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# The formulation and evaluation of orally disintegrating tablets : diphenhydramine HC1

Stephanie M. Chillas  
*The University of Toledo*

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A Thesis

entitled

**The Formulation and Evaluation of Orally Disintegrating Tablets:  
Diphenhydramine HCl**

By

Stephanie M. Chillas

Submitted as partial fulfillment of the requirements for

The Master of Pharmaceutical Sciences

with Industrial Pharmacy Option

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August 2013

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An Abstract of  
**The Formulation and Evaluation of Orally Disintegrating Tablets:  
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August 2013

Orally disintegrating tablets are a vital tool in keeping our children and elderly population healthy. Their ease of use and accurate dosing allow higher patient compliance and more reliable therapeutic effects. Superdisintegrants are the fundamental element contained in orally disintegrating tablets and are responsible for their unique ability to quickly disintegrate and dissolve on the surface of the tongue without the use of any additional liquid. In order to determine the most effective type and optimal amount of superdisintegrants for orally disintegrating tablets manufactured by direct compression, the following tablet parameters were tested (based on the standard USP 30 methods): hardness, thickness, friability, disintegration time, and wetting

time. Four superdisintegrants were tested, namely: Kollidon CL-SF<sup>®</sup>, Primojel<sup>®</sup>, Ac-Di-Sol<sup>®</sup>, and Polyplasdone XL<sup>®</sup>, and the most efficient superdisintegrant was selected based on the above mentioned studies. Polyplasdone XL<sup>®</sup> outperformed the other superdisintegrants in nearly all the concentrations and all of the testing parameters. The ideal concentration was 5% Polyplasdone XL<sup>®</sup> for the orally disintegrating tablets before the API, diphenhydramine HCl, was added. Various concentrations were analyzed using the aforementioned parameters and 10% Polyplasdone XL<sup>®</sup> was selected for the final formulation. Tablets were tested over eight weeks of accelerated stability testing at various temperatures to determine percent of diphenhydramine HCl released in dissolution, disintegration time, wetting time, hardness, thickness, and weight variation. The tablets remained stable and within the acceptable range of drug release (90%-110%) at the three temperatures analyzed. Additionally, tablets were analyzed at different levels of relative humidity for percent weight change and change in hardness. The final formulation of diphenhydramine HCl tablets was stable between 3-40°C and at 33% relative humidity or less for eight weeks.

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## Preface

Tablets remain the most conventional and cost effective way to administer pharmaceuticals, however, traditional tablets present challenges for pediatric patients such as risk of aspiration and difficulty swallowing [1]. Orally disintegrating tablets (ODTs) present a unique advantage for pediatric patients by minimizing the risk of aspiration [2]. ODTs are classified as solid oral dosage forms that disintegrate in the oral cavity without the aid of additional water into an easily swallowable residue [3]. ODTs are beneficial because they do not require water or chewing. They have better taste, improved stability, improved bioavailability, better efficacy, allow for variable dosing and are more cost effective [1, 4]. Additionally it has been shown that, over half the patient population would prefer ODTs over conventional tablets and other dosage forms according to Brown [5].

Orally disintegrating tablets are a vital tool in keeping our children and elderly population healthy. Their ease of use and accurate dosing allow for higher patient compliance and more reliable therapeutic effects. Superdisintegrants are the fundamental element of orally disintegrating tablets and are responsible for their unique ability to quickly disintegrate and dissolve on the surface of the tongue without the use of any additional liquid.

Superdisintegrants provide cohesion while allowing the tablet to quickly breakdown and dissolve in aqueous liquid (saliva).

An orally disintegrating tablet of diphenhydramine HCl was formulated for pediatric and geriatric use. A suitable diluent was selected based on interactions with diphenhydramine HCl. Several superdisintegrants were tested to determine the most effective type and optimal amount for inert 100 mg tablets. The concentration was then adjusted to optimize disintegration in tablets containing 12.5 mg of diphenhydramine HCl. The resulting formulation was evaluated over eight weeks at various temperatures for percent diphenhydramine HCl released in dissolution as well as disintegration time, wetting time, and hardness. Additionally, tablets were evaluated in various relative humidity conditions for stability.



## **Chapter One**

### **ORALLY DISINTEGRATING TABLETS (ODTs)**

#### **1.1 Introduction**

Approximately one-third of the population experiences difficulty swallowing or dysphagia [1]. Geriatric and pediatric patients encompass the largest portion of the population that demonstrate difficulty in swallowing. Fear of choking, hand tremors, dysphasia and underdeveloped muscular and nervous systems in schizophrenic patients may also lead to difficulty in swallowing [1]. In addition to the human population that experiences difficulty swallowing tablets, veterinary medicine can also benefit from advanced technology in solid dosage form delivery [2]. Orally disintegrating tablets (ODTs) can play a vital role in drug delivery to this unique subset of patients as well as those who have an aversion to swallowing tablets in general.

#### **1.2 Pediatric Dosage Forms**

Pediatric drug administration is constantly evolving to adapt and maximize the most important aspect of pharmacy practice; namely patient compliance [3]. The World Health Organization identifies the key components of an ideal drug delivery system for children as indicated by its ease of

administration, palatability, the possibility for weight-based dosing and dose titration, as well as the use of safe, well-established and stable excipients [4]. Additional considerations include: sufficient bioavailability, acceptable dose uniformity, safe administration, socio-cultural acceptability, precise and clear product information, as well as being parent and caregiver friendly [5, 6]. The ideal formulation will allow for minimal dosage frequency and provide reliable administration [7].

The pediatric population encompasses a wide range of children from newborns to adolescents [5]. The following pediatric divisions are determined by biological changes: pre-term newborn infants (<37 weeks of gestational age), term newborn infants (0-27 days), infants and toddlers (1 month to 23 months), children (2-11 years), and adolescents (12-18 years) [8]. The selection of the route of administration and dosage form is integral for successful patient compliance [9]. Parenteral administration is the preferred mode for the seriously ill, while the oral route remains the ideal route for the acutely ill [7]. There are a variety of oral dosage forms available, including: solutions, syrups, suspensions, powders, granules, effervescent tablets, orodispersible tablets, chewable tablets and gums, mini tablets, innovative granules, conventional immediate release and modified release tablets and capsules [10].

### **1.3 Liquid Dosage Forms**

Previously, liquid oral dosage forms were perceived as the most appropriate mode of administration for pediatric patients because they allowed for variable dosing and are typically palatable for children. Additionally, before 4 or 5 months of age, infants possess an extrusion reflex that enables them to swallow only liquids [8]. An important characteristic for all pediatric delivery systems is palatability; parents rate taste as the highest priority after efficacy and safety for their children's medicine [11]. Liquid dosage forms present a challenge for taste masking due to excipient restrictions and the inability to coat bitter particles as in solid dosage forms [5]. Additionally, stability, increased costs, and dosing errors remain concerns for liquid preparations [4, 5]. Dosing errors over 200% have been linked with adjusting oral liquid suspensions' graduation to half or quarter the amount to account for weight variation [12]. Therefore, a new versatile solid platform technology is required [4].

### **1.4 Solid Dosage Forms**

Solid dosage forms offer several advantages over liquid dosage forms including: the incorporation of nontoxic excipients for pediatrics; lower manufacturing costs; increased opportunity to taste mask; modify the release; provide greater stability; achieve higher content uniformity; and offer easy administration [13]. Generally, the disadvantages include: dimensions for

swallowing; the requirement of a beverage for swallowing; and the risk of aspiration [13].

## **1.5 Orally Disintegrating Tablets**

Tablets remain the most conventional and cost effective way to administer pharmaceuticals, however, traditional tablets present challenges for pediatric patients such as risk of aspiration and difficulty swallowing [1]. Orally disintegrating tablets (ODTs) present a unique advantage for pediatric patients by minimizing the risk of aspiration [5]. ODTs are classified as solid oral dosage forms that disintegrate in the oral cavity without the aid of additional water into an easily swallowable residue [14]. ODTs are beneficial because they do not require water or chewing. They have better taste, improved stability, improved bioavailability, better efficacy, allow for variable dosing and are more cost effective [1, 15]. Additionally, over half the patient population would prefer ODTs over conventional tablets and other dosage forms [16].

### **1.5.1 ODT Terminology and Definition**

Orally disintegrating tablets are also known as mouth dissolving tablets, orodispersible tablets, fast disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets or rapid melt tablets. They are defined by the FDA as “A *solid*

*dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [17, 18]. In order to accomplish disintegration in under one minute, tablets are composed of special ingredients including superdisintegrants such as crospovidone, croscarmellose sodium or sodium starch glycolate. These materials allow for rapid uptake of water or are manufactured with low compression force to achieve the same effect [14, 19, 20].*

### 1.5.2 Common Reasons and Conditions for Using ODTs

Orally disintegrating tablets can be utilized for various medical conditions and patient demographics. Table 1.1 lists generic medical conditions that may be treated with ODTs [21].

Table 1.1 Common Reasons and Conditions for Using ODTs

<b><u>Medication Type</u></b>	<b><u>Indication</u></b>
<b>Fast-acting</b>	Pain, fever, heartburn, diarrhea, migraine, anxiety, insomnia
<b>Compliance-critical</b>	Parkinson's disease, Alzheimer's disease, psychosis, schizophrenia, hypertension, cholesterol, transplantation
<b>Pediatric</b>	Cough/cold/allergy, pain, fever, ADHD

### **1.5.3 Manufacturing Methods**

There are several methods for developing ODTs that are commonly employed including: lyophilization; molding; direct compression; cotton candy process; spray drying; sublimation; mass extrusion; nanonization; and fast dissolving films [3]. Patented technologies include: Zydis<sup>®</sup> (Lilly, Patent No. 6,960,577), Durasolv<sup>®</sup> (Cima Labs, Patent No. 6,221,392), Orasolv<sup>®</sup> (PharmCast, Patent No. 6,083,531), Wowtab<sup>®</sup> (Yamanouchi Pharmaceutical Co., Patent No. 5,576,014), and Flashtab<sup>®</sup> (Ethypharm, Patent No. 20,030,050,312) technology [3].

### **1.5.4 Direct Compression**

The simplest and most cost effective method of tablet manufacture is direct compression. It is a convenient method of tableting that requires highly influenced powder characteristics such as flowability, compressibility and compactability [22]. The incorporation of superdisintegrants is critical to the rapid rate of disintegration [14].

### **1.5.5 Orally Disintegrating Tablet Characteristics**

Orally disintegrating tablets are porous to allow wettability. The low compression force allows for water to reach the superdisintegrant and perpetuate a swelling effect which in turn allows the tablet to disintegrate rapidly [17]. ODT hardness is typically less than 30 Newtons to allow for rapid

disintegration while also maintaining the mechanical strength for production and distribution [23].

### 1.5.6 Bioavailability

Disintegration in the oral cavity allows a higher degree of bioavailability by reducing the amount of drug that undergoes first-pass metabolism. Ideal ODT formulations have a log P value greater than 1 and diffuse into the epithelium of the upper gastrointestinal tract [1]. In addition to improved bioavailability, ODTs have a more rapid onset of action since the drug is absorbed when the saliva moves from the oral cavity to the gastrointestinal tract [1].

Polymers can be used to provide a controlled release pharmaceutical effect. Enteric coatings can be utilized as in Figure 1.1 to achieve this effect by remaining stable at the low stomach pH and eroding when the pH becomes more basic such as the intestinal environment [14, 21].

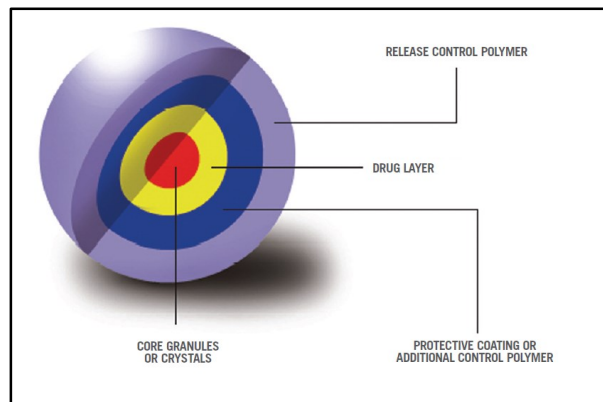


Figure 1.1 Controlled Release Coating of ODTs [14]

### **1.5.7 Palatability**

An important characteristic in oral drug delivery systems is palatability. Patient compliance is dependent on favorable taste determined by the target audience. Many APIs have an offensive or bitter taste and require flavoring and sweeteners to overcome the unpleasant flavor. In some cases, as with diphenhydramine HCl, the excessive bitterness requires a coating to prevent the bitter tasting particles from coming into contact with the patients taste buds [21]. Micro-encapsulation and incorporation in cyclodextrins can be utilized in soluble and poorly soluble substances to provide taste masking benefits. Coacervation is a coating technique that provides superior taste masking against unpleasant APIs [14].

A general rule that should be taken into consideration is that pediatric patients are not simply small adults. Additional considerations must be made to account for physiological and preferential differences [24]. Children respond to tastes different than adults. Pediatric patients prefer sweet-tasting substances and have an aversion to bitter elements from an early age [25].



## Chapter Two

### THERMAL ANALYSIS: DIFFERENTIAL SCANNING CALORIMETRY (DSC) AND THERMOGRAVIMETRIC ANALYSIS (TGA)

#### 2.1 Introduction

Thermal analysis plays a vital role in the determination and understanding of many chemical species of drugs and/or excipients. Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) have been integral components of analysis in the scientific community since the 1960's [1, 2]. Numerous disciplines utilize this technology to identify phase transitions, examine purity, and detect chemical reactions and structural changes.

#### 2.2 Differential Scanning Calorimetry

DSC is defined by the Second Edition of *Differential Scanning Calorimetry* as "the measurement of the change of the difference in the heat flow rate to the sample and to a reference sample while they are subjected to a controlled temperature program" [3].

### **2.2.1 Development of modern DSC**

Emmett Watson and Michael O'Neill submitted a US patent for the Differential Microcalorimeter in April of 1962 [1]. While thermal analysis was well established before this invention, Watson and O'Neill's method would allow smaller quantities of the sample and reference material to be used as well as provide reproducible results [1, 4]. Their technique is the framework for the modern differential scanning calorimeters. Modern instruments employ robotics to expedite the progression of samples [5].

### **2.2.2 DSC characteristics**

The instrument records the difference in heat capacity [6]. Both cells, the sample and reference, are heated with a specific temperature profile [7]. The amount of energy required to keep the sample and reference at the same temperature is used to determine the heat capacity. DSC scans can provide exponential data about the sample. Phase transitions are primarily resolved from DSC output; the specific transition temperatures of compounds are compiled and used in other aspects of research [8]. Additionally, the DSC output can be analyzed to verify exothermic or endothermic reactions. With the temperature increasing, molecules may spontaneously form a crystalline structure, an exothermic process [8]. Melting, an endothermic process, also results from increasing the system temperature [5, 8]. Figure 2.1 depicts three

common features of DSC outputs: glass transitions, crystallization, and melting [9].

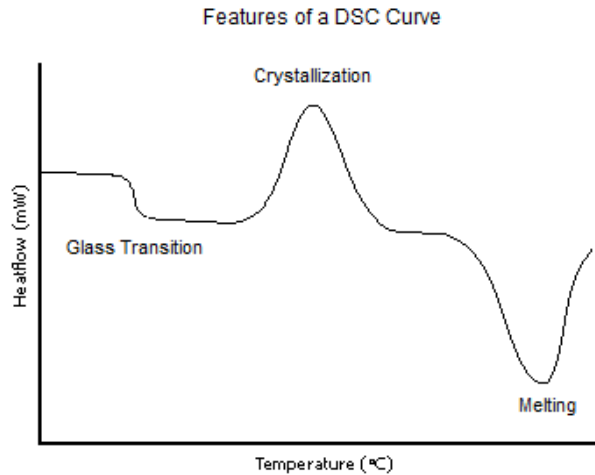


Figure 2.1 Common graphical features of a DSC scan [9]

### 2.2.3 Sample preparations

Differential scanning calorimetry requires small quantities of both the sample and reference material, typically less than five milligrams [10]. The sample is held in an aluminum or gold pan; it can be exposed to the atmosphere or sealed [11]. Nitrogen gas is employed while heating the system at the prescribed temperature rate [7, 12]. The heat capacity of the sample analyzed at the specific temperature profile produces a unique readout for the sample.

