Pharmaceutical eutectics: characterization and evaluation of tolbutamide and haloperidol using thermal analytical and complementary techniques

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Pharmaceutical Eutectics: Characterization and Evaluation of Tolbutamide and Haloperidol using Thermal Analytical and Complementary Techniques

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A considerable number of drugs on the market have been shown to have low bioavailability and solubility due to poor dissolution in the gastrointestinal tract. Different approaches have been attempted in the past to enhance the dissolution and oral absorption of drugs. Among these approaches which have been used includes binary eutectic mixture formation between drugs and hydrophilic carriers. A binary eutectic mixture is a mixture of two constituents that solidifies simultaneously when cooled from the liquid state, without changing the composition. In binary mixtures, the poorly soluble drug is dispersed in a hydrophilic carrier resulting in a reduction of particle size which increases the dissolution rate, thus changing the biopharmaceutical properties.

In this study, the dissolution rates for tolbutamide and haloperidol in the presence of hydrophilic carriers were investigated using differential scanning calorimetry (DSC), x-ray powder diffraction (PXRD), scanning electron
microscope (SEM) and dissolution testing. The physical mixture method was used for the preparation of the eutectic mixtures. A eutectic mixture was formed between 80% tolbutamide and 20% nicotinamide, 55% haloperidol and 45% aminophylline and 80% tolbutamide and 20% niacin. The PXRD results show that the eutectic mixtures are crystalline, stable with no interaction among the constituents. The SEM results show that there is a major particle size reduction which in turn enhances the dissolution rate of the drug. Dissolution studies revealed that significant increases in drug solubility are seen in the eutectic mixtures.
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Chapter One

Introduction

A considerable number of drugs on the market have been shown to have low bioavailability and solubility. Different approaches have been made in the past to enhance the dissolution and oral absorption of drugs (1). Among these approaches which have been used includes eutectic mixture formation between drugs and hydrophilic carriers using physical mixture method (2). The formulation of eutectic mixture using proper carrier, reduces the drug particle size, and increases the dissolution rate and thus changes the biopharmaceutical properties (1). This concept is fundamental in the formulation of drugs products. A eutectic mixture is a blend of two or more components, which has a lower melting point than that of any of the constituents (3). A eutectic mixture of sparingly water soluble and a highly water soluble carriers may be considered thermodynamically as an intimately blended mixture of its two crystalline (4). These components are assumed to crystallize simultaneously in a particulate size
The increased surface area for the components is mainly responsible for the increased dissolution rate of sparingly water soluble drugs (4).

![Phase diagram of a binary eutectic](image)

**Figure 1.1** Phase diagram of a binary eutectic (8)

The phase diagram which is shown in the above figure demonstrates the definition of eutectic mixtures. In this case, the very top of the diagram illustrates the two components are melted and the very bottom part of the phase diagram demonstrates the binary mixture (A and B) exist as solid. The left corner of the phase diagram which is sandwiched between the solid and liquid showed that component A exist as solid while component B is a liquid. Similarly, on the right side component B exist as solid whereas component A exists as liquid. E is the
point in which all the three phases exist at the same time. The composition of the
two components at E may vary depending upon the types two components in
the mixture.

In this study, two drugs were selected for the investigation of eutectic formation
with water soluble carriers or other drugs. These drugs were taken based on their
poor solubility in water. These drugs are tolbutamide and haloperidol. As a
result of their poor solubility in water, the bioavailability and dissolution rate of
these drugs are very limited.

In the eutectic mixtures preparation, niacin, niacinamide and aminophylline
were used as carrier. These carriers are very soluble in water. The eutectic
mixtures could be prepared using fusion method, solvent method, fusion-solvent
method and physical mixture methods. In this study, the physical mixture
method was used. Various techniques such as differential scanning calorimetry
(DSC), x-ray powder diffraction (PXRD), scanning electron microscopy (SEM),
and in vitro dissolution studies were used to characterize these mixtures.

The DSC is used to investigate the thermal behaviors of the two components in
the mixture. This instrument is also essential in identifying the formation of
eutectic and its composition. In addition, this instrument provides information
on the heat of fusion as well as the melting temperature of each component.
The PXRD is used to perform both qualitative and quantitative analysis of samples. This instrument is vital for the understanding of the structures of each component. Moreover, it also provides fundamental information on the interaction of components.

SEM is another instrument that is used in this study. SEM is an excellent tool, which is capable of providing results on particle size. Finally, dissolution analysis is used to evaluate and compare the dissolution rate of the pure drug with that of the eutectic mixtures.
Chapter Two

Introduction to Pharmaceutical Solid dispersion

2.1 Introduction

Generally drugs are administered as a solid dosage forms which includes tablet, capsules or suspensions which must be released from the dosage form and dissolved in Gastrointestinal (GI) fluid before it gets absorbed (1). The solubility and dissolution rate of many sparingly water soluble drugs limits the bioavailability of those particular drugs (2). There are two consecutive transport routes which can describe the oral absorption of drugs from solid dosage forms: dissolution of the drug in vivo to produce a solution; and transport of the dissolved drug across the gastrointestinal membrane (3). Each step can be recognized by the rate constant. The rate of dissolution can be the rate limiting steps if it is sluggish compare to the rate of absorption. Furthermore, particle size of the drug also plays enormous role in the transport from the GI tract to the site of action (3-4). There are different approaches for particle size reduction. Some of these approaches include: conventional trituration and grinding; ball milling fluid energy micronization; controlled precipitation by change of solvent or
temperature (4). Administration of liquid solutions from which, upon dissolution with gastric fluids, the dissolved drug may precipitate in very fine particles; and (5) administration of water soluble salts of poorly soluble compounds from which the parent neutral forms may precipitate in ultrafine form in GI fluids (4-6). Even though the reduction of particle size can be easily achieved with the first four methods, the reduced particle size may not produce faster dissolution and absorption (3). This could be due to possible stronger van der waals attraction between non polar molecules (5). Solvent methods seem the best way to compare to others to achieve particle size reduction. However, due to the involvement of toxic solvents, it is not very applicable in the commercial markets (3, 7).

It is vital to understand this pharmaceutical technique so that increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms can be achieved. Hence, knowing what methods of preparation to use, selection of appropriate carriers, and the determination of the physical properties, limitations, and disadvantages for all ingredient used will be important aspect in the practical and effective application of dosage forms as development.

The main goal of this study is to understand the solubility and dissolution rate of poorly water-soluble drugs. In addition to enhancing the solubility and dissolution rate of these drugs using hydrophilic carrier, it may be possible to reduce the dose and thereby lower toxicity and side effects.
2.2 Dissolution studies

The dissolution rate may be defined as the amount of drug substance that is dissolved per unit time under standardized conditions of liquid-solid interface, temperature, and solvent composition (8, 9). The most universal theory for dissolution is called diffusion layer model, which agrees with the assumption that dissolution belongs to a type of heterogeneous reaction where the rate is determined by the transport process (3).

2.3 Noyes –Whitney and Nernst-Brunner Equations

According to Noyes and Whitney (10), the rate at which a solid substance dissolves into a solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution. This can be written mathematically as follows:

\[ \frac{dc}{dt} = K(C_s - C_b) \]  \hspace{1cm} \text{Eq. 2.1}  

Where:  \( dc \) = the dissolution rate  

\( K \) = proportionality constant;  

\( C_s \) = the solubility of the solute  

\( C_b \) = the concentration at any time (t).
The equation above can be explained as: (1) a thin layer of saturated solution is formed at the surface of the solid and the rate of dissolution is governed by the rate of diffusion from this layer to the bulk of the solution, and (2) there is negligible change in the surface area with time during dissolution (1).

