, it is necessary to prolong the plasma levels to maintain the clinical effect. One method to prolong the plasma drug level is to employ the sustained release formulation. Nifedipine loaded microspheres of cellulosic polymers prepared by a solvent evaporation method exhibited slow and S-shaped release profiles with poor dissolution efficiency. And it appeared that drug incorporation efficiency in ethylcellulose microspheres decreased when organic phase viscosity was increased (Gayot et al., 1995). However, release from microspheres of ethylcellulose / hydroxypropyl cellulose and ethylcellulose / hydroxypropylmethyl cellulose was slower but more regular than that from microspheres of ethylcellulose alone.

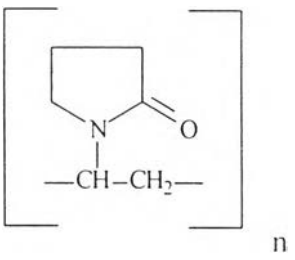
Nifedipine with water-soluble polymer solid dispersion gave fast and rapid dissolution of nifedipine. When this solid dispersions were microencapsulated with low water soluble polymer, a slow controlled complete release were observed. Chowdary and Sankar (1997) prepared nifedipine solid dispersion in hydroxypropylmethyl cellulose-microcrystalline cellulose and encapsulated with Eudragit RLPM by emulsion solvent evaporation method. It was found that drug release depended on the proportion of polymers in solid dispersion, coat to coat ratio and the size of the microcapsules but was pH independent.

In order to optimized nifedipine release, combination of water insoluble and water soluble polymer were used. Spray dried microspheres of nifedipine, Eudragit and Povidone were prepared (Sinsuebpol ,1999). It was found that nifedipine release increase with the Povidone ratio increase.

VI. Povidone

Pharmaceutical properties (Windholz, 1983)

Chemical structure



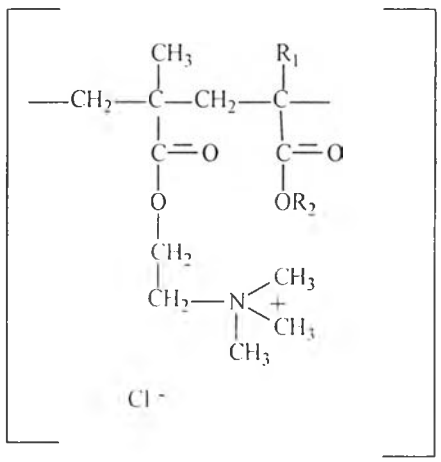
Empirical formula	$(C_6H_9NO)_n$
Chemical name	2-Pyrrolidinone, 4-ethenyl-, homopolymer 1-Vinyl-2-pyrrolidinone-polymer
Synonyms	Polyvidone; Polyvinylpyrrolidone; PVP; Kollidon; Plasdone
Molecular weight	Ranging from about 10,000 to about 700,000
K-Value	K-value refers to the average molecular weight relationship described for several grades. K-value 15, 30, 60 and 90 refer the average molecular weight of about 10,000, 40,000, 160,000 and 360,000 respectively.
Softening point	About 150 ^{o}C
Description	A white to creamy white, odorless or almost odorless, hygroscopic powder.

Solubility — Readily soluble in water, up to 60%. Freely soluble in many organic solvents, including monohydric (ethanol, methanol) and polyhydric alcohols, acids, esters, ketones, methylene chloride, chloroform, ethylene dichloride, butylamine, pyridine and di- and triethanolamine. Essentially insoluble in ethers, hydrocarbons, carbon tetrachloride, ethyl acetate and mineral oil.

VII. Polymethacrylates

Pharmaceutical properties (Windholz, 1983)

Chemical structure



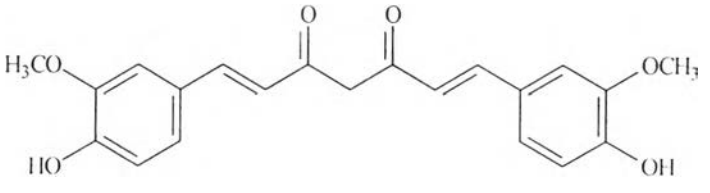
Chemical name — Poly (ethylacrylate, methylmethacrylate, trimethyl ammonioethyl methacrylate chloride) 1 : 2 : 0.1 (Eudragit RS 100)

Synonyms	Eudragit, Polymeric methacrylate, Ammonio methacrylate copolymer
Molecular weight	Approximate 150,000
Description	Eudragit RS copolymer synthesized from acrylic acid and methacrylic acid, having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers.
Solubility	Insoluble in water.