In order to eliminate impurities such as lubricants or other manufacturing byproducts, the pans used for holding the sample and reference should be heated to 400° Celsius [7]. Additionally, nitrogen gas can be used to purge the equipment of volatilized deposits when used in combination with

high temperatures [10]. Another means of cleaning the DSC is by using a solvent system, methanol or acetone, to dissolve deposits on the sensors [10]. Once the DSC and complementary equipment is sufficiently clean, a well-known standard such as indium, can be analyzed [7]. If the resulting scan parallels the recognized peak, the DSC equipment is clean and able to be used in thermal analysis.

#### **2.2.4 DSC applications**

Differential scanning calorimetry is useful in a number of industries and for diverse applications. Biochemistry utilizes DSC to understand protein folding and associated enthalpy by the respective energies [13]. Polymer composition can be concluded from standard melting points and transition temperatures. With this data, the proportion of polymer in the crystalline form and any impurities can be discovered [11]. Chemical reactions and oxidative states are evident from DSC scans; inert gas is used as a comparison with the addition of oxygen to detect deviation from the baseline. The food industry employs DSC to observe water activity and for purity testing [2, 14]. Purity testing with DSC is a large component of quality control in the pharmaceutical industry as well [7, 12]. Figure 2.2 depicts a controlled purity test utilizing differential scanning calorimetry [14]. The output contains four different samples of dimethyl terephthalate with varying degrees of contamination [14]. The top peak represents greater than 99.9% purity. The subsequent graphs

display peak broadening around 140° Celsius and develop additional peaks as salicylic acid. Giron suggests purity is “based on the assumption that impurities depress the melting point of a pure material according to the eutectic phase diagram behavior” [7]. Therefore, the lowering of peak temperature for dimethyl terephthalate results from the high levels of impurity [14].

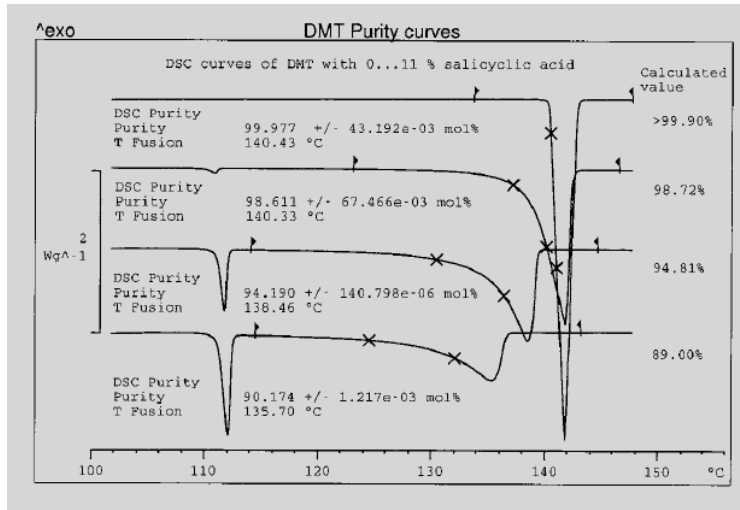


Figure 2.2: Purity of Dimethyl Terephthalate using DSC [14]

### 2.2.5 Calculations

The Van't Hoff equation is a useful tool when analyzing DSC. The change in temperature and equilibrium constant are related to enthalpy change [13, 15]. A simplified version of this equation is applied for purity analysis [14].

$$T_{fus} = T_0 - \frac{x_{2.0} * R * T_0^2 * m}{M} * \frac{1}{(A_{part} + C)} \quad (\text{Equation 2.1})$$

In the Equation 2.1 ( $T_{\text{fus}}$ ) is the temperature of the sample during melting, ( $T_0$ ) is the melting point of the pure substance, ( $x_{2.0}$ ) is the mole fraction of the impurity in the sample, ( $R$ ) is the gas constant (8.134 J/molK), ( $m$ ) is sample mass, ( $M$ ) is molar mass of the pure substance, ( $A_{\text{part}}$ ) is measured partial peak in mJ, and ( $C$ ) is linearization correction in mJ [14].

## **2.3 Thermogravimetric Analysis**

Thermogravimetric analysis (TGA) is an associated thermal analysis technique which measures the change in weight with respect to temperature. Frequently, this technique is used simultaneously with DSC to obtain more information concerning the given sample [12]. The mass of a substance is monitored as a function of temperature or time as the sample specimen is subjected to a controlled temperature program in a controlled atmosphere [16].

### **2.3.1 TGA characteristics**

A TGA thermal curve is displayed from left to right. The descending TGA thermal curve indicates a weight loss which occurred as temperature increases. Figure 2.3 portrays a 15.013 mg sample of calcium carbonate analyzed using the temperature profile to heat the sample from 100 °C to 900 °C at 10 °C/minute in Nitrogen atmosphere with a purge rate of 20 L/minute [16].

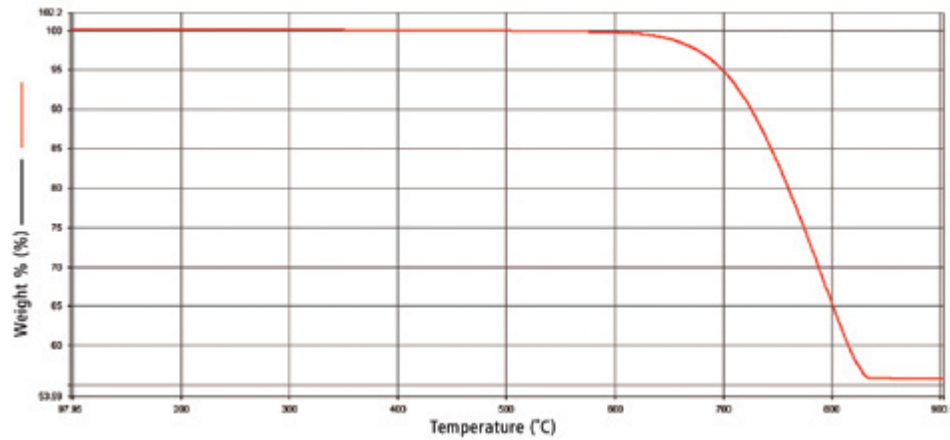


Figure 2.3 TGA Thermal Curve [16]

### 2.3.2 Sample preparation

TGA samples are prepared by accurately weighing a specific amount of powder sample in a pre-weighed aluminum pan with lid. Throughout the course of heating, the furnace is purged with nitrogen gas. The TGA contains a top-loading pan that precisely measures the mass of the sample and pan throughout the temperature profile to record the percent change or mass change over time [16].

## Chapter Three

### FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

#### 3.1 Electromagnetic Spectrum

The electromagnetic spectrum describes the entire existing light span. It is a wave of alternating electric and magnetic fields [1]. Figure 3.1 illustrates the most common features of the specific wavelengths of light [2].

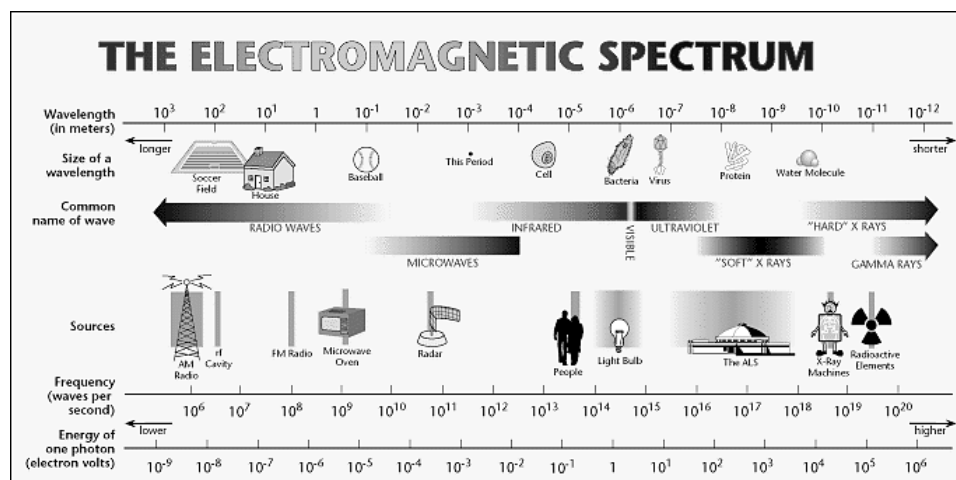


Figure 3.1 Electromagnetic Spectrum [2]

Compounds with covalent bonds absorb various frequencies of electromagnetic radiation in the infrared (IR) region. Frequency ( $\nu$ ) is inversely proportional to wavelength ( $\lambda$ ); where the equation  $\nu = c/\lambda$ , is resolved where ( $c$ ) is the speed of light ( $3.00 \times 10^{10}$  cm s<sup>-1</sup>) in a vacuum. Energy ( $E$ ) is proportional to frequency [ $\nu$ ]:  $E = h\nu$ ], where ( $h$ ) is Plank's constant



( $h = 6.626 \times 10^{-34}$  Js). Energy is proportional to the wavenumber [ $(\bar{\nu}): E = hc\bar{\nu}$ ], because [ $\bar{\nu} (cm^{-1}) = \frac{1}{\lambda (cm)}$ ]. Consequently, molecules have different energy levels of absorption: which includes rotational (microwave), vibrational (infrared), and electronic (UV-Vis).

### **3.2 Vibrational Spectroscopy**

Vibrational energy corresponds to the energy absorption in the infrared range; typically between 4000-400  $cm^{-1}$ . Due to the nature of the analysis, enantiomers cannot be differentiated. Vibrational spectroscopy is used to identify chromophoric functional groups by characteristic wavelengths. Reference spectra have been collected over time to identify molecular structure and ascertain the chemical species. Fourier transform infrared spectroscopy (FTIR) has been employed to determine molecular structure since the late 1940's [3]. FTIR is one of the most significant tools in structural analysis.

### **3.3 FTIR Spectrometer**

#### **3.3.1 Overview**

The spectrometer is based on the Michelson interferometer and utilizes mirrors and beam splitters to transmit radiation through the sample to a detector. Figure 3.2 depicts common features of the FTIR spectrometer [4]. Specialized algorithms translate the interferogram into spectra with Fourier transformation.

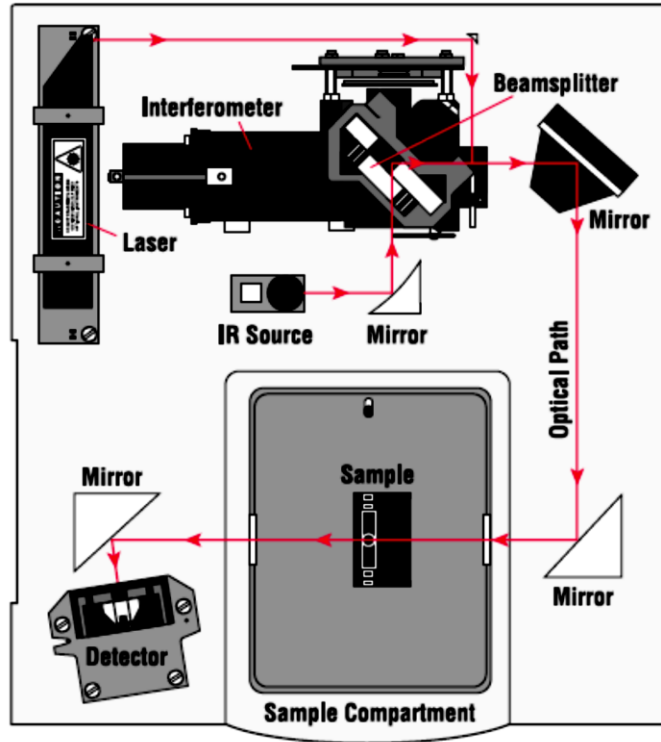


Figure 3.2 Fourier Transform Infrared Spectrometer Diagram [4]

### 3.3.2 Sources

Infrared electromagnetic radiation can be supplied from a number of sources. All sources release high amounts of heat. The most commonly used source is a Nernst Glower which is a heated rare earth oxide rod (~1500 K). Other infrared sources include Globar, a heated silicon carbide rod (~1500 K), tungsten (W) filament lamp (~1000 K) for the near-IR range, Mercury arc lamp for the far-IR range, and carbon dioxide laser for stimulated emission lines.

### **3.3.3 Detector**

Thermocouples, bolometer, pyroelectric, and photoconducting detectors have been used to perceive infrared radiation. FTIR often implements pyroelectric detectors. Pyroelectric detectors composed of triglycine sulfate piezoelectric material are fast and sensitive in the mid-IR range and work by producing a temporary voltage when the sample is heated or cooled [5].

### **3.4 Advantages**

FTIR is a useful analytical tool because it is a non-destructive technique and mechanically simple. Precise measurement, speed, and sensitivity are among the most advantageous qualities FTIR presents [4]. Increased energy throughput (Jacquinot's advantage) and higher signal-to-noise ratio ( Fellgett's advantage) are essential to FTIR's speed and sensitivity [3]. Additionally, it is a relatively inexpensive and reproducible technique and can be used to analyze solids that are crystalline, microcrystalline, amorphous, or films [6].

### **3.5 Sample Preparations**

Solid samples are combined with transparent infrared matrix in approximately 1:100 ratio [3]. The analyte being tested is ground together with the matrix material in a small mortar and compressed within a steel die to form a pressed disc. The matrix material is typically potassium bromide, although other solids can be used if they are transparent in the infrared range

such as CsI or TlBr [7]. The resulting pressed disc is placed in a vacuum for a few minutes to remove air between the particles.

Gas and liquid samples are prepared by collecting the analyte between transparent windows of sodium chloride or potassium bromide for analysis.

### 3.6 FTIR Spectra

Interferograms are converted to spectrum utilizing Fourier transform technology. Figure 3.3 visually displays the graphical results from sample to spectrum [4]. The resulting spectrum can then be analyzed by evaluating known chemical bonds with associated wavenumbers [8]. Intensity and location are used to recognize the amount and location of chemical bonds; as a result, the analyte can be identified [9].

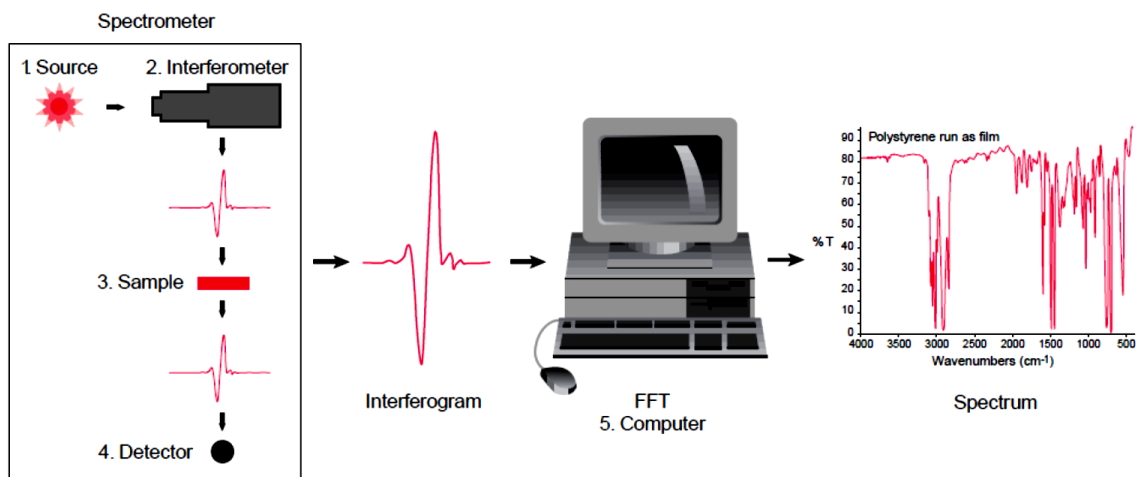


Figure 3.3 FTIR Analysis Process [4]

### 3.7 Characteristic Frequencies

Chemical bonds have characteristic infrared absorption ranges. Figure 3.4 depicts the most common functional groups and their associated wavenumber ranges [10]. Each chemical species has a unique spectra made of distinguishing absorption ranges that can be used to identify unknown chemical structures based on bending, stretching, and covalent bonds.