According to Noyes and Whitney (10) and Brunner and Tolloczko, under specific conditions of temperature and agitation, the surface area (S) is proportional to the dissolution rate.

\[
dc = K_1S(C_s - C_b) \quad \text{Eq. 2.2}
\]

Where: \( C_s = \) solubility of the solute,

\( C_b = \) concentration at any time (t)

\( K_1 = \) intrinsic dissolution rate constant

According to Fick’s law of diffusion (2), Nenst and Brunner (2) introduced a modified equation by defining the intrinsic dissolution rate constant as follows:

\[
K_1 = \frac{D}{hV} \quad \text{Eq. 2.3}
\]

Where: \( h = \) the thickness of the diffusion layer,

\( D = \) the diffusion coefficient of the solute, and

\( V = \) the volume of the dissolution medium.
2.4 Cube Root Law

This law was first introduced by Hixon and Crowell (11). The law is based on a number of theories which includes: dissolution takes place normal to the surface of the dissolving solid particle; there is no stagnant liquid all over the region, the agitation effect is equal on all parts of the solid surface; solid particles remain intact during the dissolution process and the diffusion layer thickness is independent of the diameter of the particle. The idea of changing surface area during dissolution is given by the following equation:

\[
(W_o)^{1/3} - (W_t)^{1/3} = (Np/6)^{1/3} \frac{2DC_s t}{Hp}
\]

Eq. 2:4

Where: Wo = the initial weight of solid,

\[ W_t = \text{the weight of solid at time (t)}, \]

\[ N = \text{the number of particles}, \]

\[ \rho = \text{the density of the solid}. \]

2.5 Definition of Solid Dispersion

Mohammed (3) defined solid dispersion as the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by either the melting, solvent or the melting-solvent method. This definition has become broadened in order to include nanoparticles, microcapsules, and microspheres.
In the beginning the main goal of solid dispersions was to improve bioavailability of poorly water soluble drugs. However, this concept has been changed recently to engage the aim of achieving others goals such as sustained release drugs and changing solid state properties (12).

2.5.1 Classification of solid dispersions

According to Chiou and Riegelmen (5,9), solid dispersions are classified into six major groups, namely: Simple eutectic mixtures, Solid solutions, glass solutions of suspensions, compound or complex formations between the drug and the carrier, amorphous precipitations of a drug in a crystalline carrier and any combination of these groups.

2.5.1.1 Simple eutectic mixtures

According to Goldberg (1), a simple eutectic mixture consists of two compounds (A and B) that are completely miscible in the liquid state but have only a very limited distribution in the solid state. The melting point of the two compounds is plotted against mixture composition. At a specific composition, the eutectic point is reached. The composition at that particular point is the eutectic mixture which has the lowest melting point for the two compounds. The technique has been applied to many drugs (13).
Differential Scanning Calorimetry (DSC) of the two compounds usually produces two endothermic peaks. However, in the case of a eutectic mixture, the two compounds produce a single peak which show a lower melting point compared to the individual components. A simple eutectic mixture can be prepared in four different ways. These include the physical mixture method, solvent method, fusion method and solvent-fusion method.

2.5.1.2 Solid Solutions

In solid solution the two components crystallize together in a homogenous one phase (15). According to Goldberg (4), particle size is reduced in a solid solution
to a molecular level. This means that the dissolution of the drug happens in the solid state matrix. As a result of these, the eutectic mixture dissolution rate is enhanced. According to Mohammed (3), for binary systems, in which the formation of solid solutions is apparent, the phase diagram is described by the disappearance of thaw points at a higher temperature than the eutectic point. Based on their miscibility, solid solutions are divided into being continuous and discontinuous space. On the other hand, depending on how the solvate distributed in the solvent, solid solutions are classified into Amorphous substitutional and interstitial.

2.5.1.3 Continuous solid solutions

In continuous solid solutions, the two components (A and B) are miscible in all proportions. In the case of continuous solid solutions, the bond strength between the two components is stronger than the bond strength between the molecules of each individual component (3). According to Raul (5), Solid solutions of this type have not been reported in the pharmaceutical literature to date. The concept of continuous solid solution is summarized in the following diagram.
2.5.1.4 Discontinuous solid solutions

In discontinuous solid solutions, components are not miscible in all proportions. According to Goldberg (4), the concepts of discontinuous solid solutions need only to be applied when the mutuality of the two components exceeds 5%. The following solid solution diagram demonstrates the miscibility of two components (A and B) miscibility in various proportions. Figure 2.3 shows that, in the (α) region component (A) is considered as a solvent where as component (B) is a solute. In this region above the eutectic point temperature, component B is completely soluble in solid (A). Below the eutectic point temperature the two components exist as a solid. On the other hand, the β region demonstrates that component (B) acts as a solid solvent where as component (A) is as solute. Discontinuous solid solutions exist in both the left and right regions above the eutectic point temperature.
2.5.1.5 **Substitutional crystalline solid solutions**

In substitutional crystalline solid solutions (5), the solute molecules can either replace solvent molecules in the crystal lattice or squeeze into the interstice spaced between the solvent molecules. Substitutional solid solutions can only take place if the solute molecule is smaller than the solvent molecules by 15% (14). Figure 2.4 demonstrates the above explanation.

![Phase diagram of a substitutional solid solutions](image)

**Figure 2.4** Phase diagram of a substitutional solid solutions (5)
2.5.1.6 Interstitial crystalline solid solutions

In interstitial crystalline solid solutions the dissolved solute molecules hold on to the space between the solvent molecules (5,15). Similar to the substitutional crystalline solid solutions, the interstitial crystalline solid solutions are highly dependent on the size of the solute molecules. Interstitial crystalline solid solutions, the solute molecule diameter should not be greater than (0.59) of the solvent molecular weight (8). Moreover the total volume for the solute should not exceed 20% of the solvent (6).

Figure 2.5 Phase diagram of interstitial crystalline solid solutions (5)
2.5.1.7 Amorphous solid solutions

In amorphous solid solutions, the solute molecules are dispersed irregularly between the solvent molecules (5). According to Chiou and Riegleman (9), griseofulvin in citric acid was the first to report that these materials form an amorphous solid solution which enhanced the dissolution properties of the drug. More water soluble carriers are used for this purpose today. In addition, polymers including Polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) have shown the tendency to form amorphous solid solutions specially when the polymers exist in an amorphous form. In this case, the solute molecules acts as a plasticizer for the polymer which causes the polymer to weaken the glass transition temperature.

![Diagram of amorphous solid solutions](image.png)

**Figure 2.6** shows the structure of amorphous solid Solutions (5)
2.6 Glass transition and Glass suspensions

According to Chiou and Rigeleman (9), a glass solutions defined as a homogenous solution in which a solute dissolve in a glassy solvent. According Habib (4), when PVP is dissolved in organic solvents, it undergoes a transition to a glassy state upon evaporation of the solvent (4,16). The term ‘glassy’ is characterized by being the transparent and brittle below the glass transition temperature, (Tg) (17). It softens gradually and continuously without showing a sharp melting point.

2.7 Compound or Complex Formation

Compound or complex formation is characterized by the formation of complex between two components in a binary system upon solid dispersion preparation (2). According to Muhammad (4), the bioavailability of a drug from the complex relies up on the solubility, dissociation constant, and the intrinsic absorption rate for the complex. For instance, PVP has shown to reduce the pharmacological action of penicillin (9).

2.8 Preparation Methods

The preparation of a solid dispersion can be performed in one of four ways. These include the solvent method, fusion method, fusion-solvent method and physical mixture methods which will be described below.
2.8.1 Solvent method

In the solvent method (5,12), the preparation is done by mixing the carrier with the active ingredient and dissolving them in an appropriate organic solvent. This is followed by the evaporation of the organic solvent under vacuum or using an elevated temperature. After removal of the solvent, the precipitation constituents result in a solid residue upon drying under vacuum. This part of the process is important in order to remove any organic solvent that gets trapped between the particles and particles surface. However, there is the risk of solvate formation with any of the constituents (3,12). The main advantage of solvent method is the absence of applying high temperature to the carrier and the other active ingredients during preparation. This eases the possibility of thermal decompositions of the ingredients (5). On the other hand, there are a number of disadvantages using this method (13). The primary disadvantage is the use of organic solvents. It is difficult to remove all the solvent molecules from the constituents. As a result the remaining solvents in the constituents can cause adverse effects and reduce the stability of the ingredients. In addition, higher cost of preparation, selection of common solvents, and reproducing crystal forms are major risks that are associated with the use of the solvent method (5).

2.8.2 Fusion method

The fusion method is also called the melting method (13). It was first introduced by Sekigushi and Obi (14). The preparation is carried out in the presence of heat.
The carrier and other active ingredient melt together followed by solidification using an ice bath with continuous stirring. Finally, the product gets crushed, pluverized and sieved after drying. If the active ingredient shows high solubility in the carrier, the active ingredient may stay dissolved in the solid state. This is then called a solid solution (3). Particle reduction enhances molecular dispersion of the drug in the carrier matrix. Moreover, super saturation of the drug in the system can be produced by quenching the melt rapidly from high temperatures. The major concern of using fusion method is drug exposure to elevated temperatures, specifically when the drug is heat sensitive and the carrier is a high melting solid.