VIII. Curcumin

Pharmaceutical properties (Windholz, 1983)

Chemical structure



Empirical formula	($C_{21}H_{20}O_6$)
Chemical name	1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione
Synonyms	Diferuloyl methane
Molecular weight	368.37
Melting point	183 ^{o}C

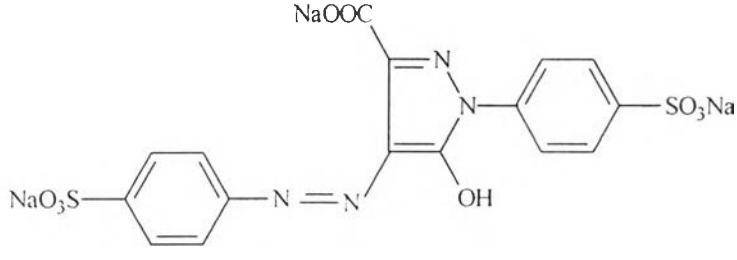
Description	Orange-yellow, crystal powder.
Solubility	Insoluble in water, ether. Soluble in alcohol, glacial acetic acid. Gives a brownish-red color with alkali; a light-yellow color with acids.

Curcumin is an important constituent of the rhizomes of *Curcuma longa* Linn (Zingiberaceae) which has been used down to the ages as colorant, antiseptic, antibacterial, anti-inflammatory and vermicidal agent. Curcumin, itself, has gained importance as a medicine as it exhibited pharmacological properties that include, anti-inflammatory, antineoplastic and antioxidant actions (Tonnesen et al., 1993; Suresh and Prasad, 1999). Its antioxidant properties have been attributed to the phenolic group present in the molecule. It is non-toxic even at high dosage (Tonnesen and Greenhill, 1992).

IX. Tartrazine

Pharmaceutical properties (Windholz, 1983)

Chemical structure



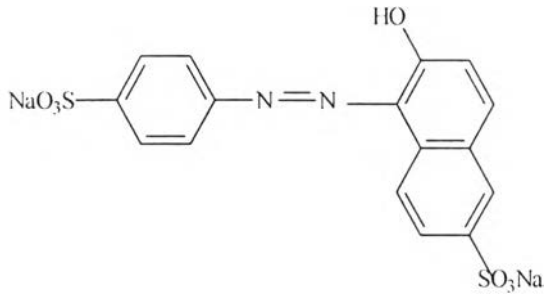
Empirical formula $(C_{16}H_9N_4Na_3O_6S_2)$

Chemical name	4,5-Dihydro-5-oxo-1-(4-sulfophenyl)-4-[(4-sulfophynyl) azo]-1-H-pyrazole-3-carboxylic acid trisodium salt 3-Carboxy-5-hydroxy-1-p-sulfophenyl-4-p-sulfophenylazopyrazole trisodium salt 5-Hydorxy-1-(p-sulfophenyl)-4-[(p-sulfophenyl)azo]pyrazole-3-carboxylic acid trisodium salt
Synonyms	C.I. acid yellow 23; Hydrazine yellow; FD&C Yellow No. 5; C.I. Food Yellow 4; C.I. 19140
Molecular weight	534.39
Description	Bright orange-yellow powder.
Solubility	Freely soluble in water. Aqueous solution becomes redder with sodium hydroxide.

X. Sunset Yellow

Pharmaceutical properties (Windholz, 1983)

Chemical structure



Empirical formula $(C_{16}H_{10}N_2Na_2O_7S_2)$

Chemical name	6-Hydroxy-5-[(4-sulfophenyl)azo]-2-naphthalenesulfonic acid disodium salt 1-p-Sulfophenylazo-2-naphthol-6-sulfonic acid disodium salt
Synonyms	FD&C Yellow No. 6; C.I. Food Yellow 3; C.I. 15985
Description	Orange-red crystals
Solubility	Soluble in water. Slightly soluble in ethanol.

XI. Sodium Bisulfite

Pharmaceutical properties (Windholz, 1983)

Empirical formula	($NaHSO_3$)
Synonyms	Sodium acid sulfite
Molecular weight	104.07
Description	White, crystalline powder, SO_2 odor, disagreeable taste, on exposure to air it loses some SO_2 and is gradually oxidized to sulfate.
Solubility	Soluble in 3.5 parts cold water, 2 parts boiling water, in about 70 parts alcohol.