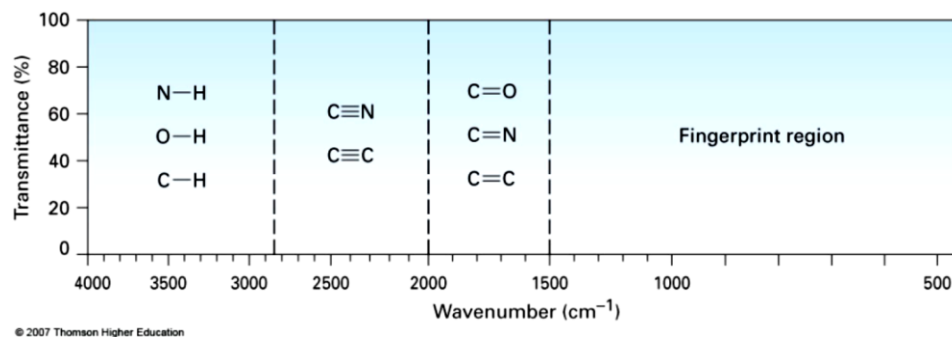


Figure 3.4 Characteristic Functional Group Absorption [10]

## Chapter Four

### ULTRAVIOLET-VISIBLE SPECTROSCOPY

#### 4.1 Introduction

Ultraviolet-Visible Spectroscopy is commonly used for quantitative and qualitative analysis. UV-Vis plays a vital role in quality assurance and quality control, analytical testing and regulatory laboratories [1]. UV-Vis is a useful technique for detecting chromophoric groups that can be used for quantitative analysis. Qualitative data must be supplemented with other physical or chemical analysis [2]. A UV-Vis spectrometer measures the amount of light absorbed at each wavelength of the UV and visible regions of the electromagnetic spectrum. Figure 4.1 illustrates the electromagnetic spectrum and the small portion that contains ultraviolet and visible radiation [3]. The near ultraviolet wavelength region is commonly found between 200-380 nm, with a lower limit around 190 nm and upper limit around 370 nm [4, 5]. Whereas, the visible light wavelength region is commonly found between 380-780 nm [4, 6]. A spectrum, for a particular sample, is a plot of absorption intensity versus the wavelength. The absorption characteristics of a sample are defined by both the

wavelength of maximum absorption ( $\lambda_{\max}$ ) and the range of wavelengths over which absorption occurs [7].

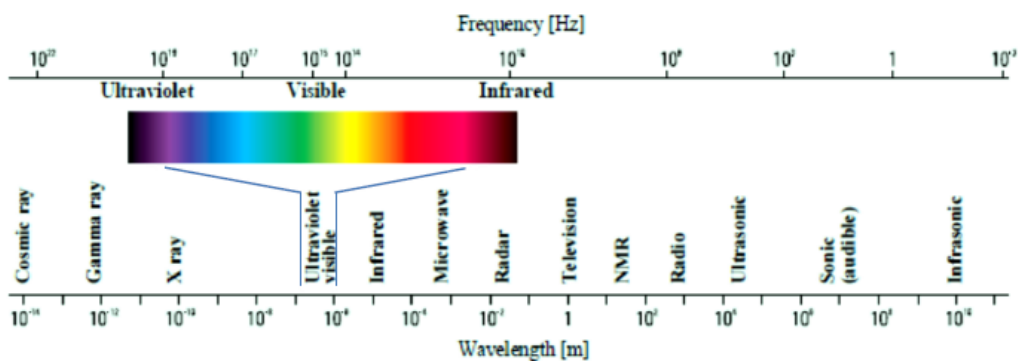


Figure 4.1 Electromagnetic Spectrum [3]

## 4.2 Instrument Components

A typical UV-Visible spectrometer consists of a light source, wavelength selector, sample holder/compartments, detector, and a data acquisition collector [8].

### 4.2.1 Light Source

The light source provides the light to be directed towards the sample [8]. Two lamps are required to produce radiation across the entire wavelength range. A hydrogen or deuterium lamp is used to cover the ultraviolet range whereas a tungsten filament lamp is used for the visible range [9].

### **4.2.2 Wavelength Selector**

A wavelength selector, or monochromator, functions by selecting a narrow band of wavelengths to pass through the sample cell [7]. It utilizes a “dispersing element” by dispersing the light into individual wavelengths [8]. The separated light then enters a narrow exit slit to ensure a narrow waveband [9]. The size of the exit slit is proportional to the size of the bandwidth of radiation [10].

### **4.2.3 Sample Holder/Compartment**

The sample holder is where the solution to be measured is placed. The compartment is an enclosed, light tight box allowing for the sample to be irradiated by the light from the monochromator. The sample is held in a container called a cuvette [8]. Cuvettes must be made from a material, such as silica, quartz glass or plastic, which does not absorb light in the sample’s wavelength region for evaluation [9].

### **4.2.4 Detector**

The detector is used to convert the change in light intensity into an electrical signal measuring the degree of absorption [8]. The most popular detectors used are either photomultiplier or photodiode which convert photons of radiation into an electrical current. The spectrum is then created by comparing the current generated by the reference to that of the sample [9].



### 4.3 Types of Instruments

There are two general types of UV-Visible Spectrometers available: Single beam or double beam.

#### 4.3.1 Single Beam

The “basic instrument” with all of the components in single sequence is found in this instrument [8]. This is the simplest, least expensive, and most robust instrument [6]. The reference sample containing the solvent for the “blank” is measured separately from the test sample and should be performed before each absorbance measurement to minimize fluctuation in absorbance over time [2, 6]. Figure 4.2 illustrates the sequence of the components within the single beam system.

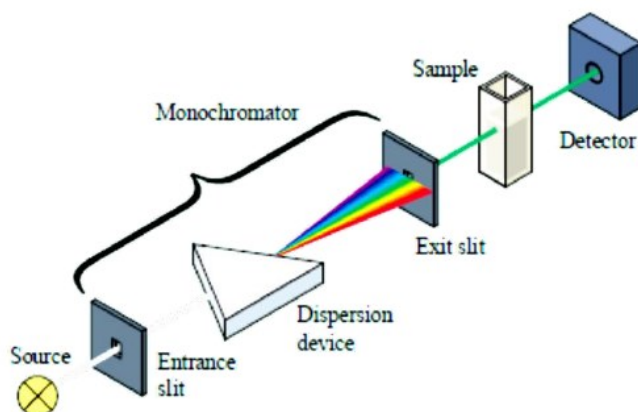


Figure 4.2: Single Beam Spectrometer [3]

### 4.3.2 Double Beam

Double beam spectrometers allow for the light from the source to be split into two equal beams after passing through the monochromator [6]. The light has the ability to pass through the sample and reference at the same time. The advantage of using a double beam over single beam is the fact that the sample and blank do not have to continually be replaced and also minimizes error due to fluctuations [8]. Figure 4.3 illustrates the sequence of the components within the double beam system.

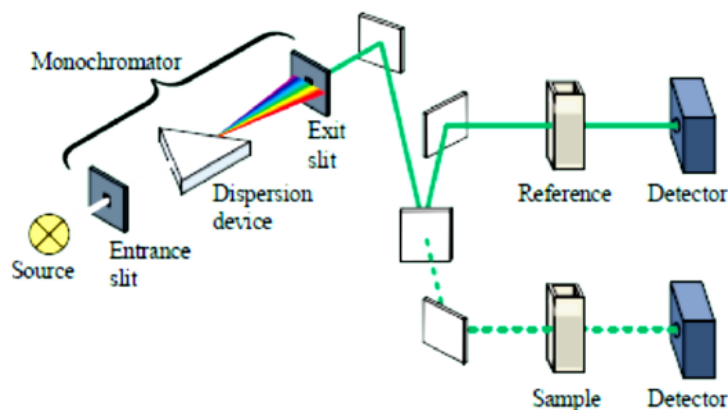


Figure 4.3: Double Beam Spectrometer [3]

### 4.4 Beer-Lambert Law

The fundamental relationship between the UV-Vis spectral response and concentration of the sample is described by the Beer-Lambert law [6]. The law is composed of two principal laws of light absorption, Lambert's law and Beer's law. Lambert's law states that the proportion of light absorbed by a medium is independent of intensity of the incident light and the medium

absorbs an equal fraction of the incident light. Beer's law states that the amount of light absorbed is proportional to the number of absorbing molecules which the light passes through [11]. The combined Beer-Lambert law is shown below in Equation 4.1 [6]. Absorbance is directly proportional to the path length (b) and the concentration (c) of the absorbing material.

$$A = \epsilon bc \quad \text{(Equation 4.1)}$$

Where (A) is the absorbance; ( $\epsilon$ ) is the absorptivity; (b) is the pathlength; and (c) is the concentration. In order for this law to determine analyte species of unknown concentrations in a solution, a calibration curve of absorbance versus concentration of known analyte concentrations must be constructed with linear regression to quantify unknown concentrations. The absorbance for the unknown can be measured using UV-Vis and the concentration can be extrapolated from the calibration curve [7].

#### **4.4.1 Limitations of Beer-Lambert Law**

The linearity of the Beer-Lambert law is limited by chemical and instrumental factors. Nonlinearity can be caused by deviations in absorptivity coefficients at high concentrations (>0.01M) due to electrostatic interactions between molecules in close proximity [12]. Incomplete filtration and scattering of light can also occur due to particulates in the sample. Changes in refractive index can occur at high analyte concentrations. Stray light leaking into the

sample compartment can also cause nonlinearity with respect to the Beer-Lambert Law.

#### **4.5 Application**

UV-Visible spectrometers are present in most laboratories and are beneficial to research because the analysis does not alter the sample and requires short analysis times [13]. The samples analyzed are mostly found in dilute solutions but solids and gaseous samples can be analyzed [1]. The solvents used to dissolve the samples being analyzed must be transparent and should dissolve the sample sufficiently. Commonly used solvents and their lower wavelength limit include water (191 nm), ethanol (204 nm), methanol (203 nm), hexane (201 nm), and cyclohexane (195 nm) [14]. The advantage associated with using UV-Visible spectrometry is the ability for the instrument to cover the widest range of applications such as, nucleic acids, proteins, enzymes, quantitative analysis, and quality control of beverages, plastics, and pharmaceuticals [1].

## **Chapter Five**

### **PREFORMULATION CONSIDERATIONS**

#### **5.1 Introduction**

There are several aspects of preformulation considerations which will be needed before diphenhydramine HCl can be fully formulated. Diluent selection is one of the most important preformulation concerns. Chemical reactions between the API and other ingredients are a primary concern and should be avoided. Additionally, superdisintegrant choices are the fundamental element of orally disintegrating tablets and are responsible for their unique ability to quickly disintegrate and dissolve on the surface of the tongue without the use of any additional liquid. Superdisintegrant selection is vital to the formulation of orally disintegrating tablets.

#### **5.2 Maillard Reaction**

Diphenhydramine HCl contains an amine moiety and forms the Maillard reaction when combined with reducing sugars in the presence of heat [1]. The reactive carbonyl group of the sugar reacts with the nucleophilic amine to give off water and other byproducts [1]. Consequently, the diphenhydramine HCl concentration would decrease and not be bioavailable. Reducing sugars such as lactose, maltose, galactose, glyceraldehyde, and

glucose are capable of undergoing the Maillard reaction in close proximity to chemicals with an amine in the presence of heat [2].

The Maillard reaction was first discovered by Louis Camille Maillard in 1912 during his analysis of amino acids and sugars [3]. John E. Hodge later outlined the Maillard reaction pathway in his 1953 paper on the chemistry of browning reactions [4]. The reaction is most commonly associated with food products due to the regularly occurring presence of both sugar and amino acids in proteins [5]. It is a non-enzymatic thermal reaction. The Maillard reaction is a complex series of reactions between reducing sugars and amino acids when heated. The Maillard reaction is responsible for the color, flavor and nutritive nature in the food and is dependent on the specific amino acid or functional group [5]. When the food or sample is heated, reducing sugars break and the aldehyde group in the sugar reacts with the amino acid to give a brown color [2]. The Maillard reaction can be observed when food or samples are heated above 154°C.

The reaction is accelerated in alkaline environments or at elevated temperatures [6]. The amino groups deprotonate causing increased nucleophilicity. Acrylamide and other byproducts are commonly formed from the Maillard reaction [1].

The Maillard reaction should be avoided in pharmaceutical dosage forms to avoid hazardous byproducts and ensure API concentration. A reaction involving diphenhydramine HCl would result in decreased API bioavailability

and smaller dosages would reach systemic circulation. Therefore, analysis of diphenhydramine HCl concentration would indicate lower than 12.5 mg of diphenhydramine HCl per tablet.

Trehalose is a suitable disaccharide because the anomeric carbons of the rings are joined together and cannot open [7]. The non-reducing qualities are of foremost importance in diluent selection for the formulation of diphenhydramine HCl orally disintegrating tablets. Trehalose contains two glucose molecules bonded by  $\alpha, \alpha$ -1, 1 glycosidic link and is derived from starch. It is less sweet than sugar and can suppress bitter flavors [7]. Trehalose also serves as a dietary alternative to table sugar and has a low caloric value [8]. Additionally, trehalose is non-hygroscopic and is resistant to high humidity levels which is ideal for orally disintegrating tablets [7, 8]. This property allows for a free flowing dry crystal that can be directly compressed into tablets.

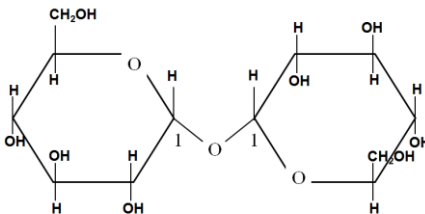


Figure 5.1 Trehalose

### 5.3 Superdisintegrants

Superdisintegrants are a crucial aspect of an orally disintegrating tablet formulation. In order to accomplish disintegration in under one minute, tablets are composed of special ingredients including superdisintegrants such as crospovidone, croscarmellose sodium or sodium starch glycolate [9]. Figure 5.2 illustrates how the disintegrating agent encourages water uptake and disrupts the tablet structure to fragment the tablet and allow further disintegration [10]. These materials allow for rapid uptake of water and are manufactured with low compression force to achieve the same effect [11, 12, 13].

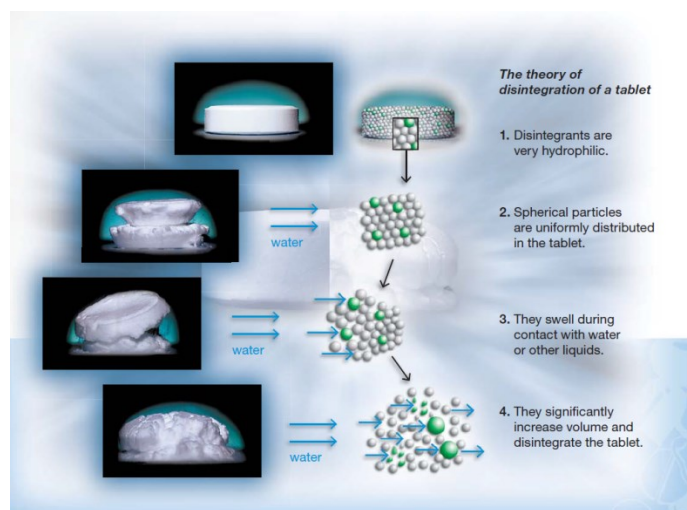


Figure 5.2 Theory of Disintegration of a Tablet [10]

#### 5.3.1 Kollidon CL-SF®

Kollidon CL-SF® is super fine cross-linked polyvinylpyrrolidone [10]. The super fine particle size provides a good mouth feel when used in orally



disintegrating tablets [10]. Kollidon CL-SF<sup>®</sup> has the highest water uptake capacity of all the crospovidones produced by BASF [10].

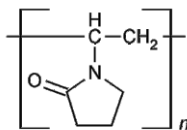


Figure 5.3 Kollidon CL-SF<sup>®</sup>

### 5.3.2 Primojel<sup>®</sup>

Primojel<sup>®</sup> is chemically cross-linked and carboxymethylated potato starch in the form of croscarmellose sodium [14].

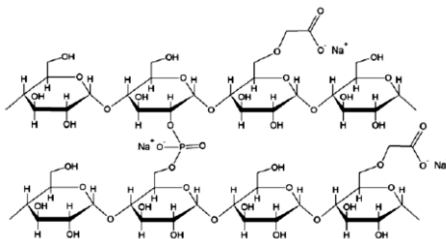


Figure 5.4 Primojel<sup>®</sup>

### 5.3.3 Ac-Di-Sol<sup>®</sup>

The superdisintegrant Ac-Di-Sol<sup>®</sup> is cross-linked sodium carboxymethylcellulose [15].