2.8.3 Fusion-solvent method

In the fusion-solvent method, the drug is incorporated in the form of a solution after the carrier has melted (5,16). The solvent is evaporated until a clear film remains. A few factors involved when using this method. Some of these factors include the possibility that the solvent that used to dissolve the drug may not be miscible with the carrier (3). In addition the solvent may affect the polymorphic form of the drug (17).

2.8.4 Physical method

In the physical method, the drug and the carrier are mixed together for 10-15 minutes using a mixer or mortar and pestle. This method shows some
advantages that it avoids the use of toxic organic solvents to dissolve the samples as well as heating the samples. The disadvantage of this method is reproducibility of the results.

2.9 Role of carriers in solid dispersion

Solid dispersions can be prepared in different ways, however, each method needs their particular association with carriers during preparation. There are a number of water soluble carriers that are used in the preparation of solid dispersions (3). Some of these are Polyethylene glycol (PEG), Polyvinylpyrrolidone (PVP), Polyvinylalcohol (PVA), and urea(4). Sugars, such as manitol and sucrose are carriers that provide comparable use in solid dispersion (3). In addition to polymers and sugar, water soluble drugs such as nicotinamide and niacin can also be used in the preparation of solid dispersions (4).
Chapter Three

Dissolution Studies

3.1 Introduction

Dissolution studies for drugs are essential for the successful performance of a dosage form. The term dissolution can be defined as a process in which a known amount of drug dissolves in a given medium per unit of time under standardized conditions (1). Dissolution testing is important to evaluate and compare intra and inter-batch performance compliance of dosage forms (2). Both the bioavailability and bioequivalence data that are obtained from the dissolution studies can be utilized for the development of new formulations for the pharmaceutical industry. In addition, a drug release study in vitro, using dissolution testing can be used to understand the drug releasing profile in vivo (1). For this reason it is necessary to perform dissolution studies for drugs. In general, dissolution studies must be based on the specific conditions that are required to study each particular drug. These conditions include selecting the appropriate media, dissolution apparatus and operation variables (3-6).
addition, dissolution studies are carried out by following the specifications outlined in the United States Pharmacopeia (USP) (3).

3.2 Instrumentation

3.2.1 Dissolution Apparatus

The USP provides seven various dissolution apparatuses that are used for the dissolution testing of different dosage forms (7). In addition, the USP is also provides a specific guideline for each apparatus. These dissolution apparatus contain specific identification numbers provided by the USP (3, 4).

3.2.1.1 Dissolution apparatus 1

Dissolution Apparatus 1 is also known as basket apparatus (8). It is mostly used to study dissolution profiles for tablets. It contains cylindrical baskets, dissolution vessel and motor. The baskets vary based on the mesh size required for the test.

Figure 3.1 Shows the various mesh sizes basket
The cylindrical vessel height ranges from 160-210 mm, inside diameter is from 98-106 mm. The nominal capacity of the vessel is 1000 mL. Both the basket and the vessels are made of stainless steel. During the experiment the basket position must be kept 25±2 mm above the bottom of the vessel.

3.2.1.2 Dissolution Apparatus 2

Dissolution Apparatus 2 is also known as the paddle apparatus (7). It is mostly used for immediate release study for capsules. The shaft position is 2 mm away from the vertical axis of the vessel and rotates smoothly without major wobble (1). The shaft and blade are made of a single unit that may be coated with Teflon or gold. The distance between the bottom of the vessel and blade must be maintained at 25±2 mm.
3.2.1.3 Dissolution Apparatus 3

Dissolution Apparatus 3 is also called the reciprocating basket (7). It consists of a set of glass reciprocating cylinders, screen made of suitable non interactive material and flat bottom glass vessels. The vessels should be kept in water bath. The temperature of the water bath must be equivalent to body temperature. The major advantage of dissolution Apparatus 3 is that gastrointestinal tract conditions can be easily simulated and it is easy to make time dependent pH changes (2). This apparatus is mostly used for extended release or delayed release dosage forms.
3.2.1.4 Dissolution Apparatus 4

Dissolution Apparatus 4 is also known as the flow through cell (8). The assembly of this apparatus consists of a reservoir and a pump for the dissolution medium, a flow through cell, a water bath that maintains dissolution medium at body temperature (3). The flow through cell can be of various sizes depending on the drug delivery system. This apparatus is usually used for nondisintegrating drug delivery systems (4).

3.2.1.5 Dissolution Apparatus 5

Dissolution Apparatus 5 is also known as paddle over disk (8). It is a modified form of Apparatus 2 with the addition of stainless steel disk that is designed to hold and test the transdermal systems at the bottom of the vessel. This apparatus evaluates the dissolution profile for transdermal drug delivery systems.

3.2.1.6 Dissolution Apparatus 6

Dissolution Apparatus 6 is also known as the rotating cylinder (7). This instrument is a modification of Apparatus 1 except that the basket is replaced by a hollow stainless steel cylinder and the transdermal dosage form is kept at the center of the circumference of the cylinder with the drug releasing side directed outward.
3.2.1.7 Dissolution Apparatus 7

This instrument is a modification of dissolution Apparatus 5. It is also called the reciprocating holder (8). It is designed for the dissolution testing of both nondisintegrating drug delivery system and transdermal drug delivery system. This instrument has similar arrangement with dissolution Apparatus 3.

3.3 Applications of dissolution apparatus

The application of dissolution testing is essential in order to understand and characterize the release rate of drugs in vivo (7). After the drug shows promising result in phase I trials, the preformulation process including the dissolution testing will be carried out. During the dissolution testing, the effect of diluents on the dissolution profile of the active ingredients will be studied (1). Different pH buffer media should be used to get the needed solubility. Some of the most common buffer media are pH 4.5 acetate, pH 6.8 phosphate and 0.1N HCL (8). The temperature of the media must be kept at 37 ± 0.5ºC. Samples must be withdrawn from the media in a timely manner.
Chapter Four

Differential Scanning Calorimetry (DSC)

4.1 Introduction

Thermal analysis techniques can be described as techniques, which involve measuring the physical and chemical properties of a substance, mixtures of substances or reaction mixture as a function of temperature or time, whilst the sample is subjected to a controlled temperature program (1). It provides essential data on the properties of substances for processing and application (2). Some of these techniques include thermal mechanical analysis (TMA), thermal gravimetric analysis (TGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC).

TMA is important in order to measure changes in dimension and allows determining the thermal coefficients of expansion and phase transition (3). Whereas TGA measures mass changes which allows us to determine thermal stability and degradation curves, DTA is used to measure the temperature difference between the sample to be investigated and a reference sample as a
function of temperature or time (4). According to Hohne (1), the advantage of DTA as compared to conventional calorimetry, is the scanning mode which allows reactions to be analyzed which are thermally activated and with high sensitivity anomalies seen with the temperature time function. The further advancement of DTA led to the construction of the DSC (3).

Differential Scanning Calorimetry (DSC) can be described as the measurement of the change in the difference in heat flow rate to the sample as compared to a reference sample while they are both subjected to a controlled temperature program (5). The way the DSC works is that it monitors the effect of heat related to the phase transitions and chemical reactions as a function of temperature (6). The reference heat flow compared to the sample heat flow is recorded as a function of temperature. The reference may be an empty platinum, aluminum or gold pan.
Figure 4.1 Features and properties of a DSC curve (7)

The temperature for both the sample and reference pans is increased at a constant rate. Since the pressure in the sample and the reference pan is equal, then the heat flow is equivalent to the enthalpy which is shown in the following equations

\[
\frac{dq}{dp} = \frac{dH}{dt} \quad \text{Eq. 4.1}
\]

Where: \( \frac{dq}{dp} \) = enthalpy

\[
\frac{dH}{dt} = \text{heat flow}
\]

Heat flow can be expressed as follows:

\[
\frac{dH}{dt} = (\frac{dH}{dt})_{\text{sample}} - (\frac{dH}{dt})_{\text{reference}} \quad \text{Eq. 4.2}
\]
The change in heat flow can be either positive or negative. In an endothermic process, which occurs in most phase transitions, heat is absorbed and, as a result, heat flow to the sample is higher than the reference (1, 6). In the case of an exothermic reaction such as crystallization, oxidation reactions and some decomposition reactions the heat flow is negative (8).