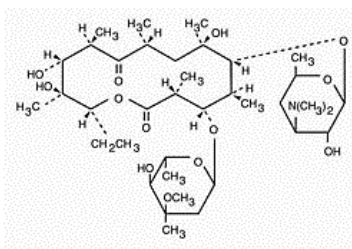


Figure 5.5 Ac-Di-Sol<sup>®</sup>

### 5.3.4 Polyplasdone XL<sup>®</sup>

Polyplasdone XL<sup>®</sup> is a synthetic, insoluble, crosslinked homopolymer of N-vinyl-2-pyrrolidone [16]. It produces good compressibility and smooth, robust tablets. The porous chemical structure allows for rapid disintegration, enhanced rate of drug dissolution and strong tablets [16].

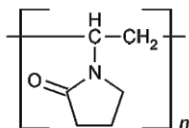


Figure 5.6 Polyplasdone XL<sup>®</sup>

## **Chapter Six**

### **TABLETING**

#### **6.1 Introduction**

The most common drug delivery systems for pharmaceuticals are solid dosage forms such as tablets and capsules [1]. Tablets offer several advantages over capsules: reduced cost, tamper resistance, simplicity of handling and packaging, ease of identification, and manufacturing efficiency [1]. Compressed tablets have been manufactured for many years and continue to be the most commonly used dosage form.

#### **6.2 Tablet Manufacturing Methods**

##### **6.2.1 Wet Granulation**

Wet granulation utilizes water-based adhesives, diluents, and the active pharmaceutical ingredient (API). The resulting powder mixture is a granular product which flows freely and is easily compressible [2]. The diluent and API are first mixed to create a homogenous powder blend. An aqueous solution containing water-based adhesives is mixed into the dry powder blend until all particles are wet to the consistency of damp snow. Next, the wetted particles

are passed through a sieve to create uniform particle size before drying in the oven [1]. The excess water evaporates from the wet particles to improve flow properties and prevent chemical instability in an aqueous environment. After drying, the glidant, lubricant, and disintegrating agent are added to the uniform particles and mixed thoroughly [3]. The final powder mixture can then be compressed into tablets.

Wet granulation is a widely used method to improve flow and compressibility qualities. Unfortunately, there are several disadvantages with this method. The aqueous granulating fluid can cause instability and hydrolysis with the tableting ingredients [1]. Additionally, the process of evaporation of fluid by heating can also affect the API and accelerate any hydrolytic reactions [1].

### **6.2.2 Dry Granulation**

Dry granulation offers an alternative to wet granulation if the addition of granulating fluid and the drying process hinder the final product. Dry granulation uses binders, diluents, disintegrants, glidants and lubricants in addition to the API [4]. All dry ingredients are mixed thoroughly to create a homogenous mixture which is compacted in one of two ways. “Slugging” utilizes a conventional tableting press to produce slugs which are then broken down to form a granular product [1]. Lower pressure used for the first compression leads to ease of compressibility of the formulation at the second

compression [1]. Another method of dry granulation uses roller compaction to form a cake. The compressed cake is broken down to form a granular product that can easily be recompressed with the addition of lubricant.

### **6.2.3 Direct Compression**

Wet and dry granulation are both multi-stage processes that improve fluidity and compressibility of the powder mixture to create a readily compressed powder blend for tableting [1, 5]. Direct compression is a simple method of tableting that can only be utilized when the powder mixture possesses adequate flowing properties and compressibility. The most important aspect in direct compression is the diluent selection. The diluent contributes the main flowing and compressibility aspects to the powder mixture. Binders, diluents, disintegrants, glidants, lubricants, and the API are all mixed together to form a powder mixture that can easily be compressed into tablets without any additional steps [6].

## **6.3 Ingredients**

### **6.3.1 Diluents**

Common excipients used as the tableting diluent are sugars: dextrose, fructose, lactose, maltodextrin, maltose, mannitol, sucrose, xylitol, and confectioner's sugar (powdered sugar) [4, 7]. Other diluents such as calcium

carbonate, microcrystalline cellulose, and sodium chloride are useful bulking agents for tableting [1].

### **6.3.2 Binders**

Powder mixtures often require a binding agent to provide adhesion in the compressed tablet. Starch, povidone, and microcrystalline cellulose are commonly used binding agents for tableting.

### **6.3.3 Glidants and Lubricants**

Glidants, or anticaking agents, are useful additions to the powder mixture. They improve flow of the ingredients to uniformly fill the die [1, 6]. The most frequently used glidants are colloidal silicon dioxide, starch, and talc.

Lubricants are employed to minimize friction between the compressed tablets and die wall [8]. Lubricants such as magnesium stearate, sodium lauryl sulfate, and talc are commonly used.

### **6.3.4 Disintegrating Agents**

A cohesive, strong tablet is essential for drug delivery. However, before the drug can be absorbed in the gastrointestinal tract, the tablet must disintegrate [1]. The addition of disintegrating agents such as crospovidone, microcrystalline cellulose, and croscarmellose sodium aid in the disintegration

process [4]. The disintegrating agent encourages water uptake and disrupts the tablet structure to fragment the tablet and allow further disintegration.

#### 6.4 Tableting Press

A tableting press utilizes a die, upper punch, lower punch, filler shoe, and hopper [8]. The lower punch drops to create a cavity for the powder mixture to freely flow from the hopper [6]. The filler shoe directs the powder mixture into the cavity while leveling off any excess powder [1, 2]. The upper punch then lowers into the die to compact the powder into a tablet. The tablet is then ejected when the lower punch rises and the filler shoe pushes the compressed tablet away from the punch set. Figure 6.1 illustrates the manufacturing process of tablet formation [9].

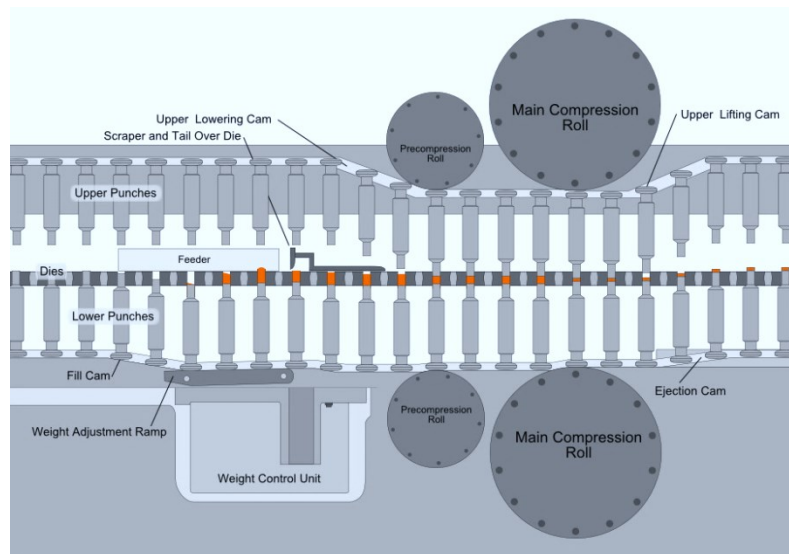


Figure 6.1 Tablet Formation [9]

## **Chapter Seven**

### **TABLET TESTING**

#### **7.1 Introduction**

Tablet testing is essential for verifying acceptable tablet manufacture. Tablets can be evaluated for a number of parameters. Weight variation, tablet dimensions, hardness, friability, disintegration time, and wetting time are measured to provide a comprehensive overview of the tablet characteristics.

#### **7.2 Weight Variation**

The United States Pharmacopeia 30 describes the analysis of weight variation of uncoated tablets in Uniformity of Dosage Units [1]. Ten randomly selected tablets are to be carefully weighed on an electronic analytical balance using forceps and tarred weighing paper [1, 2]. Tablets with a total tablet mass less than 130 mg have a 10% weight variation limit; therefore 90-110 mg tablets containing diphenhydramine HCl are within acceptable limits for the goal tablet weight of 100 mg [1].



### **7.3 Tablet Dimensions**

The dimension of tablets are critically important for swallowing and handling [3]. Additionally, orally disintegrating tablets often have a larger diameter than thickness to increase surface area for disintegration purposes. Diameter and thickness are measured in mm to analyze tablet formation.

### **7.4 Hardness**

Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing environment, in the drug distribution system, and tablet handling by consumers [4]. Ideally, orally disintegrating tablets have a hardness of 20-30 Newtons and can pass friability. Tablets with a lower breaking force, hardness, or crushing strength break apart more easily and can then disintegrate and dissolve quickly for systemic absorption. Modern technology utilizes mechanical drives, strain gauge-based load cells for force measurements, and electronic signal processing to provide a reliable method of analysis [4]. Round tablets without scoring are to be placed in any position allowing compression for breaking along the diameter of the tablet. A minimum of six tablets should be evaluated for breaking force [4].

## 7.5 Friability

Tablet friability of compressed uncoated tablets can be determined using the USP 30 method to simulate shipping and packaging stress [5].

Drum dimensions are outline in Figure 7.1 [6].

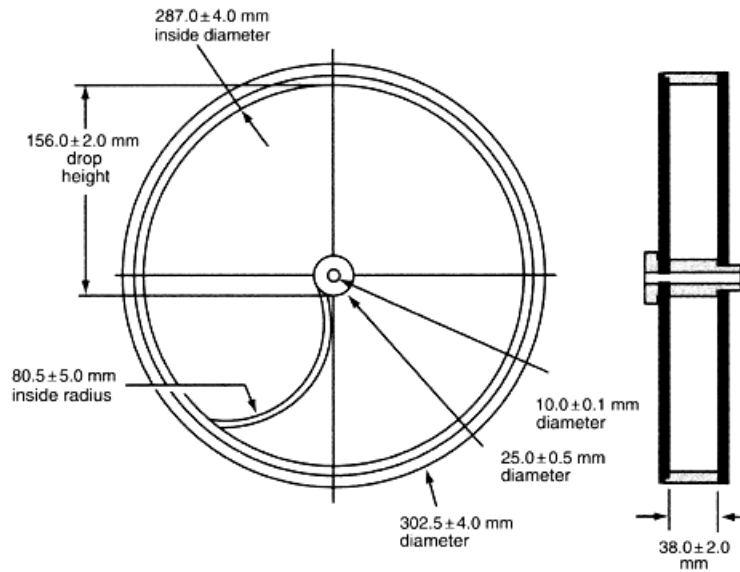


Figure 7.1 Tablet Friability Apparatus Dimensions [6]

USP 30 recommends tablets with a unit weight less than 650 mg utilize approximately 6.5 g of tablets for one determination [5]. Tablets are to be brushed to remove excess powder prior to their initial weight determination and after 100 revolutions (25 revolutions per minute for four minutes). According to the USP, less than 1% loss and no tablet breakage is acceptable for tablet friability. The test can be performed additional times if tablets are cracked, breakage occurs, or results are inconclusive. Figure 7.2 depicts the friability apparatus used for analysis [7].



Figure 7.2 Erweka Tablet Friability Apparatus [7]

## 7.6 Disintegration Time

Disintegration time of uncoated tablets was determined by combining the USP 30 standard method and Bi, et al.'s procedure for analyzing tablet disintegration time [8, 9]. The disintegration apparatus consists of a basket-rack assembly, a 1000 mL beaker, and a device that consistently raises and lowers the basket-rack assembly at a rate of 29 and 32 times per minute [9]. Figure 7.3 outlines the dimensions of the disintegration apparatus in mm [10].

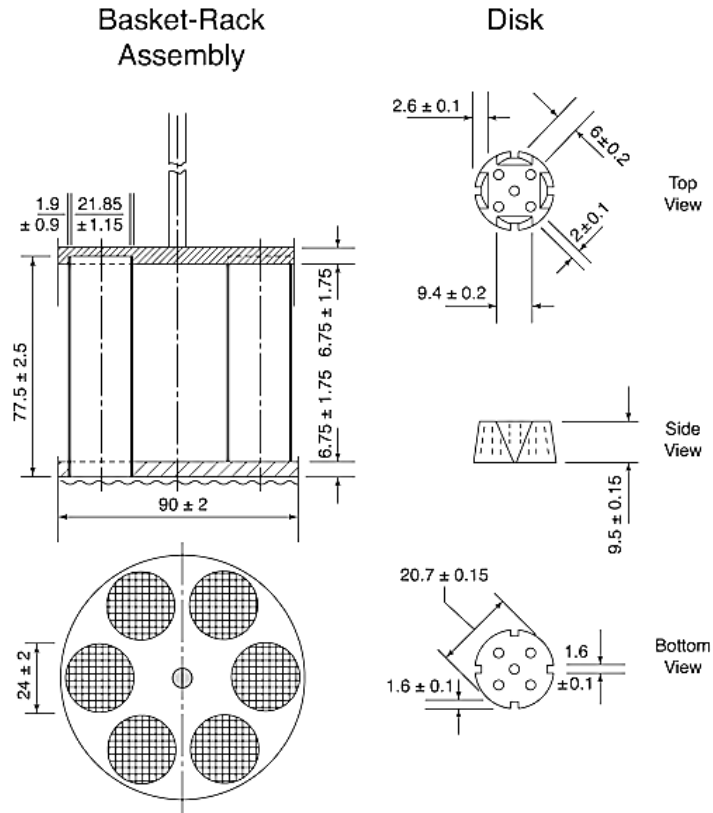


Figure 7.3 Disintegration Apparatus Dimensions [10]

The USP 30 recommends placing one tablet in each of the six-tubes of the basket with disks [9]. The disintegration medium should be maintained at  $37 \pm 2^\circ\text{C}$  [9]. Allow the device to raise and lower the basket-rack assembly in the disintegration medium for the prescribed amount of time (described in the monograph or research protocol), then remove the baskets from the medium and observe if the tablets completely disintegrated and passed through the mesh [9]. Bi, et al. suggested recording the amount of time required for tablets to disintegrate completely and pass through the mesh of the basket-rack assembly [8]. The disintegration time of each tablet was recorded and the average time was used to compare different formulations tested under the

same conditions. Figure 7.4 illustrates the basket-rack assembly used for disintegration time with the disks shown in Figure 7.5 [11, 12]. Figure 7.6 captures the disintegration of an orally disintegrating tablet [13].



Figure 7.4 Disintegration Test Basket-Rack Assembly [11]

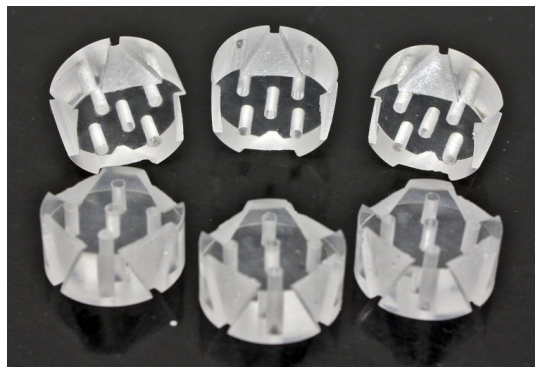


Figure 7.5 Disintegration Test Disks [12]

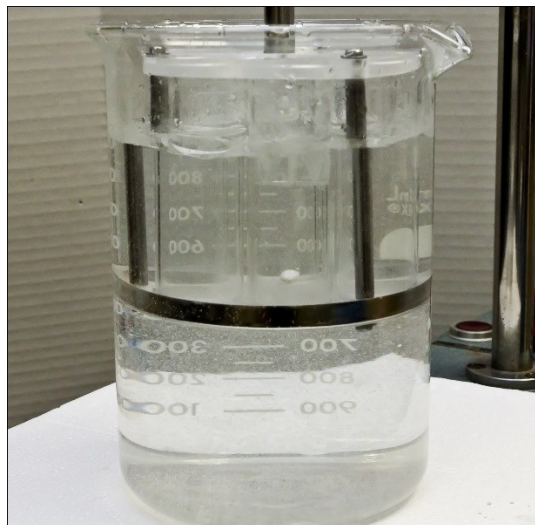


Figure 7.6 Disintegration of Orally Disintegrating Tablet [13]

### 7.7 Wetting Time

Wetting time is relative to the inner structure of tablets and the hydrophilicity of excipients and therefore is important for orally disintegrating tablets [8]. The USP does not have a monograph outlining the method for performing a wetting test. A commonly cited wetting test is described by Bi, et al. in *Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity* [8]. Slight variations have been employed to determine the wetting time of uncoated tablets. The typical wetting test utilizes tissue paper folded in a six-inch diameter petridish. The tablet is placed on the tissue paper near the center of the petridish and 6 mL of water is added [8]. The tissue paper wicks the water and the tablet begins to uptake water. The wetting time is recorded as the time when complete wetting of the tablet occurs.