4.2 Types of DSC

Depending upon the operation mechanism of the DSC; it can be grouped into two categories, namely:

(1) Heat flux
(2) Power compensation

4.2.1 Heat Flux DSC

In a heat flux measuring system, the main heat flows from the furnace to the samples, via a disc of medium thermal conductivity (3, 8). When heat is applied to the furnace, heat flows via the disc to the samples. If the samples are positioned symmetrical to the center, the differential temperature signal (T) is zero. If the steady state equilibrium is disturbed as a result of a sample transition, a differential signal will be generated. This signal is proportional to the difference between the heat flow rates to the samples and to the reference sample as follows:

\[ \Delta T = T_S - T_R \]

Eq. 4.3
Where: 

\[ T_S = \text{sample temperature} \]

\[ T_R = \text{reference temperature} \]

\[ \Delta T = \text{change in temperature} \]

The heat capacity of the sample there exists a temperature difference between the sample and reference pans which is measured by area thermocouples and the series heat flow is determined by the thermal equivalent of Ohm’s law as (3):

\[ q = \frac{\Delta T}{R} \quad \text{Eq. 4.4} \]

Where: 

\[ q = \text{sample heat flow} \]

\[ \Delta T = \text{temperature difference between sample and reference} \]

\[ R = \text{resistance of thermoelectric disk} \]

4.2.2 Power compensation DSC

In power compensation DSC, the sample and reference pan are in separate furnaces heated by separate heaters (3). The principle behind its functions is that this system consists of two similar microfurnaces that are mounted inside a thermostated aluminum block. The microfurnace is around 9 mm in diameter with an approximate height of 6 mm and has a mass of 2 g. Upon heating, equal heating power is provided to both microfurnaces via a control circuit. If there is
identical thermal symmetry, the temperature of the microfurnaces is always the same. However in the case of any temperature variation between the microfurance containing the sample and the microfurnace containing the reference, this differential will be measured and compensating power will be provided which is proportional to the remaining temperature difference (1). Figure 4.2 shows the difference between the power compensation and heat flux DSC processes.

Figure 4.2 Power compensation (a) and heat flux (b) DSC (9)

4.3 Fundamental parameters for analyzing samples in the DSC

There are guidelines that must be followed in the use of DSC instruments. These guidelines include both the researcher as well as the computer software that is
attached to the DSC instrument. These guidelines include the selection of the correct pan for the experiment, calibration of the instrument, sample preparation, choosing the correct temperature range, setting the purge gas flow rates and loading the sample (10).

4.3.1 Sample pans

DSC sample pans differ based on the material from which they are made and the temperature range required for the experiment. The materials for pans includes are aluminum, gold, copper, platinum, and graphite (11). Experiments that go up to 600°C can use aluminum pans (3). Gold, copper, platinum, and graphite pans can be used up to 725°C (12). Pans can be used as open, closed or pin hole depend on the experiment that will be performed. Closed pans and pin hole pans can be prepared using the DSC pan press. Closed pan is relatively more advantageous than others. It improves the thermal contact between the sample, pan and disc, while reducing thermal gradients in the sample, minimizes spillage, and enables retention of the sample for further study (12, 13). Hermetic pans are used for volatile liquids for the determination of specific heat (13).

4.3.2 Sample mass

Generally, sample size in the DSC analysis can be between 1-10 mg. It is essential to exactly measure the mass because it reduces thermal gradients across the sample. During sample preparation; it is not a good idea to touch the sample
with your bare hand. This is because some dirt from the hand may fall into the sample which can eventually affect the final results.

4.3.3 Purge Gas

Atmospheric air that may cause oxidation of the samples can be controlled by using a purge gas. The most common purge gases used in DSC are nitrogen, helium and argon (3). Flow rate can vary between 50 mL/min to 80 mL/min depending upon the experiment. However, a flow rate between 50-80 ml/min is most often used.

4.3.4 Calibration of DSC Instrument

Calibration of the DSC must be performed before the experiment begins in order that the results can be accurate. The calibration procedure which is needed can vary depending on the DSC model and heat flow. In most cases Indium and Zinc are used to calibrate the instrument (2).

4.4 Temperature calibrations

According to W.F. Hemminger (1), temperature calibration means refers to unambiguous assignment of the temperature “indicated” by the instrument to the “true” temperature. In this case, the true temperature can be defined by fixed points with the help of calibration substances. The temperature “indicated” by the instrument must be derived from the measured curves that need
extrapolation to zero heating rates in order to eliminate the influences of instrument and sample parameters (2).

4.5 Calorimetric Calibrations

Caloric calibration can be defined by the proportionality factor between the measured heat flow rates, \( \phi_{\text{true}} \) and the true heat flow rate, \( (\phi_m) \) between the measured exchanged heat and the heat truly transformed (2).

\[
\phi_{\text{true}} = k \phi m \quad \text{Eq. 4.5}
\]

\[
Q = K_Q Q_m \quad \text{Eq. 4.6}
\]

Heat flow calibration can be carried out in one of two ways: the first is by installing an electric calibration heater in place of the sample or inside the sample (1). This method has some advantages and disadvantages. Some of the advantages are heating power can easily be determined with great accuracy, heater can be switched on and off and any temperature changes results in the shift of the position of the baseline which can be then determined (2). Disadvantages for using electric calibration include installation of the heater in the sample or in place of the sample are difficult. The installation can cause systemic errors and heat fluxes can cause heat leaks. The other method for heat flow calibration is using a known heat capacity of a sample (2). The advantage for using this method includes its ability to all DSCs, no wire is required so that
no heat leaks can occur; and calibration of the heat flux at the sample location is relatively simple.

4.6 Sample preparations

Sample preparation for DSC analysis is essential for the success of the experiment. Glove wearing is important during sample preparation in order to prevent sample contamination that may lead to incorrect results (12). Weigh papers must also be clean so that it will minimize systemic errors such as mixing in of dust which may occur during sample preparation (14). The pan size is another important factor during sample preparation. Hence, the amount of sample which can be used depends on the pan size. In addition, the pan size should be equivalent to the reference pan in order to obtain accurate result. Small sample size shows smaller temperature gradients than large sample sizes. For this reason, small samples are considered advantageous in thermal analysis studies (15). Particle shape and particle size of the samples are important factors in the thermal analysis studies (16). There must be good thermal contact between the sample and the pan in order to produce a uniform thermal gradient (17).
5.1 Introduction

Scanning electron microscopy (SEM) is a technique, which is used to produce magnified images of small selected areas of solid samples (1). Imaging is produced by scanning the sample with an electron beam while displaying the signal from the electron detector on a TV screen or computer monitor (2). SEM generally operates under a high vacuum and dry environment in order to emit the high energy electrons beams that are needed for imaging. The imaging system relies primarily on the specimen being adequately electrically conductive to ensure that the bulk of the incoming electrons are the grounded (3). One of the most critical factors in the success of SEM is that images of three-dimensional samples are usually amenable to interpretation by the observer (3, 4). SEM image formation relies on collecting the different signals that are scattered as a result of the high-energy beam interacting with the sample (5). Backscattered electrons and secondary electrons are the two major image signals that are used for image formation. These are generated within the primary beam and with sample
interaction (1). Backscattered electrons are used to show compositional variations, where one could secondary electrons are used to reveal topographic features of the specimen (4).

5.2 Focusing, Magnification and Resolution

Correct focus setting is attained by adjusting the control to acquire the sharpest feasible image of fine detail in the specimen (4). Setting a high magnification value usually supports this. Magnification values can be expressed as the ratio of the size of the image as viewed to that of the raster scanned by the beam on the specimen (1). Resolution is expressed as the smallest feature clearly visible depending upon the size of the image (1). Resolution is limited to both the diameter of the electron beam and the interaction between the electron and the specimen. Shorter working distances produce a higher resolution image.
5.3 Instrumentation

5.3.1 Electron Gun

An electron gun, also known as an electron emitter, is an electrical component which is capable of producing an electron beam. Inside the electron gun, there is a major component called the filament which is the source of the electrons (1,3).
An electron gun is usually composed of a tungsten filament that emits electrons (1). The standard filament or cathode is composed of V-shaped wire with an approximate diameter of 100 µm (2). By applying a high voltage approximately between 20keV to 40keV, electrons can be pushed out of the outer most shell of the tungsten filament. The overall design of the electron gun is shown in figure 5.2.

![Figure 5.2 Schematic of an electron gun (6)](image)

The electron gun performance is highly dependent on the operating temperature. At the optimal temperature, the electron gun can easily produce electrons. This prolongs the life of the filament. The mean life of a tungsten filament is roughly 25 hours for older models and 200 hours for newer models which contain a good vacuum system in the microscope (1, 7). The major causes of filament failure include poor vacuum, high voltage and air contamination due to age (1). The electron gun also contains negative potential (wehnelt cap). The Wehnelt cap (1)
is responsible for forcing electrons into the proper direction. The Wehnelt cap is a negative potential through which electrons get repelled to the anode. The anode is attached to the ground into which highly negative electrons get pulled towards it. The negative shield and the anode act as an electrostatic lens to produce an image of the electron source near the electron (8).

5.3.2 Electromagnetic Lenses

Electromagnetic lenses are important to capture electrons that travel off the axis. Electromagnetic lenses have two poles that are intended to focus electrons in the correct direction. Electromagnetic lenses demagnify the beam of electrons into a small area known as a spot. The spot size can be adjusted by a control called the spot size controller which is an essential tool of SEM (9).

5.3.3 Detector

Unique detectors must be installed in order to collect backscattered electrons. Installation of detectors affects the performance for collecting electrons. The efficiency of collecting electrons can be enhanced by increasing the surface area of the detectors and positioning them above the specimen in which backscattered electrons most probably will be encountered (1). There are different kinds of detectors for backscattered electrons. From among these, the one most commonly used is the solid state detector. Solid state detectors are less expensive, sensitive to differences in atomic number and easy to operate (2). In addition, a secondary
electron detector, in particular a cathodoluminescence is used mainly for conventional imaging utilizing topographic contrast. A cathodoluminescence detector has a better sensitivity. Other detectors that are used in SEM include a scintillator-photomultiplier and specimen current detector.
Chapter Six

Ultraviolet spectrometer

6.1 Introduction

For several years, UV-Vis spectroscopy has been used for both qualitative and quantitative analysis studies (1). The qualitative analysis aspect for this instrument is associated with identifying unknown samples and the detection of impurities in known samples (2). The quantitative analysis is carried out by comparing sample absorption or transmission spectra with the control spectra. A UV-Vis spectrometer is used to determine the concentration of a particular sample using the Beer’s law (4).

Figure 6.1 Schematic of a UV/Vis spectrophotometer (3)
It is used in the pharmaceutical industry, cosmetic industry and for environmental pollution studies. The UV-Vis spectra results from electron transitions taking place in the analyte molecules of the sample (4). Many electron transitions occur due to superimposition of vibration levels at the electronic level which results in continuous spectra rather than simple line spectra which characterizes the overall spectra of the atoms (5). The main application for UV spectroscopy includes identification of chromophoric groups, quantitative determination of molecules and the identification of unsaturated groups within organic molecules.

6.2 Instrumentation

The fundamental parts of the UV visible instrument are: (1) light source; (2) absorption cell (filter); (3) monochromator and (4) detector.

6.2.1 Light source

The most common light source in the UV instrument is the deuterium lamp. If the instrument contains only a deuterium lamp as the source of light, then the instrument is called a UV-spectrophotometer (1). However, if the instrument contains a dual lamp, usually tungsten lamp together with a deuterium lamp, then the instrument is called a UV-Vis spectrophotometer. Deuterium, which is an isotope of hydrogen, is present in the lamp at low pressure. A current applied
to the electrodes in the lamp produce a UV emission due to the presence of deuterium in the lamp. The emitted wavelength ranges from 185 nm to 375 nm.

Figure 6.2 Shows a deuterium lamp for a UV- spectrophotometer (3)

Several instruments use a light lamp with a tungsten filament for the visible region. A tungsten filament lamp is very powerful and produces light in the entire visible region of the spectra (2). In addition to the above two light sources xenon can also be used in order to produce both UV/visible lights (2).

Figure 6.3 depicts of a xenon arc lamp (3)
6.2.2 Absorption filters

Absorption filters are used in order to separate wavelength bands. Colored glass can be used to identify the wavelength of the spectra which is transmitted. An absorption filter wavelength ranges from 30-250 nm (1).

6.2.3 Monochromators

Monochromator (mono-one, chromator-color) is made up of three parts: an entrance slit; dispersing slit; and an exit slit (6). The entrance slit is the first gate where light enters from the source to the monochromator. The function of the entrance slit is to create a unidirectional beam of light which, when originally emitted is a multidirectional beam of light from the source (6, 7). After entering the monochromator via the entrance slit, it will encounter the dispersing slit which is basically present to disperse the unidirectional beam of light into its constituent wavelength (1). Finally, the spectrum exits via the exit slit. A double grating monochromators is most commonly used for the measurement of the UV/visible spectrum.

6.2.4 Detectors

The most common detectors for this instrument are the photodiode, also called a light sensor, and a photomultiplier tube.
6.2.4.1 Photodiodes

Photodiodes are most commonly used for the detecting of highly intensified pulsed exciter laser radiation when a dynamic range is needed. Photodiodes can be made of semiconducting materials with silicon (7). Photodiodes work under the principle of converting the incident photons to electrons that are directed to either the electron rich junction (n-junction) or electron poor junction (p-junction) (1). Light shining via the p-junction forms an additional layer in the n-junction which finally creates an electric current and this current will be measured.

6.2.4.2 Photomultiplier

A photomultiplier is a light sensor together with a signal amplifier. The light entering into the sample compartment encounters the photosensitive surface and this result in an amplified electric signal (1).

6.3 The Beer-Lambert Law

Beer’s law fundamentally relies on the relationship between the absorbance of light to the properties of the sample through which the light is passing (2). It is given by the following equation:

\[ A = - \log \left( \frac{I}{I_0} \right) = \varepsilon lc \]  

Eq. 6.1
In which \( A \) is the absorbance of the sample, \( I \) is the intensity of the transmitted light, \( I_0 \) is the intensity of the incident light, \( \varepsilon \) is the molar absorptivity; \( l \) is the path length; \( c \) is the concentration of the sample. Where the concentration is expressed in mole/liter and the path length is given in centimeters, then, \( \varepsilon \) can be determined as:

\[
\varepsilon = \frac{A \times 1000 \text{cm}^3/\text{moles}}{L(\text{cm})c} \quad \text{Eq. 6.2}
\]
Chapter Seven

X-Ray Powder Diffraction

7.1 Introduction

X-ray diffraction technique is used to investigate the physical behaviors of materials that include metals, minerals and other solid materials (1). This technique is highly applicable in the life sciences as well as geological field of studies. It is extremely vital to characterize the nature of various samples whether samples such as drugs are in the crystalline or amorphous form (2). X-ray powder diffraction technique is currently used to identify both quantitative and qualitative information of structures of molecules. Pharmaceutical industries use this technique for such purposes. In simple eutectic mixture, crystalline form of the mixture can easily identified based on the spectra that are produced. X-ray powder diffraction is an important tool to differentiate the eutectic mixture from the drug as well as the carrier alone based on the positions of the spectra (3). The following schematic shows X-ray powder diffractometer.
7.2 X-Ray Diffraction

X-rays are transverse electromagnetic radiation similar to visible light, but of much shorter wavelength (5). Range of wavelength of X-ray is corresponds with wavelength between ultraviolet radiation and gamma radiation. X-ray wavelength is given by angstrom (Å), which lies between 0.5-2.5Å. X-rays generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the target (6). When the x-rays pass via a sample their energy is dissipated due to the ejection of orbital electrons causes scattering (3, 7). When incident rays radiations interact with the electrons of the atom, scattering (diffraction) happens and this scattering vibrates with identical frequency as that of the x-rays (3). These scattered waves from their specific atoms interfere with one another destructively and constructively that leads to a diffraction film on the detector (3, 9). These diffractions are then detected and counted.

Figure. 7.1 Schematic of an X-ray powder diffractometer (4)
7.3 X-ray instrumentation

X-ray diffractometer consists of three fundamental components. These are x-ray tube, sample holder and detector. Incident rays are produced in a cathode ray tube by applying heat to a filament that is capable of producing electrons. Then applied voltage accelerates the electrons towards the metal target and bombarded the electrons with the target (10). When the electrons contain sufficient energy to displace inner shell electrons of the target characteristics of x-ray spectra are produced. These spectra contain a number of components such as $K_{\alpha}$ and $K_{\beta}$. Target materials can be copper, iron or chromium based on the specificity of the wavelength (5). These x-rays are directed to the sample. As the sample and detector are rotated, the intensity of the reflected x-rays is recorded. Constructive interference occurs when the geometry the incident rays imposing the sample fulfill Bragg’s equation.