We, at the University of Toledo, have developed an alternative method to determine wetting time and mimic saliva production and tongue surface to be recommended to USP for consideration. Wetting was assessed by determining the time required for three individual tablets to completely uptake water and visually wet the tablet throughout and to the surface. A small (1 cm x 1 cm), dry sponge and 1 mL of room temperature deionized water were used to simulate the saliva production in one minute and the surface of the tongue. Figure 7.7 illustrates the wetting test of a tablet over one minute utilizing our method of determination [14].

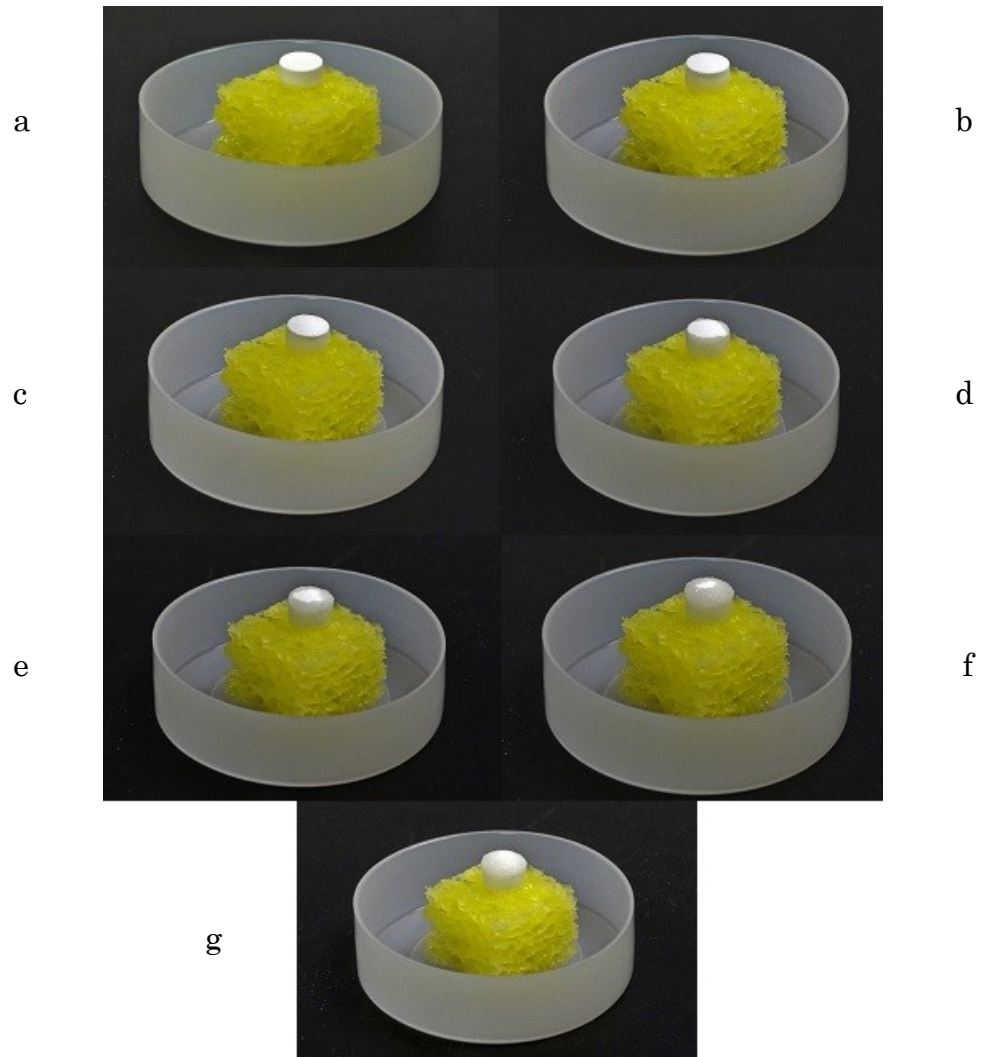


Figure 7.7 University of Toledo Wetting Test Method where the water wicks from the bottom to top as seen from left to right (a) through (g) while atop the sponge [14]



## **Chapter Eight**

### **POWDER FLOW**

#### **8.1 Introduction**

The fluidity of powder mixtures is crucial to successful tablet manufacture. Poor powder flow largely influences tablet characteristics such as: content uniformity, inconsistent hardness, disintegrating time, and dissolution rate [1]. Flow properties can be classified in a number of ways and improved by granulation and the use of glidants [2].

The US Pharmacopeia recognizes several methods of powder flow characterization in an attempt to standardize test methods. The most frequently employed methods of analysis are outlined in USP 30 [3]. Tests are often used in conjunction with other methods of analysis to gain a comprehensive understanding of powder fluidity and compressibility because there is not one single, simple method for adequate characterization [3]. Angle of repose, compressibility index or Hausner ratio, flow rate through an orifice, and shear cell are the most commonly reported methods of analysis [3].

## 8.2 Angle of Repose

A steady and reliable flow of powders is essential to manufacturing a consistent product. The angle of repose determines the flow properties of bulk solids. The angle of repose investigates interparticle friction or resistance to movement between particles [3]. The angle of repose is a “constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of the basic methods” [3].

USP 30 recommends the following procedure to determine angle of repose. The base should be free of vibration. The peak of the cone may become distorted by the impact of the powder flowing from the funnel. Therefore, the height of the funnel should vary (maintaining 2-4 cm from the top of the symmetrical cone) to build up a conical pile of powder. The angle of repose is calculated using Equation 8.1 [3]. Table 8.1 characterizes the angle of repose with its associated flow property [3]. Powder mixtures with an angle of repose greater than 50 are rarely acceptable for the manufacturing process [3].

$$\tan(\alpha) = \frac{\text{height}}{0.5 \times \text{base}} \quad (\text{Equation 8.1})$$

Table 8.1 Flow Properties and Corresponding Angles of Repose which Characterizes Various Grades of Powder [3]

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

### 8.3 Compressibility Index and Hausner Ratio

The compressibility index and Hausner ratio are closely related simple and fast methods for powder characterization. They indirectly measure bulk density, particle size, shape, surface area, moisture content, and cohesiveness of materials [3]. The compressibility index and Hausner ratio require the bulk density and tapped density of a powder mixture to be determined or known.

USP 30 recommends using a 250 mL graduated cylinder with a test sample weight of 100 g [3]. The average of three determinations is recommended. The compressibility index is calculated according to Equation 8.2 [3].

$$\text{Compressibility Index} = 100 \times \left( \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \right) \quad (\text{Equation 8.2})$$

The Hausner ratio was determined by using Equation 8.3 [3].

$$\text{Hausner Ratio} = \left( \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \right) \quad (\text{Equation 8.3})$$

The flow characteristics are described in Table 8.2 with respect to compressibility index and Hausner ratio [3].

Table 8.2 Scale of Flowability based on Compressibility Index and Hausner Ratio [3]

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

#### 8.4 Flow Through an Orifice

The time it takes for a powder mixture to flow through an orifice can be a useful classification of fluidity. Although there is no defined interpretation of results, it can be used for comparative purposes. The flow rate is dependent on particle interaction as well as factors involving the process. Flow through an orifice often utilizes 100 g samples and relates the amount of time required for the powder to flow through a cylinder, funnel or hopper. USP 30 describes this method and emphasizes the effect diameter and shape of orifice, type of container used (metal, plastic, glass), and diameter and height of the powder bed have on the results.

The FlowRatex<sup>®</sup> instrument is an alternative method for analyzing a powder mixture's ability to flow through an orifice. This analysis takes into consideration parameters such as particle size and shape, actual and bulk density, porosity settling and electrostatic charge [4]. The sample flows through the funnel and into the cylinder. Next, the lever is released and the

powder has the ability to flow through a variable size orifice. Care should be taken to avoid vibration and impact which can skew results. If the powder possesses adequate fluidity, the powder mixture will run out of the cylinder and the orifice will remain unclogged [4]. An arbitrary scale of 4-40 mm is used for comparison between powder mixtures. The most freely flowing powder will pass through 4 mm, while a powder with very, very poor flowability will be 40 mm.



Figure 8.1 FlowRatex® Apparatus [4]

### 8.5 Shear Cell

The shear cell method is useful in testing pharmaceutical ingredients. The shear cell takes into consideration such aspects as the loci of stress-shear strain relationships, angle of internal friction, tensile strength, and a variety of other parameters such as the flow factor. Shear properties of powders can be tested using a cylindrical shear cell that is split horizontally, annular shear cell design, or plate-type of shear cell that consists of a sandwich of powder

between a lower stationary rough surface and a moveable rough upper surface. The process involved in the analysis utilizes more in-depth methodology and requires specialized equipment [3]. Shear strength in both consolidated and unconsolidated powder mixtures can be measured [5]. Specialized software is used in conjunction with the different shear cell apparatuses to provide the shear strength, internal angle of friction, and cohesive properties [5]. Figure 8.2 illustrates a basic schematic of shear cell powder flow determination with annular shear cell [6].

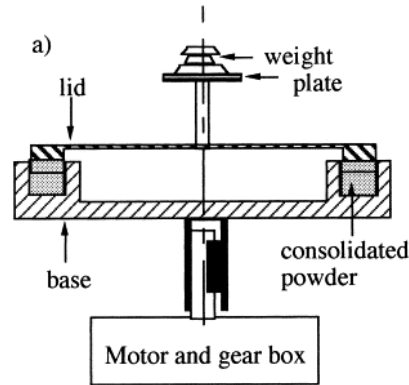


Figure 8.2 Schematics of annular shear cell used for measuring powder flow functions [6]

## **Chapter Nine**

### **DISSOLUTION**

#### **9.1 Introduction**

Dissolution is the process by which molecules leave the solid phase and enter into solution [1, 2]. The dissolution characteristics of a specific drug are affected by the physical characteristics of the dosage form, the wettability, penetration ability of the dissolution medium, and the disintegration and deaggregation of the dosage form [2]. The solid dosage form disintegrates into granules, and then the granules deaggregate into fine particles. While this process is occurring, dissolution is also taking place simultaneously with the release of the drug from each step [3]. Figure 9.1 shows the steps in the dissolution process of solid dosage forms.

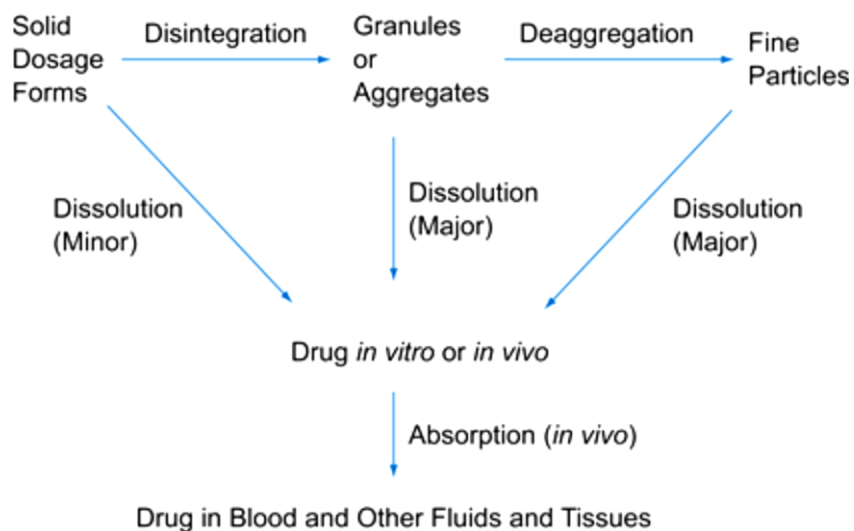


Figure 9.1: Dissolution process of solid dosage forms [2]

The dissolution rate of a drug from a dosage form is used as a biopharmaceutical parameter for evaluating the effectiveness of drug release from a solid dosage form [1]. The rate of dissolution of a drug from a solid dosage form becomes the rate limiting step for absorption into the blood [2]. Under certain circumstances the *in vitro* release profile can be used for assessing bioequivalence [4].

Dissolution profiles are essential in new dosage form development to ensure the drug dissolution occurs appropriately [4, 5]. A dissolution profile is defined as the calculated fraction of a drug that is released from a dosage form at a number of predetermined time points when tested in a dissolution apparatus [6]. The dissolution studies conducted during the drug development process assess the lot-to-lot quality of a product, conduct development of new formulations, and ensure product quality and performance after any changes



that may occur in the formulation, manufacturing process, or scale-up of the final dosage form [7, 8].

## **9.2 Instrumentation**

There are seven types of dissolution apparatuses used to evaluate the rate of dissolution. The USP provides the different methods in addition to guidelines for each apparatus [2]. The four basic types of apparatus' include the rotating basket (Apparatus 1), paddle method (Apparatus 2), reciprocating cylinder (Apparatus 3), and flow through cell (Apparatus 4). If any dissolution testing conditions were to change such as, stirring rate, apparatus, pH of the dissolution medium, or temperature, this may alter the dissolution profile of the dosage form [7].

### **9.2.1 Apparatus 1 (Basket Apparatus)**

The basket apparatus utilizes a vessel made of glass or another transparent inert material, motor, metallic drive shaft, and cylindrical basket [9]. Dissolution medium is maintained at  $37 \pm 0.5^{\circ}\text{C}$  with constant, smooth medium circulation [9]. The vessels are cylindrical with a hemispherical bottom [9]. Typical vessel volumes are 1 L, 2 L, and 4 L [9]. The shaft rotation speed is prescribed in the specific monograph being analyzed. The basket is to be positioned  $25 \pm 2$  mm from the bottom of the vessel. Figure 9.2 outlines the standard dimensions of USP dissolution Apparatus 1 [10].

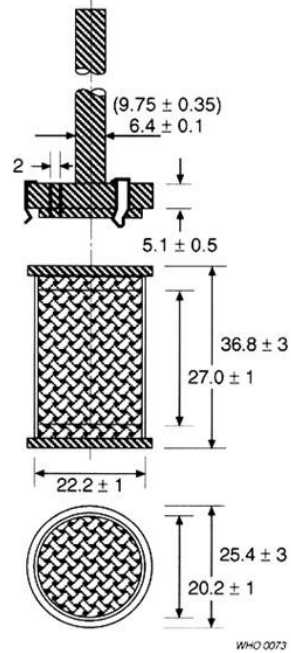


Figure 9.2 Apparatus 1 Basket Stirring Element [10]

### 9.2.2 Apparatus 2 (Paddle Apparatus)

The paddle apparatus utilizes a vessel made of glass or another transparent inert material, motor, and a paddle made from a metallic drive shaft and blade [9]. Dissolution medium is maintained at  $37 \pm 0.5^\circ\text{C}$  with constant, smooth medium circulation [9]. The vessels are cylindrical with a hemispherical bottom [9]. Paddles can be coated with inert material [9]. Sinker devices can be used to ensure tablets reach the bottom of the dissolution vessel [9]. The shaft rotation speed is prescribed in the specific monograph being analyzed. The paddle is to be positioned  $25 \pm 2$  mm from the bottom of the vessel. Figure 9.3 outlines the standard dimensions of USP dissolution Apparatus 2 [10].

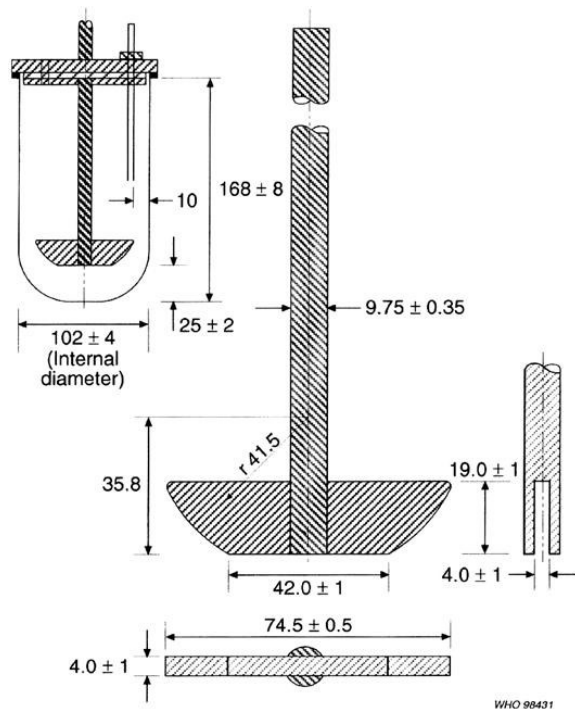


Figure 9.3 Apparatus 2 Paddle Stirring Element [10]

### 9.3 Procedure

For immediate release dosage forms, place the prescribed amount of dissolution medium ( $\pm 1\%$ ) in the vessel [9]. Allow the medium to reach  $37 \pm 0.5^\circ\text{C}$  [9]. Assemble apparatus and set rotation speed according to monograph or research protocol [9]. Place dosage unit in the apparatus and begin dissolution analysis. Withdraw a specified volume of sample midway between the surface of dissolution medium and top of blade or basket, not less than 1 cm from vessel wall [9]. Where more than one sample is extracted, an aliquot of fresh  $37^\circ\text{C}$  dissolution medium shall be replaced to maintain the original volume [9]. Where replacement of the dissolution medium is not necessary, one must correct for volume changes in the calculations [9].

## 9.4 Release Kinetics

Methods used to compare dissolution profiles are categorized as exploratory data analysis, mathematical, or statistical and modeling [6]. The quantitative analyses of the values obtained from a dissolution test are easier to express when using mathematical formulas. The drug, its polymorphic form, crystallinity, particle size, solubility, and amount of drug within the dosage form influence the release kinetics [4]. The most popular release kinetic models include zero order, first order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas.

### 9.4.1 Zero Order Kinetics

The zero order release has the ability to deliver a drug at a rate independent of time and drug concentration in a dosage form. Zero order ensures a steady amount of drug is released over time. This model represents the drug dissolution from dosage forms that do not disaggregate and release the drug slowly including transdermal systems or matrix tablets with low soluble drugs. The model is represented by the Equation 9.1 below [4].

$$Q_1 = Q_0 + K_0 t \quad \text{(Equation 9.1)}$$

Where ( $Q_1$ ) is the amount of drug dissolved; ( $t$ ) is the time; ( $Q_0$ ) is the initial amount of drug in the solution; and ( $K_0$ ) is the zero order release constant.

### 9.4.2 First Order Kinetics

This first order model is used to describe the absorption and elimination of some drugs. This model releases the drug proportionally to the amount of drug remaining in the interior of the dosage form, allowing for the amount of drug released per unit of time to diminish. The dosage forms which follow this dissolution profile include water soluble drugs in porous matrices. The model is represented by Equation 9.2 below [4].

$$\log Q_1 = \log Q_0 + \frac{K_1 t}{2.303} \quad (\text{Equation 9.2})$$

Where ( $Q_1$ ) is the amount of drug released; ( $Q_0$ ) is the initial amount of drug in solution; ( $t$ ) is the time; and ( $K_1$ ) is the first order release constant.

#### 9.4.3 Higuchi Model

The Higuchi model is used to study the release of water soluble and low soluble drugs incorporated in a semi-solid or solid matrix. This model describes drug release as a diffusion process based on Fick's law. The Higuchi model is used to describe drug dissolution from several types of modified release dosage forms such as transdermal systems or matrix tablets containing water soluble drugs. The model is represented by Equation 9.3 below [4].

$$Q_1 = K_H \sqrt{t} \quad (\text{Equation 9.3})$$

Where ( $Q_1$ ) is the amount of drug released; ( $K_H$ ) is the Higuchi dissolution constant; and ( $t$ ) is the time.

#### 9.4.4 Hixson-Crowell Model

The Hixson-Crowell model is used for dosage forms, such as tablets, where the drug surface of the tablet diminishes proportionally, resulting in the same geometrical form at all times. This model assumes the release rate is limited by the drug particles dissolution rate and not by the diffusion that might occur through a polymeric matrix. The model is represented by Equation 9.4 below [4].

$$W_0^{1/3} - W_1^{1/3} = K_s t \quad (\text{Equation 9.4})$$

Where ( $W_0$ ) is the initial amount of drug in the dosage form; ( $W_1$ ) is the remaining amount of drug in the dosage form; ( $t$ ) is the time; and ( $K_s$ ) is the surface-volume relation constant.

#### 9.4.5 Korsmeyer-Peppas Model

The Korsmeyer-Peppas model is a simple model relating, exponentially, the drug release to the elapsed time. The different release mechanisms are characterized by using an n-value, which differs depending on a slab or a cylinder. This model is used to analyze polymeric dosage forms that do not have a well-known release mechanism or more than one type of release is occurring simultaneously. The model is represented by Equation 9.5 below [4].

$$F = M_t / M_\infty = K_m t^n \quad (\text{Equation 9.5})$$

Where ( $F$ ) is the fraction of drug release at specific time; ( $M_t$ ) is the amount of drug release; ( $M_\infty$ ) is the total amount of drug in dosage form; ( $K_m$ ) is the structural and geometric constant; and ( $n$ ) is the release exponent.

## 9.5 Small-Volume Dissolution

Small-volume dissolution is required when analyzing the dissolution rate of low-dose, highly potent drugs or drugs that do not have a sensitive method of analysis [11]. The diphenhydramine HCl tablets required small-volume dissolution in conjunction with additional tablets because of UV-Vis detection limits of diphenhydramine HCl. The small-volume dissolution method parallels that of standard volumes discussed in USP 30 [9, 11]. The method uses 100 mL cylindrical vessels with a hemispherical bottom with mini paddles or baskets to facilitate dissolution. Figure 9.4 illustrates the small-volume dissolution vessels used with apparatus 2 [12].



Figure 9.4 Dissolution Apparatus 2 with small-volume vessels [12]



## **Chapter Ten**

### **STABILITY TESTING**

#### **10.1 Introduction**

Drugs are defined as a substance used in the diagnosis, cure, treatment or prevention of disease, intended to affect the structure and function of the body [1]. All medicinal products decompose over time [2]. Over-the-counter products must have an expiration date where product specifications remain within their given ranges and the active ingredient is proven to be safe and effective [1]. Accelerated stability studies can be used to detect decomposition and formulation limitations [2]. High stress environments encourage significant changes to occur more quickly in order to establish beyond-use and expiration dates [2].

#### **10.2 Accelerated Stability Testing**

New drug formulations must be analyzed for stability [1]. The Code of Federal Regulations (CFR) 21, Part 210 and 211, outlines requirements for a compliant stability procedure [1]. No specific details on acceptable stability data are included. Additionally, the FDA does not have a protocol established

for stability testing and recommends the International Conference of Harmonization (ICH) guideline Q1A as the accepted guideline for the stability testing of New Drug Substances and Drug Products [1]. General accelerated stability storage conditions are  $40 \pm 2^{\circ}\text{C}$  and  $75 \pm 5\%$  Relative Humidity (RH) [1]. Drug products packaged in semi-permeable containers have accelerated stability storage conditions of  $40 \pm 2^{\circ}\text{C}$  and  $25 \pm 5\%$  RH [1]. The ICH requires four points of analysis over six months to establish a two year expiration date [1]. The Consumer Healthcare Products Association (CHPA) Parent Guideline requires three points of analysis over three months to establish a two year expiration date for active ingredients currently being marketed [1].

### **10.3 Limitations**

Instability in formulations, in general, are only detectable after considerable storage periods under normal conditions [2]. Therefore, high stress conditions prompt faster chemical degradation and accelerate the process [2]. Extrapolation of the data is only valid when degradation depends on temperature [2]. Degradation caused by diffusion, microbial contamination, and photo-chemical reaction are not adequate predictors for stability testing [2].

## 10.4 Humidity Testing

In order to test the tablet sensitivity to humidity, tablets can be analyzed in a variety of relative humidity conditions over extended periods of time by utilizing different salts [3]. Relative humidity chambers are established by creating an excess of water soluble salt in contact with its saturated solution in an enclosed environment according to the CRC Handbook of Chemistry and Physics [3]. Relative humidity can be calculated according to Equation 10.1 using the values from Table 10.1 [CRC].

$$RH = Ae^{(B/T)} \quad \text{(Equation 10.1)}$$

Where (RH) is the percent relative humidity (generally accurate to  $\pm 2\%$ ); (T) is the temperature in kelvin; and constants (A) and (B) are described in Table 10.1 for the temperature range listed.

Table 10.1 Salts for Constant Humidity Solutions [3]

Compound	Temperature range (°C)	RH (25°C)	A	B
NaOH · H <sub>2</sub> O	15–60	6	5.48	27
LiBr · 2H <sub>2</sub> O	10–30	6	0.23	996
ZnBr <sub>2</sub> · 2H <sub>2</sub> O	5–30	8	1.69	455
KOH · 2H <sub>2</sub> O	5–30	9	0.014	1924
LiCl · H <sub>2</sub> O	20–65	11	14.53	–75
CaBr <sub>2</sub> · 6H <sub>2</sub> O	11–22	16	0.17	1360
LiI · 3H <sub>2</sub> O	15–65	18	0.15	1424
CaCl <sub>2</sub> · 6H <sub>2</sub> O	15–25	29	0.11	1653
MgCl <sub>2</sub> · 6H <sub>2</sub> O	5–45	33	29.26	34
NaI · 2H <sub>2</sub> O	5–45	38	3.62	702
Ca(NO <sub>3</sub> ) <sub>2</sub> · 4H <sub>2</sub> O	10–30	51	1.89	981
Mg(NO <sub>3</sub> ) <sub>2</sub> · 6H <sub>2</sub> O	5–35	53	25.28	220
NaBr · 2H <sub>2</sub> O	0–35	58	20.49	308
NH <sub>4</sub> NO <sub>3</sub>	10–40	62	3.54	853
KI	5–30	69	29.35	254
SrCl <sub>2</sub> · 6H <sub>2</sub> O	5–30	71	31.58	241
NaNO <sub>3</sub>	10–40	74	26.94	302
NaCl	10–40	75	69.20	25
NH <sub>4</sub> Cl	10–40	79	35.67	235
KBr	5–25	81	40.98	203
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	10–40	81	62.06	79
KCl	5–25	84	49.38	159
Sr(NO <sub>3</sub> ) <sub>2</sub> · 4H <sub>2</sub> O	5–25	85	28.34	328
BaCl <sub>2</sub> · 2H <sub>2</sub> O	5–25	90	69.99	75
CsI	5–25	91	70.77	75
KNO <sub>3</sub>	0–50	92	43.22	225
K <sub>2</sub> SO <sub>4</sub>	10–50	97	86.75	34

## 10.5 Shelf-Life Determination

Shelf-life can be extrapolated from three 12-month stability studies at one fixed temperature [2]. Multiple samples for each study can be tested at 0, 1, 3, 6, 9, and 12 months for drug content to provide a mean and standard deviation [2]. Drug content is plotted on the y-axis and time on the x-axis with 95% confidence interval [2]. The lower 95% confidence interval intersects minimum potency (90% required for shelf-life) and establishes shelf-life [2]. Figure 10.1 illustrates shelf-life determination from real time stability testing [2].

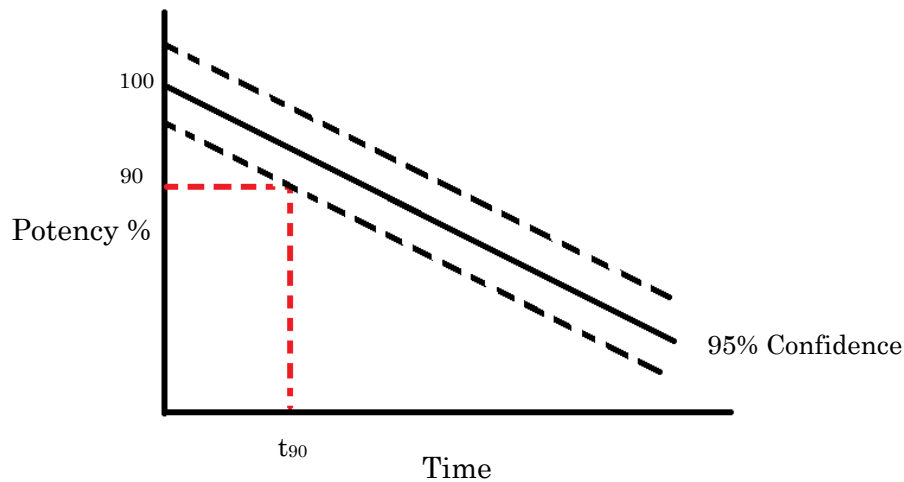


Figure 10.1 Shelf-Life Determination from Real Time Stability Testing [2]

## Chapter Eleven

### MATERIALS AND METHODS

#### 11.1 Materials

##### 11.1.1 Diphenhydramine Hydrochloride

Diphenhydramine hydrochloride (HCl), chemical structure illustrated in Figure 11.1, was used as the API to provide antihistamine properties in the orally disintegrating tablet. Diphenhydramine HCl (Lot No. XQ0021) was purchased from Spectrum Chemical Co (New Brunswick, NJ).

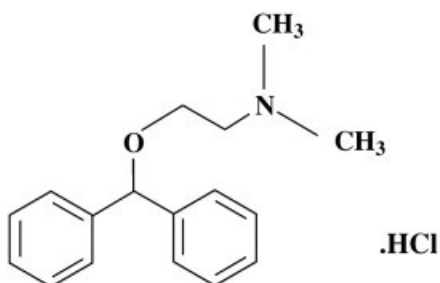


Figure 11.1 Diphenhydramine HCl

##### 11.1.2 Sugars

Compressible sugar and sugar alcohols were analyzed for purity and used as bulk excipients and sweeteners in the diphenhydramine HCl orally disintegrating tablet. Lactose, Figure 11.2, was purchased from Foremost Food Company (San Francisco, CA). Dextrose (Lot No. 406453), Figure 11.3,

was purchased from JT Baker Chemical Company (Phillipsburg, NJ). Fructose (Lot No. A018414301), Figure 11.4, was purchased from Acros Organics. Maltodextrin (Lot No. A3533), Figure 11.5, was supplied by Grain Processing Corporation (Muscatine, IA). Sucrose, Figure 11.6, was purchased from Sherman Research Laboratories (Toledo, OH). Mannitol (Lot No. E052P), Figure 11.7, was purchased from Roquette America, Inc. (Keokuk, IA). Isomalt (Lot No. L121095000), Figure 11.8, was donated by GalenIQ (Mannheim, Germany). A sample of Trehalose (Lot No. 2F101), Figure 11.9, was obtained from The Endowment for Medical Research and Cargill (Wayzata, MN).