7.4 Bragg’s Law

When a crystal is bombarded with x-rays of a fixed wavelength at specific angles, intense reflected x-rays are produced when the wavelengths of the scattered x-rays interfere constructively (11). Diffracted waves from different atoms can interfere with each other and the resultant intensity distribution is strongly modulated by this interaction. In order for the waves to interfere constructively, the differences in the travel path need to be equal to integer multiples of the wavelength. When this constructive interference happens, a diffracted beam of x-
rays will leave the crystal at an angle equal to that of the incident beam. In general Bragg’s equation can be expressed mathematically as follows:

\[ n\lambda = d \sin \theta \]  

Eq. 7.1

Where is \( n \) is an integer determined by the order given, \( \lambda \) is the wavelength of x-rays, \( d \) is the space between the atomic lattice and \( \theta \) is the angle between the incident ray and the scattering planes.

Figure 7.2 X-rays reflections on atoms of solids (12)

Figure 7.2 demonstrates that a crystal with crystal lattice planar distances \( d \), where the travel path length variation between the rays that passes through A and C are an integer multiple of the wavelength, constructive interference will take place for a arrangement of that specific wavelength, crystal lattice planar
spacing and angle of incidence (θ). Each rational plane of atoms in a crystal will produce refraction at a single, unique angle for x-rays of a fixed wavelength.

7.5 PXRD Applications

X-ray powder diffraction is mostly used for characterization and identification of crystalline materials. Identification of unknown materials is based on known wavelength of incident rays and angle (θ) where constructive interference takes place. Using Bragg’s equation one can determine the spacing between (d) crystal lattice atoms that produce the constructive interference. A particular crystal can have many planes of atoms in its structure; thus set of reflections of all the planes can be utilized to specifically identify that particular crystal. Generally, crystals with high symmetry for instance isometric system demonstrate relatively few atomic planes, whereas crystals with low symmetry tend to have a great number of possible atomic planes in their structures (13).

Figure 7.3 Modern X-ray diffractometer (14)
7.6 Sample preparations

Sample preparation is an important factor of eutectic mixture analysis by PXRD. The most common and simplest way of sample preparation is to grind the sample into a powder fine enough to mount in the focal plane of diffractometer. However, there are limitations associated with sample preparations. These are the degree of preferred orientation of crystals, accurate position of the planar sample surface within the instrument, differential settings and thickness (15). It is essential that the upper surface of the sample precisely flat to obtain accurate d-spacing. Any offset of that flat surface is possible to cavity mount that needs the powder be packed into recessed cavities (15, 16). Thickness is also another factor in the preparation of sample. Reproducibility is highly depending on thickness. The energy of the beam at the infinite thickness is effectively consumed by diffraction and absorption phenomena. Failure to have infinite thickness causes greater reduction of peaks at higher 2θ angles. Particle size must be fine enough in order to obtain sufficient statistical representation of the constituent and their various diffracting crystal planes. Particle size reduction can be performed by ball milling, mortar and pestle or blender (17).

7.7 Identification of samples

Sample identification is carried out based on the d-spacing and relative peak intensities. Identification is much simpler if the given sample contains only a single element but eutectic mixtures do not contain only single element. Eutectic
mixtures produce complex PXRD patterns that show a challenge for identification. Generally, identification of mixture that contains crystals must be based on the positions and intensities of peaks on the spectra (3, 18).
Materials and Methods

8.1 Materials

8.1.1 Tolbutamide

Tolbutamide is also known as Orinase®. It is a first generation sulfonylurea potassium channel blocker. It is used for the treatment of type two diabetes (1). It is soluble in organic solvents such as acetone and methanol but it is insoluble in cold and hot water (2). It is a white crystalline compound. Tolbutamide is light sensitive and has a melting point of 128-131°C (3).

Figure 8.1 Shows tolbutamide structure (6)
Tolbutamide causes hypoglycemia by mimicking insulin release from the pancreatic β cell (4). The general effect in the treatment of diabetes is more complex. The acute administration of Tolbutamide for type 2 diabetes mellitus (DM) patients increases the release of insulin from the pancreas. Tolbutamide also stimulates release of somatostatin, and it may repress the secretion of glucagon. According to Goodman and Gilman, Tolbutamide attaches to the sulfonylurea receptor 1 (SUR1) subunits and blocks the ATP-sensitive potassium ($K^+$) channel (1, 4). Tolbutamide also reduces the conductance of this channel. Tolbutamide absorption occurs in the gastrointestinal tract. The presence of food and hypoglycemia can reduce its rate of absorption. Hyperglycemia can hinder the motility of intestine and thus can hinder the absorption of the drug. The volume of distribution for Tolbutamide is about 0.2 L/kg. Tolbutamide is metabolized by the liver and its metabolites are excreted in the urine. The adverse effects seen with Tolbutamide include nausea, vomiting, cholestatic jaundice, and agranulocytosis, aplastic and hemolytic anemia (5).

8.1.2 Nicotinamide

Nicotinamide is also known as niacinamide. It is the amide form of nicotinic acid (1,7). It is a white crystalline and odorless compound. It has a melting point of 130 ºC. It is water soluble vitamin. It has an anti inflammatory effect. It also represses antigen induced lymphocytic transformation and the inhibition of 3'-5'
cyclic AMP phosphodiesterase (1). Nicotinamide may prevent Type I diabetes mellitus. Nicotinamide has shown the ability to block the inflammatory actions of iodides known to precipitate or exacerbate inflammatory acne (1, 8).

Figure 8.2 shows nicotinamide structure (9)

Nicotinamide also exhibits an anti-inflammatory effect via the inhibition of the synthesis of pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, interferon (IFN)-γ), inhibition of inducible nitric oxide synthase (iNOS), modulation of free radical scavenging, and suppression of the expression of MHC Class II and some adhesion molecules on immune cells (8,9). Adverse effects seen with nicotinamide include diarrhea, dizziness, itching; nausea, stomach upset, temporary feeling of warmth and headache (8).

8.1.3 Haloperidol

Haloperidol is known commercially as Haldol® (10). It has a molecular weight of 375.87g/mol and a molecular formula of C21H23ClFNO2 respectively. It was purchased from Sigma Chemical Company, Lot No. 35F-0127. Physical
descriptions of haloperidol includes that it is a white microcrystalline powder, odorless, sensitive to light and non-hygroscopic. It is soluble in organic solvents such as chloroform and ether. It is less soluble in water (0.01mg/1mL).

![Haloperidol Structure](image)

*Figure 8.3* Shows the structure of haloperidol (11)

Haloperidol has high a neuroleptic antipsychotic activity, which is due to its antagonist relative selectivity to D₂ dopamine receptors (1,10)). Haloperidol has strong activity against delusions and hallucination, which is the result of its antagonist activity. It blocks the dopaminergic action in the nigrostriatal pathways, which is the probable reason for the high frequency of autonomic and neurologic side effects such as severe anxiety and restlessness. In addition, haloperidol has a risk of developing extrapyramidal effects, which include tardive dyskinesia (1). It has little antihistaminic and anticholinergic properties and as such cardiovascular and anticholinergic side effects includes constipation; hypotension and dry mouth are seen quite infrequently. Haloperidol also has sedative properties and shows a strong action against psychomotor agitation due to a specific action in the limbic system (10). Haloperidol may aggravate
psychomotor agitation via its potent Dopamine receptor antagonism. Dopamine receptor antagonism, particularly the D<sub>2</sub> receptor subtype, can cause akathisia, and psychomotor agitation, which may worsen the condition of some patients. Haloperidol administration is via IM and IV and its dose for adult is 2-20 mg.

8.1.4 Aminophylline

Aminophylline is also known as 1, 3-dimethyl-7H-purine-2, 6-dione; ethane-1, 2-diamine. It is a white crystalline, odorless powder which has a bitter taste. Its melting point is 270°C. The molecular formula of aminophylline is \( C_{16}H_{24}N_{10}O_{4} \). Aminophylline is used for asthma (11). Plant alkaloids were the original source for aminophylline (12).

![Figure 8.4 Shows the structure of aminophylline (13)](image)

Aminophylline inhibits nucleotide phosphodisterease (PDEs). Thus, it inhibits the breakdown of cyclic AMP and cyclic GMP to 5'-AMP and 5'-GMP respectively. Inhibition of PDEs will direct to an accumulation of cyclic AMP and cyclic GMP which finally enhance the signal transduction via these pathways.
Aminophylline is a competitive antagonist at adenosine receptors (1). In addition, aminophylline also may play a part in its antiinflammatory action due to its ability to trigger histone deacetylases in the nucleus. Thus, the deacetylation of histones could reduce the transcription of several proinflammatory genes and potentiate the effect of corticosteroids (1).