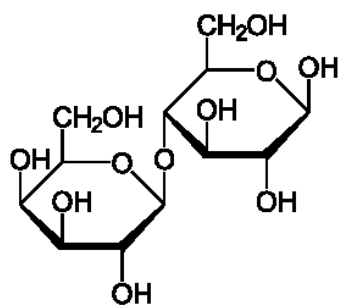


Figure 11.2 Lactose

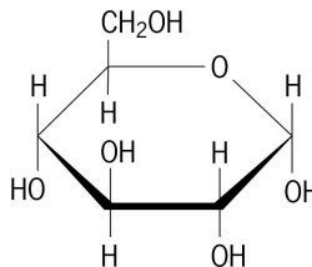


Figure 11.3 Dextrose

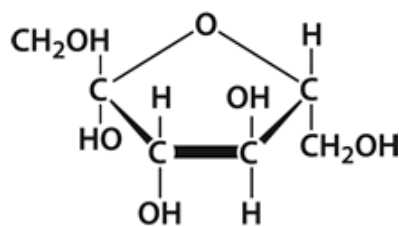


Figure 11.4 Fructose

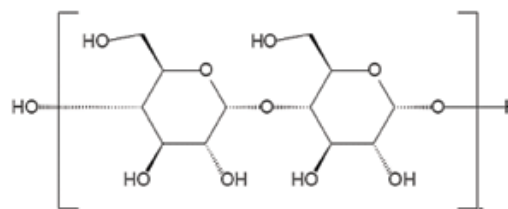


Figure 11.5 Maltodextrin

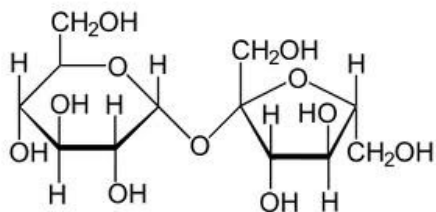


Figure 11.6 Sucrose

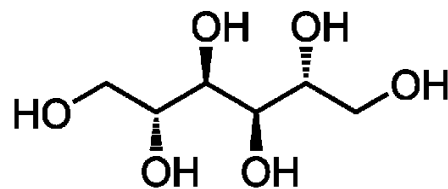


Figure 11.7 Mannitol

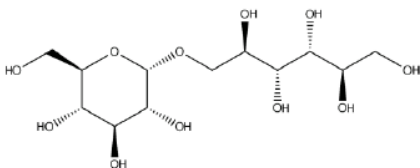


Figure 11.8 Isomalt

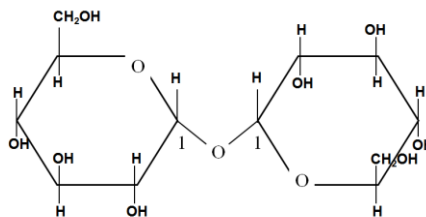


Figure 11.9 Trehalose

### 11.1.3 Superdisintegrants

A sample of Kollidon CL-SF® (Lot No. 91173168E0) was provided by BASF (Ludwigshafen, Germany). Primojel® (Lot No. 4AU061OH) was purchased from Chelsea Labs, Inc. (Monroe, NC). Ac-Di-Sol® (Lot No. T426) was purchased from FMC Corporation (Newark, DE). Polyplasdone XL® (Lot No. 82) was purchased from GAF Chemicals (Wayne, NJ).

### 11.1.4 Lubricant

Talc powder (Lot No. 10151214) was purchased from Letco Medical Supplies (Decatur, AL). Magnesium stearate (Lot No. 742748) was purchased from Fisher Scientific (Fair Lawn, NJ).

### **11.1.5 Simulated Gastric Fluid without Enzymes**

Simulated gastric fluid without enzymes was prepared according to the USP 30 standard method to be used as a dissolution medium [1]. Hydrochloric acid (Lot No. M153KMCP) was purchased from Chempure (Houston, TX) and diluted with deionized water. Sodium chloride was purchased from Sherman Research Laboratories (Toledo, OH) and dissolved in the acidic solution. The resulting pH ranged from 1.2 to 1.5.

### **11.1.6 Deionized Water**

Deionized water was supplied by the University of Toledo Health Science Campus deionization system.

### **11.1.7 Humidity Testing Salts**

Sodium chloride, purchased from Sherman Research Laboratories (Toledo, OH), was used to create 75% relative humidity in sealed baby food jar desiccators. Magnesium chloride (Lot No. 104F-0649) was purchased from Sigma Chemical Company (St. Louis, MO) to create the 33% relative humidity. Calcium bromide (Lot No. 0451) created a 16% relative humidity environment and was purchased from Mallinckrodt (St. Louis, MO).



### **11.1.8 Over-the-Counter Diphenhydramine Orally Dissolving Tablets**

Equate Children's Allergy Relief® (Lot No. P81317) was purchased from Walmart (Bentonville, AR). Rite Aid Children's Allergy Relief® (Lot No. P78527) was purchased from Rite Aid Pharmacy (Camp Hill, PA). Up&Up Children's Allergy Melts® (Lot No. P80545) were purchased from Target (Minneapolis, MN).

## **11.2 Methods**

### **11.2.1 Diphenhydramine HCl Analysis**

A DSC model 822e with a TS0801R0 Robot from Mettler-Toledo was used to analyze the diphenhydramine HCl sample for its thermal behavior. Samples (10 mg) were weighed in 100 µl aluminum pans and a lid crimped to the top with a hole punched at the top. The thermograms were recorded from 25-250°C at a rate of 10°C/min under nitrogen gas purge at 50 mL/min. Mettler Toledo STARe software (version 10.0) was used to collect and analyze the data.

### **11.2.2 DSC Analysis of Sugar and Diphenhydramine HCl**

The DSC model 822e was also used to analyze the diphenhydramine HCl, individual sugars, and 1:1 physical mixtures of diphenhydramine HCl and sugar samples for thermal behavior. Samples (10 mg) were weighed in 100 µl aluminum pans, crimped and pin-holed as previously described. The thermograms were recorded from 50-200°C at a rate of 10°C/min under

nitrogen gas purge at 50 mL/min. Mettler Toledo STARe software (version 10.0) was used to collect and analyze the data.

### **11.2.3 FTIR Analysis of Trehalose and Diphenhydramine HCl**

Trehalose, diphenhydramine HCl, and a 1:1 mixture were each individually analyzed. The samples were mixed with potassium bromide in approximately 1:100 ratio and formed into a pressed disc. The resulting disc was placed in a vacuum to expel air trapped between particles. The FTIR spectra of the samples were collected using a Germanium ATR (Attenuated Total Reflection) crystal in the Digilab Excalibur FTS 4000 FTIR spectrometer from Bio-Rad Laboratories fitted with a UMA 600 microscope. The spectra for these samples were obtained by accumulating 256 scans with a resolution of 4  $\text{cm}^{-1}$  in the range of 800-4000  $\text{cm}^{-1}$ .

### **11.2.4 UV-Vis Analysis of Trehalose and Diphenhydramine HCl**

UV-Vis model Genesys 6, Thermo Fisher Scientific, Madison, WI was used to analyze the quantity of diphenhydramine HCl in a physical mixture of trehalose and diphenhydramine HCl. Plastic one-centimeter path length cuvettes were used in the analysis. The wavelength ( $\lambda_{\text{max}}$ ) where diphenhydramine HCl has the highest absorption was determined by scanning the dissolved sample of pure diphenhydramine HCl in deionized water from 200 to 300 nanometers. Trehalose was analyzed at the experimental lambda

max of diphenhydramine HCl to determine if absorption occurred at that wavelength. A calibration curve was plotted using the Beer-Lambert law. Several diphenhydramine HCl concentrations were analyzed between 0.2-0.8 absorbance. Linear regression was used to correlate absorbance to diphenhydramine HCl concentration at its lambda max. The resulting Beer-Lambert equation was used to quantify the diphenhydramine HCl concentration in the trehalose: diphenhydramine HCl mixture to determine if degradation of diphenhydramine HCl occurred in a known sample.

### 11.2.5 Preparation of Superdisintegrant Powder Mixtures

Tablets containing 150 mg of powder were mixed according to Table 11.1 for the superdisintegrant Primojel®.

Table 11.1 Composition of 150 mg Blank Tablets Prepared on the Korsch Model 9015-70 Tablet Machine

Ingredients	Sample Composition (%)					
	S1	S2	S3	S4	S5	S6
Trehalose	94	93	92	91	90	89
Talc	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1
Primojel®	2	3	4	5	6	7

Tablets containing 100 mg of powder were mixed according to Table 11.2 for the superdisintegrants Kollidon CL-SF<sup>®</sup>, Ac-Di-Sol<sup>®</sup>, and Polyplasdone XL<sup>®</sup>.

Table 11.2 Composition of 100 mg Blank Tablets Prepared on the Manesty A 28 Tablet Machine

Ingredients	Sample Composition (%)											
	S 1	S 2	S 3	S 4	S 5	S 6	S 7	S 8	S 9	S 10	S 11	S 12
Trehalose	93	92	91	90	94	93	92	91	94	93	92	91
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Kollidon CL-SF <sup>®</sup>	3	4	5	6	-	-	-	-	-	-	-	-
Ac-Di-Sol <sup>®</sup>	-	-	-	-	2	3	4	5	-	-	-	-
Polyplasdone XL <sup>®</sup>	-	-	-	-	-	-	-	-	2	3	4	5

Trehalose was ground in a mortar with a pestle to create a free-flowing powder and break up any agglomerated particles. The four components of each powder mixture: trehalose as the bulk excipient, magnesium stearate as a lubricant, talc as a glidant and lubricant, and superdisintegrant were mixed in a small custom made V-shell blender (2.5 inch diameter x 6.5 inch per side) for at least five-minutes until homogenous. The V-shell used was fabricated by the Physics and Astronomy Shop (University of Toledo, OH) to fit our own Link-Belt V-shell blender stand.

### **11.2.6 Superdisintegrant Tableting**

Blank tablets of 150 mg were manufactured using the powder mixtures from Table 11.1 with a 7.97 mm round, convex tableting punch set using a Korsch Model 9015-70 Tableting Press, Korsch (Berlin, Germany). The compression force was adjusted to produce tablets with a hardness of 20-25 N to provide some mechanical strength while optimizing rapid oral disintegration.

Blank tablets of 100 mg were manufactured using the powder mixtures from Table 11.2 with a 5.64 mm round, convex tableting punch set and a Manesty A 28 Tableting Press, Manesty (Liverpool, England). Compression force was adjusted to produce tablets with a hardness of 20-25 N.

### **11.2.7 Superdisintegrant Tablet Testing**

The physical and mechanical parameters evaluated included: weight variation; friability; thickness; and hardness.

The weight of ten randomly selected tablets was measured in grams using an Intelligent Weighing Technology's model PM-300 balance, Intelligent Weighing Technology, Inc. (Camarillo, CA) [2].

Friability measurements were based on the official test method described in USP 30 using an Erweka Friability Apparatus Model TAP 23644, Erweka (Western Germany) [3]. Tablets (totaling approximately 6.0 g) were tested in triplicate to simulate shipping and packaging stress. Tablets were

brushed to remove excess powder prior to their initial weight determination and after 100 revolutions. According to the USP, less than 1% loss and no tablet breakage is acceptable for 100 revolutions in four minutes [3].

Thickness and hardness of six tablets were measured with the Sotax Hardness Tester Model HT1 4127.013, Sotax Corp. (Switzerland) in mm and Newtons (N), respectively using the USP 30 standard method.

Disintegration of three tablets was evaluated by the amount of time necessary for each tablet to disintegrate at 37°C in deionized water to the point where it was small enough to pass through the small basket apertures on the Erweka model ZT2 27151 apparatus, Erweka (Western Germany) using the USP 30 standard basket method with disks [4].

Wetting was assessed by determining the time required for three individual tablets to completely uptake water and visually wet the tablet throughout and to the surface. A small (1 cm x 1 cm), dry sponge and 1 mL of room temperature deionized water were used to simulate the saliva production in one minute and the surface of the tongue. This unique method was developed by us (University of Toledo, OH) and will be recommended to USP for consideration.

### 11.2.8 Powder Properties for the Optimal Choice of Superdisintegrant and its Concentration

The angle of repose for the optimal superdisintegrant and its concentration was determined by using the standard USP 30 method [5]. The funnel height was varied to maintain a distance of 2-4 cm from the top of the powder pile as the powder flowed to create a conical shape [5]. The angle of repose was calculated using Equation 11.1 below [5].

$$\tan(\alpha) = \frac{\text{height}}{0.5\text{base}} \quad (\text{Equation 11.1})$$

The compressibility index and Hausner ratio were calculated by weighing a sample of approximately 100 g using the Intelligent Weighing Technology's model PM-300 balance. The sample was then transferred to a 200 mL graduated cylinder. The initial volume was recorded with special care given to minimizing vibration. The sample and graduated cylinder was tapped 100 times until the volume no longer changed. The compressibility index was calculated using Equation 11.2 below [5].

$$\text{Compressibility Index} = 100 \times \left( \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \right) \quad (\text{Equation 11.2})$$

The Hausner ratio was determined by using Equation 11.3 [5].

$$\text{Hausner Ratio} = \left( \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \right) \quad (\text{Equation 11.3})$$

A Flowratex, Lab EXC model PF-21-101-150, was used to determine the orifice diameter that allows the powder mixture to freely flow through the opening. A smaller orifice indicates a free-flowing powder that has excellent flow properties.

### 11.2.9 Preparation of Diphenhydramine HCl Powder Mixture with Polyplasdone XL<sup>®</sup>

Tablets containing 100 mg of powder were mixed according to Table 11.3 for Polyplasdone XL<sup>®</sup> and Diphenhydramine HCl.

Table 11.3 Polyplasdone XL<sup>®</sup> and Diphenhydramine HCl Tablets

Ingredients	Sample Composition (%)							
	S1	S2	S3	S4	S5	S6	S7	S8
Trehalose	78.5	77.5	76.5	75.5	74.5	73.5	72.5	71.5
Talc	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1
Polyplasdone XL <sup>®</sup>	5	6	7	8	9	10	11	12
Diphenhydramine HCl	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5

Trehalose was ground in a mortar with a pestle to create a free-flowing powder and to break up any powder agglomerates. All components were mixed in a custom made V-shell blender for at least five-minutes until homogenous.

### 11.2.10 Diphenhydramine HCl Tableting

Tablets of 100 mg were manufactured using the powder mixtures from Table 11.3 with a 5.64 mm round, convex tableting punch set and a Manesty A 28 Tableting Press. The compression force was adjusted to produce



tablets with a hardness of 20-25 N as described in Section 11.2.6 Superdisintegrant Tableting.

#### **11.2.11 Diphenhydramine HCl Tablet Testing**

Tablets were tested using the same methods described in Section 11.2.7 Superdisintegrant Tablet Testing. Weight variation, friability, thickness, hardness, disintegration time, and wetting time were analyzed.

#### **11.2.12 Powder Properties for the Optimal Polyplasdone XL<sup>®</sup> Concentration with Diphenhydramine HCl**

The powder flow properties were analyzed using the same method as the Powder Properties for the Optimal Superdisintegrant and Concentration in Section 11.2.8.

#### **11.2.13 Preparation of the Final Diphenhydramine HCl Tablets with 10% Polyplasdone XL<sup>®</sup>**

The final powder mixture of diphenhydramine HCl tablets were prepared using the procedure from Section 11.2.9 Preparation of Diphenhydramine HCl Powder Mixture with Polyplasdone XL<sup>®</sup> with 10% Polyplasdone XL<sup>®</sup>.

The 200 g of formulation include: 73.5% trehalose, 3% talc, 1% magnesium stearate, 10% Polyplasdone XL<sup>®</sup>, and 12.5% diphenhydramine HCl.

#### **11.2.14 Final Diphenhydramine HCl Tablets with 10%**

##### **Polyplasdone XL<sup>®</sup> Tableting**

A 200 g sample of powder mixture to prepare tablets containing 10% Polyplasdone XL<sup>®</sup> and diphenhydramine HCl using the procedure from Sections 11.2.6 Superdisintegrant Tableting and 11.2.10 Diphenhydramine HCl Tableting.

#### **11.2.15 Tablet Packaging**

Tablets were packaged using a JVM Automatic Tablet Distributing & Packing System Model ARP-350SL6, JVM Co, Ltd. (Korea). Each package contained five 12.5 mg diphenhydramine HCl tablets. The packaging was composed of 2.5 inch amber cello and thermal paper to create a heat seal (University of Toledo Medical Center, OH). Figure 11.10 shows the tablet packaging used for the stability studies [6].



Figure 11.10 Diphenhydramine HCl ODT Packaging [6]

### 11.2.16 Stability Testing

Tablets were tested according to Sections 11.2.7 Superdisintegrant Tablet Testing and 11.2.11 Diphenhydramine HCl Tablet Testing. Hardness, disintegration time, and wetting time were analyzed at time zero, weeks 1, 2, 4, 6, and 8 for three temperature conditions: room temperature (25°C), oven (40°C), and refrigeration (3°C).

Additionally, dissolution tests were performed in triplicate according to the USP 30 standard method using Vanderkamp model VK600 Dissolution Apparatus (Edison, NJ) [7]. Initially, diphenhydramine HCl tablets were tested in simulated gastric fluid without enzymes as well as deionized water at  $37 \pm 0.5^\circ\text{C}$  and 75 revolutions per minute (rpm) [7]. Subsequent dissolution tests were only performed using deionized water as the dissolution medium. Apparatus 2 (Paddle Apparatus) was used with small volume 100 mL vessels [7]. Due to the detection limit of the UV-Vis Spectrometer, four tablets were used in addition to the small volume vessels to accurately quantify the concentration of diphenhydramine HCl dissolved.