8.1.5 Niacin

Niacin is also known as 3-Pyridine carboxylic acid (1). Its molecular formula is C₆H₅NO₂ with a molecular weight of 123.11 g/mol. Niacin is a white crystalline powder. It is a light sensitive compound and has a slight odor. It is highly soluble in water. It has a melting point of 235 ºC.

![Figure 8.5 Shows the structure of niacin (13)](image)

Niacin functions as vitamin only after it converts to NAD or NADP in which it occurs as amide. Oral administration of niacin can affect the level of lipids in the body (13). In addition niacin is the best agent available in increasing HDL-C and
lowers triglyceride. Niacin is also the only lipid-lowering drug that reduces lipid levels.

8.1.6 Polyethylene Glycol

PEG is also known as poly (oxy-1-2-ethanediyl), hydro- - hydroxyl which has a molecular formula of HO-CH₂-(CH₂-O-CH₂)ₙ-CH₂-OH. Its molecular weight is given by 44n+62 where n is the number of oxyethylene groups.

![Polyethylene Glycol](image)

*Figure 8.6* Shows the structure of polyethylene glycol (11)

PEGs can exist in liquid, semisolid and solid form relying on the molecular weight of the polymer. PEGs are soluble in water but less soluble in ethanol. The water solubility and hygroscopicity decreases in organic solvent as the molecular weight increases. PEGs are mostly used in the pharmaceutical and cosmetic industries for both topical and oral preparations. This is due the fact that it has low toxicity and ability to blend easily with other ingredients (14).
8.2 Methods

8.2.1 Eutectic mixture preparations

Eutectic mixtures were prepared by the physical mixture method. Various compositions of drug and carrier were mixed in the mortar. These mixtures were triturred using mortar and pestle for 12 minutes and passed through a number 100 mesh sieve. The mixtures were then transferred into labeled brown bottles and kept in the desiccators.

8.2.2 Differential Scanning Calorimeter

The differential scanning calorimeter (DSC) Mettler Toledo DSC 822e with a TS0801R0 Sample Robot and a TS0800GCI Gas Controller using Star® Software V8.10, Hightstown, NJ was used to evaluate thermograms and to identify the ratio of the eutectics mixture formulations. Between 3-7 mg samples were weighed (Mettler MT5) and placed into a 100 μL crimped aluminum pans (Mettler Instrument). 100 μL empty pan was used as a reference. The samples were scanned at 10°C min⁻¹ in the presence of a 50 mL min⁻¹ nitrogen purge for each formulation. Indium was used for the calibration.

8.2.3 X-Ray Diffraction

The X-ray powder diffraction (PXRD), PANalytical X-Pert Pro v. 1.6 with X-Pert Data Collector v. 2.1, equipped with a CuKα2 anode tube was used to determine the physical state of the drug, carriers and the eutectics. The angular range (2θ)
was 5-55° for Tolbutamide and 5-40° for Haloperidol. Scanning rate was 1.0°C min\(^{-1}\) between 1° and 2° slits with 0.0083 step sizes. The volt and current was fixed at 45KV and 40 mA respectively. The samples were powdered and passed through a 100 mesh sieve. A 1 inch plastic sample holder was used.

8.2.4 Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was used in the study to evaluate the surface morphology of the pure drug, carriers and eutectics. A snappy 4 software digital camera was used to take the pictures. Double sided adhesive tape was used to fix the samples onto a brass tub and coating was carried out in a sputter coater, Denton Vacuum desk II under vacuum. SEM resolution was 100X.

8.2.5 Dissolution Apparatus

A Vanderkamp 600, six-spindle apparatus was used for the dissolution study. The study was performed in 900 mL deionized water. A calibration curve was prepared to determine the wavelength for maximum drug absorption. In addition, calibration was performed before each dissolution study. Stock solutions were prepared for all drugs and 4 mL were withdrawn from it and transferred into a cuvette. The concentration was determined from the absorbance and at specific intervals. The absorbance was obtained using a (Beckman DU640B Spectrophotometer), for the samples, after discarding the first few milliliters, were determined. The dissolution medium was maintained at
37±1°C and the paddle rotation was adjusted according to USP (15). The maximum absorbance (λ) of tolbutamide and haloperidol occurred at 251nm.
Chapter Nine

Results and Discussion

9.1 Tolbutamide – Nicotinamide

9.1.1 DSC Study

The DSC curves, as seen in figure 9.1 indicate endothermic peaks for the drug, carrier and eutectic mixture at different proportions of the components. Pure tolbutamide and nicotinamide show melting point of 128°C and 130°C respectively. 80-20 % (w/w) of tolbutamide to nicotinamide has an endothermic peak at 100°C. The eutectic mixture peak in the DSC indicates a broadening compared to the tolbutamide and nicotinamide alone.
9.1.2 PXRD Study

The PXRD pattern for the pure drug, carrier and its eutectic mixture are seen in Figure 9.2. The x-ray diffractogram for tolbutamide and nicotinamide show sharp peaks at (2θ) 9, 12, 13, 14, 22 and 14, 26, 27, 28 respectively. The eutectic mixture was compared with the x-ray pattern of the tolbutamide and nicotinamide. The result showed that the peak pattern is identical with the two components and this proves that no interaction takes place during the physical mixture of the two components.
**Figure 9.2** PXRD pattern of 80-20 Tolbutamide–nicotinamide (top), nicotinamide (second) and Tolbutamide (third)

### 9.1.3 SEM Study

The SEM pictures for pure tolbutamide, pure nicotinamide and 80-20% eutectic mixture are seen in Figure 9.3. The particle size for the two components can be seen as different. The two components are well dispersed in the eutectic mixture and this evidence may be used as a complement to dissolution testing.
9.1.4 Dissolution Study

9.1.4.1 Calibration Curve for Tolbutamide

The calibration of curve for tolbutamide was prepared in triplicate. Calibration data were collected at a \( \lambda \) max of 251 nm. Various standard concentrations of tolbutamide were prepared in 1mL of acetone and diluting with pH 6.8.
phosphate buffers. A Beer’s curve was prepared using absorbance and concentration as the variables:

**Table 9.1** Data for tolbutamide calibration curve

<table>
<thead>
<tr>
<th>Concentration (mg/mL)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.023</td>
<td>0.072</td>
</tr>
<tr>
<td>0.033</td>
<td>0.135</td>
</tr>
<tr>
<td>0.044</td>
<td>0.205</td>
</tr>
<tr>
<td>0.058</td>
<td>0.296</td>
</tr>
<tr>
<td>0.066</td>
<td>0.373</td>
</tr>
</tbody>
</table>

**Figure 9.4** Calibration Beer’s curve for tolbutamide
9.1.4.2 Tolbutamide – Nicotinamide Dissolution

Dissolution of tolbutamide-nicotinamide eutectic mixture and pure Tolbutamide were studied in 900 mL phosphate buffer solution. In vitro cumulative drug released was calculated and plotted versus time. The cumulative drug released from tolbutamide alone at 15 minutes was 30% while the eutectic mixture was 46%. Only 60% of the eutectic mixture was released at the 30 minutes while 49.5% of tolbutamide alone was released at the same period of time.

Figure 9.5 Dissolution profiles for the tolbutamide-nicotinamide eutectic mixture and tolbutamide alone
9.2 Haloperidol-Aminophylline

9.2.1 DSC Study

The DSC results for pure haloperidol, pure aminophylline and 55-45% eutectic mixture are given in figure 9.6. The melting point of the pure haloperidol and pure aminophylline were 152°C and 267°C, respectively. In the hand, the melting point of the eutectic mixture of the two components was 124 °C.

Figure 9.6 DSC thermogram of pure haloperidol, aminophylline and eutectic mixture of the two components
9.2.2 PXRD study

PXRD pattern for the pure drug, carrier and its eutectic mixture are shown in Figure 9.2. The X-ray diffractogram for haloperidol and amionphylline have showed sharp peaks at 2θ 6, 8,14,18,19, 21, 23, 25 and 7, 11, 13, 15, 21, 23 respectively. The eutectic mixture was compared with x-ray pattern of haloperidol and amionphylline. The result showed that the peak pattern is identical with the two components and this proves that there is no interaction take place during the physical mixture of the two components.

Figure 9.7 PXRD pattern of aminophylline (top), 55-45 % (w/w) haloperidol-aminophylline (second) and tolbutamide (third)
9.2.3 SEM study

The SEM pictures for pure haloperidol, pure aminophylline and 55-45% eutectic mixture are given in Figure 9.8. The particle size for the two components is very different. The two components are well dispersed in the eutectic mixture and this evidence may be used as a complement for dissolution testing. The melting point of haloperidol is lower than aminophylline. According to Tamman’s rule (1), haloperidol is the major component in the mixture.

**Figure 9.8** SEM pictures of pure haloperidol (a), pure aminophylline (b), and 55-45 % (w/w) haloperidol-aminophylline eutectic mixture (c).
9.2.4 Dissolution Study

9.2.4.1 Calibration Curve for Haloperidol

The calibration of curve for haloperidol was prepared in triplicate. Calibration data were collected at a \( \lambda \) max of 251nm. Various standard concentrations of haloperidol were prepared in 1mL of acetone and diluting with simulated gastric fluid. A Beer’s curve was prepared using absorbance and concentration as the variables.

Table 9.2 data for haloperidol calibration curve

<table>
<thead>
<tr>
<th>Concentration(mg/mL)</th>
<th>Absorbance</th>
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</thead>
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<tr>
<td>0.0012</td>
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<td>0.18</td>
</tr>
<tr>
<td>0.014</td>
<td>0.27</td>
</tr>
</tbody>
</table>
9.2.4.2 Haloperidol-Aminophylline Dissolution

The dissolution of the haloperidol-aminophylline eutectic mixture and pure haloperidol were studied in 900 mL simulated gastric fluid. The dissolution study was carried out for 80 minutes duration. In vitro cumulative drug released was calculated and plotted versus time. The cumulative drug released from the drug alone at 30 minutes was 33% while the eutectic mixture was 57%. 79% of the eutectic mixture was released at the 60 minutes while the drug only released 49%.

![Figure 9.9 Calibration Beer’s curve for Haloperidol](image)

The equation of the calibration Beer’s curve for Haloperidol is:

\[ y = 18.917x + 0.0198 \]

\[ R^2 = 0.9977 \]
9.3 Tolbutamide – Niacin

9.3.1 DSC Study

The DSC curves indicate endothermic peaks for the drug, carrier and various proportions of eutectic mixture for the two components. Pure tolbutamide and niacin have given melting points of 128°C and 141°C respectively. 80-20 % (w/w) of tolbutamide to Niacin mixture gave an endothermic peak at 115°C. The eutectic mixture peak in the DSC indicates broadening as compare to the tolbutamide alone as well as niacin.
9.3.2 PXRD Study

Figure 9.12 shows the PXRD diffractogram for tolbutamide, niacin and the 80-20 % eutectic mixture of the two components. The x-ray patterns for tolbutamide and niacin have sharp peaks at 2θ 9, 12, 13 and 22 and 14, 25, 26, 27, 28 and 34 respectively. The eutectic mixture was compared with x-ray pattern of the tolbutamide and niacin. The result showed that the peak pattern is identical with the two components and this proves that there are no interactions that take place during the physical mixture of the two components.
9.3.3 SEM study

The SEM pictures for pure tobutamide, pure niacin and the 80-20 % (w/w) eutectic mixture are seen in Figure 9.13. The particle size for the two components is different. The two components are well dispersed in the eutectic mixture and this evidence may be used as a complement to dissolution testing. The melting point for tobutamide is lower than that of niacin. According to Tamman’s rule (1), tobutamide is the major component in the mixture.
Figure 9.13 SEM pictures of pure Niacin (a), pure Tolbutamide (b), and 80-20% Tolbutamide-Niacin eutectic mixture (c).

9.3.4 Dissolution Study

9.3.4.1 Calibration Curve for Tolbutamide

Calibration of curve for tolbutamide was prepared in triplicate. Calibration data were collected at $\lambda_{\text{max}}$ of 251nm. Various standard concentrations of tolbutamide were prepared in 1mL of acetone and diluting with pH 6.8 phosphate buffers. Beer’s curve was prepared using absorbance and concentration.
Table 9.3 Data for tolbutamide calibration curve

<table>
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<td>0.205</td>
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<tr>
<td>0.058</td>
<td>0.296</td>
</tr>
<tr>
<td>0.066</td>
<td>0.373</td>
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</tbody>
</table>

Figure 9.14 Calibration Beer’s curve for tolbutamide

\[ y = 6.852x - 0.0908 \]

\[ R^2 = 0.9948 \]
9.3.4.2 Tolbutamide-Niacin Dissolution

Dissolution of the tolbutamide-niacin eutectic mixture and pure tolbutamide were studied in 900 mL phosphate buffer solution. The in vitro cumulative percent drug release was calculated and plotted versus time. The cumulative percent drug release from the drug alone at 15 minutes was 30% while the eutectic mixture was 41%. A total of 56% of the eutectic mixture was released within the 30 minutes while 49.5% of Tolbutamide alone was released within the same time manner.

Figure 9.15 Dissolution profiles of tolbutamide-niacin eutectic mixture (top) and tolbutamide alone (bottom)
Chapter Ten

Conclusions and Recommendations

10.1 Conclusions

Poor water soluble drugs are considered to be the number one challenge in the pharmaceutical industry to develop a future dosage forms. The bioavailability of a large number of poorly water soluble drugs is restricted by their dissolution rates. Different approaches have been made in the pharmaceutical industry to overcome these problems. One of these approaches is by the method of using physical mixture methods. Physical mixture method is prepared by mixing the poorly water soluble drug with a carrier using mortar and pestle. This technique has advantages over the other three solid dispersion preparations. Physical mixture prevents the use of organic solvents which are toxic to human body. Physical mixture also prohibits the use of heat which may change the physical as well as chemical properties of the ingredients. For this reason, it is the best approach to study poorly water soluble drugs. The main objective of this study was to enhance the solubility of poorly water soluble drugs such as tolbutamide.
and haloperidol. For this purpose, different excipients such as nicotinamide, niacin and aminophylline were used.

The physicochemical properties for each sample were characterized using different complimentary techniques. These techniques include differential scanning calorimetry (DSC), scanning electron microscopy (SEM), x-ray powder diffraction (PXRD) and dissolution testing. The result showed that three eutectic mixtures were formed. These mixtures are listed as follows:

I. The mixture of 80% of Tolbutamide with 20% nicotinamide was able to form eutectic mixture. The melting point for the pure tolbutamide was 128°C while the melting point for the pure nicotinamide was 130°C. The eutectic mixture of these two components has a melting point of 100°C.

II. 55% Haloperidol with 45% aminophylline formed a eutectic mixture. The melting point for the pure Haloperidol was 152°C. The melting point of aminophylline was 267°C. Whereas, the melting point for the eutectic mixture was 124°C.

III. The mixture of 80% tolbutamide with 20% niacin was able to form a eutectic mixture. The melting point of the pure tolbutamide was 128°C while the melting point of niacin was 141°C. The melting point for the eutectic mixture was 115°C.

In a binary mixture, the major phase is formed by a component, which has the relatively lower melting point than that of the other component (1). PXRD was
used to characterize the crystalline pattern of the ingredients. In addition, PXRD was also used to evaluate any type of chemical interaction between the components. The role of DSC in this study was to evaluate the melting point for each component and compare it to the individual mixtures. SEM was used to evaluate particle size for each component in the mixture. The effect of the particle size of the drugs on their dissolution rates and biological availability was reviewed by Fincher (2). According to Noyes-Whitney equation, as the particle size reduce the surface area of the drug molecules increase and thus increase the dissolution rate of the drug (1). In the preparation of eutectic mixture, the two components are blended intimately using mortar and pestle which reduce the particle size of the components. According to Ford (3), the dissolution rate for eutectic mixtures can be enhanced by maximizing the surface area for the components which in turn improve the wettability and dispersibility of the drug by the carrier.

In conclusion, the cumulative percentage released was calculated for both drug alone and the eutectic mixture. The result showed significant improvements for both drugs in the presence of carrier.

10.2 Recommendations

Future work should be able to concentrate on the stability study of these compounds. It may also be possible to improve the solubility of these drugs
using other excipients. The use of other excipients might produce better solubility of these drugs. In addition, based on the solubility concept using excipients, one can also modify the compounds, which might finally be able to enhance the solubility of the drug itself.
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Chapter Nine


Chapter Ten