A UV-Vis model Genesys 6, Thermo Fisher Scientific Madison, WI was used to analyze the quantity of diphenhydramine HCl concentration in the dissolution medium. Plastic one-centimeter path length cuvettes were used in the analysis. The wavelength determined from Section 11.2.4 UV-Vis Analysis of Trehalose and Diphenhydramine HCl was used as the  $\lambda_{\text{max}}$ . A calibration curve was plotted using known diphenhydramine HCl concentrations in

simulated gastric fluid without enzymes and deionized water according to the Beer-Lambert law. Several diphenhydramine HCl concentrations were analyzed between 0.2-0.8 absorbance in each dissolution medium. Linear regression was used to correlate absorbance to diphenhydramine HCl concentration at its lambda max. The resulting Beer-Lambert equation was used to quantify diphenhydramine HCl concentration from the dissolution of four tablets over time. A 3 mL sample was drawn with individual pipettes at 2, 5, 8, 12, 15, 20, and 30 minutes without replacement of the dissolution medium. The samples were then filtered using 2 inch x 2 inch Ahlstrom Filtration filter paper squares. The blank solutions (simulated gastric fluid without enzymes and deionized water) were prepared by incorporating trehalose, Polyplasdone XL<sup>®</sup>, talc, and magnesium stearate in the same ratio as the final tablet formulation. The blank solution was then filtered using the same type of Ahlstrom Filtration paper.

The effect of the filter paper on UV-Vis absorption was tested by analyzing 50 mg of diphenhydramine HCl in 100 mL of deionized water. The solutions were held in the same conditions as the dissolution test. Deionized water was used as the dissolution medium at 37°C, paddles stirred the solution at 75 rpm for 30 minutes. The resulting solutions were either filtered as previously described or analyzed directly from the dissolution apparatus. The difference in apparent concentrations was used to account for the filter paper effect on diphenhydramine HCl quantification.

### 11.2.17 Humidity Testing

In order to test the tablet sensitivity to varying humidity levels, tablets were tested at three relative humidity levels at room temperature over eight weeks. Figure 11.11 illustrates relative humidity chambers that were established by creating an excess of water soluble salt in contact with its saturated solution in a baby food jar according to the CRC Handbook of Chemistry and Physics [8, 9]. Three tablets were weighed at time zero for each humidity chamber and placed in a glass basket to elevate the tablets above the salt slurry. Relative humidity levels of 16%, 33% and 75% were achieved by sealing two containers with three tablets each. Calcium bromide was used to create a 16% relative humidity environment at room temperature. Magnesium chloride created a 33% relative humidity and sodium chloride was used for 75%. The six resulting tablets were weighed after weeks 1, 2, 4, 6 and 8 to determine percent weight change. Additionally, the hardness was determined by using the Sotax Hardness Tester Model HT1 4127.013, Sotax Corp. (Switzerland) in Newtons (N).



Figure 11.11 Relative Humidity Chamber for Diphenhydramine HCl  
ODT [9]

### **11.2.18 Physical and Mechanical Testing of Currently Available Diphenhydramine HCl Orally Dissolving Tablets**

Tablets were tested using the same methods described in Sections 11.2.7 Superdisintegrant Tablet Testing and 11.2.11 Diphenhydramine HCl Tablet Testing. Weight variation, thickness, hardness, disintegration time, and wetting time were analyzed.

## Chapter Twelve

### RESULTS AND DISCUSSION

#### 12.1 Diphenhydramine HCl Analysis

The DSC thermogram in Figure 12.1 illustrates the purity of diphenhydramine HCl with a single sharp peak at 170°C for melting and subsequent degradation above 200°C. The experimental melting point is consistent with literature values [1].

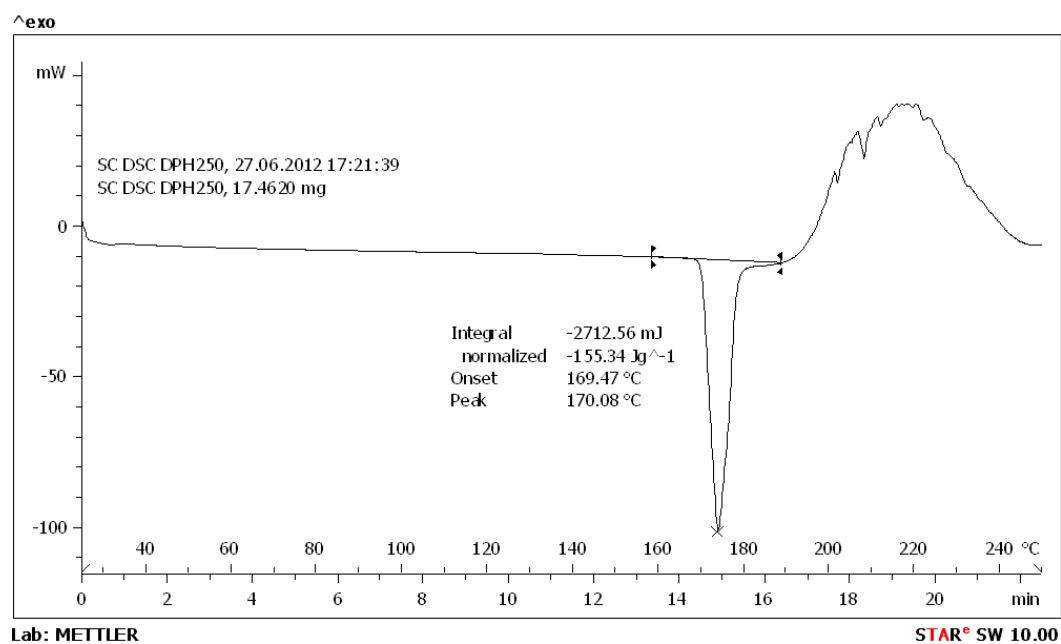


Figure 12.1 DSC Thermogram for Diphenhydramine HCl

## 12.2 DSC Analysis of Sugar and Diphenhydramine HCl

Diphenhydramine HCl contains an amine and forms the Maillard reaction when combined with reducing sugars in the presence of heat [2]. The reactive carbonyl group of the sugar reacts with the nucleophilic amine to give off water and other byproducts [2]. Consequently, the diphenhydramine HCl concentration would decrease and not be bioavailable.

The DSC thermogram in Figure 12.2 shows diphenhydramine HCl (170°C) and lactose (148°C) individually while Figure 12.3 illustrates the 1:1 physical mixture. Figure 12.3 shows a significant 20°C peak shift which suggests there is a reaction between lactose (127°C) and diphenhydramine HCl (149°C).

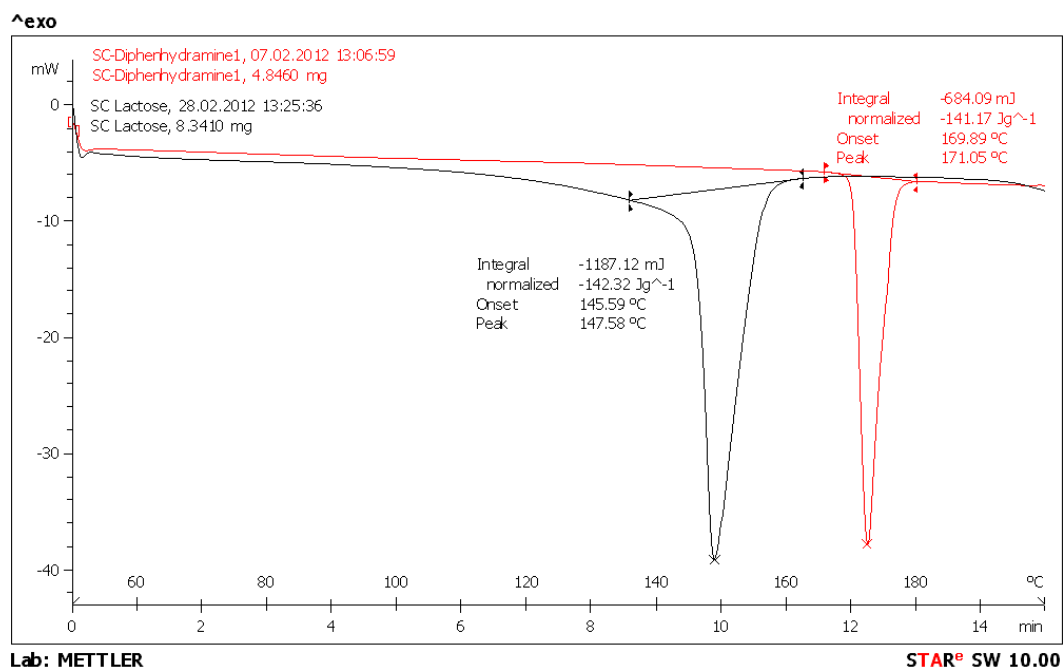


Figure 12.2 DSC Thermogram for Diphenhydramine HCl and Lactose



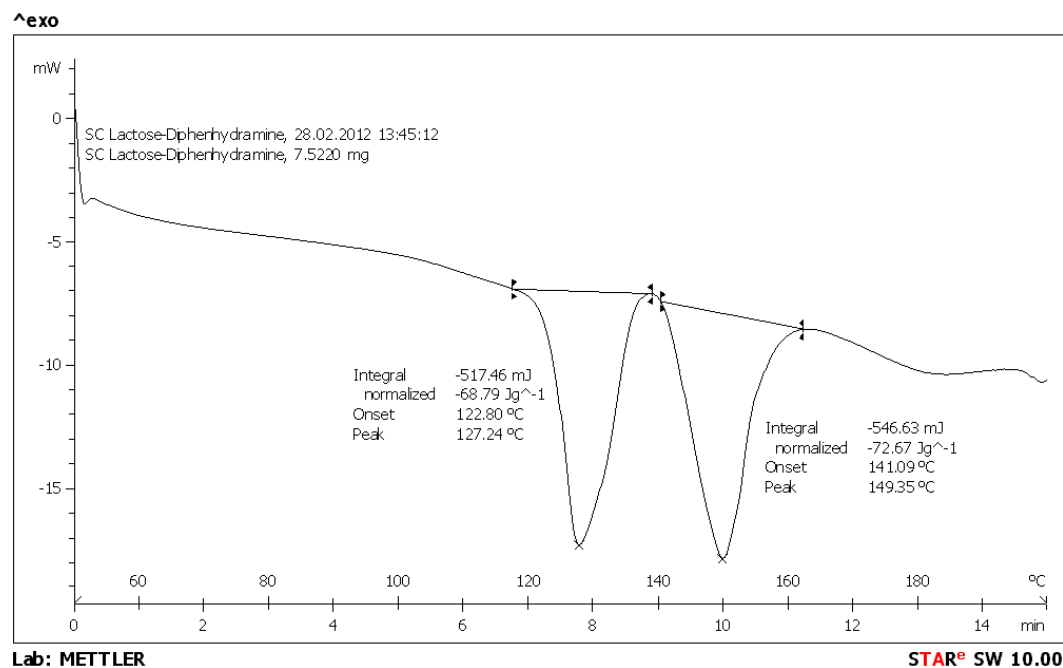


Figure 12.3 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Lactose

The individual thermograms for diphenhydramine HCl and dextrose in Figure 12.4 displays sharp prominent peaks that require a high heat of fusion (Joules/g) for phase transition. Figure 12.5 shows a shift in the peaks and a diminished diphenhydramine HCl peak heat of fusion from 141 J/g to 2 J/g. The significant change in heat of fusion proposes a probable Maillard reaction between dextrose and the drug.

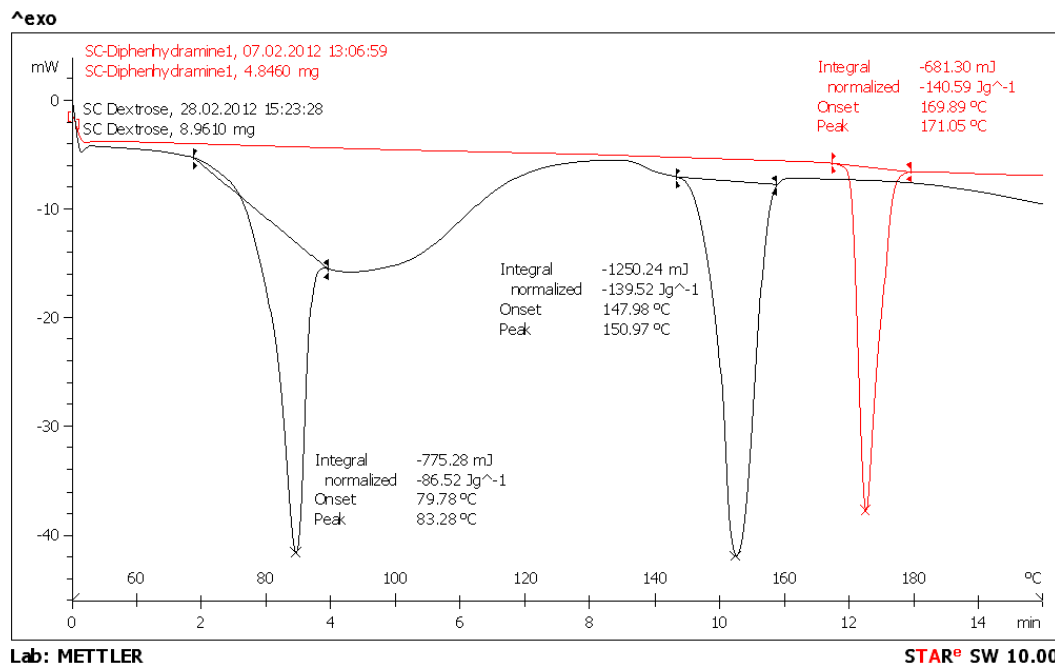


Figure 12.4 DSC Thermogram for Diphenhydramine HCl and Dextrose

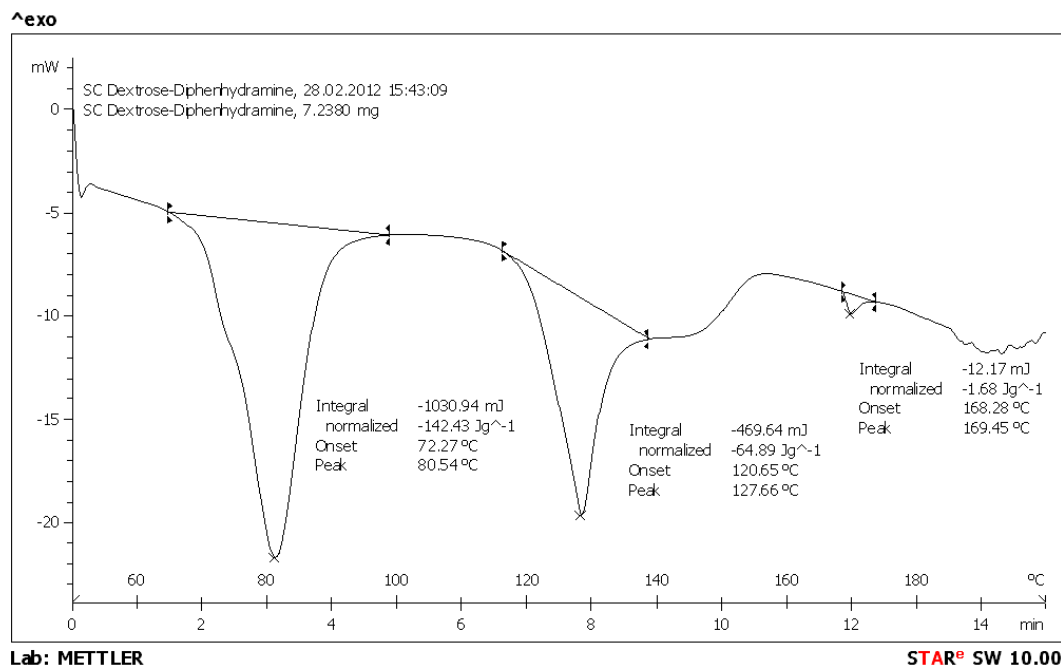


Figure 12.5 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Dextrose

The DSC thermogram in Figure 12.6 shows diphenhydramine HCl and fructose individually while Figure 12.7 illustrates the 1:1 physical mixture.

Figure 12.7 has broad shifted peaks, the first peak (126°C) with shoulder (118°C) suggests there is a reaction between fructose and diphenhydramine HCl. The Maillard reacted chemicals stabilize product; i.e. decomposition greater than 170°C is diminished.

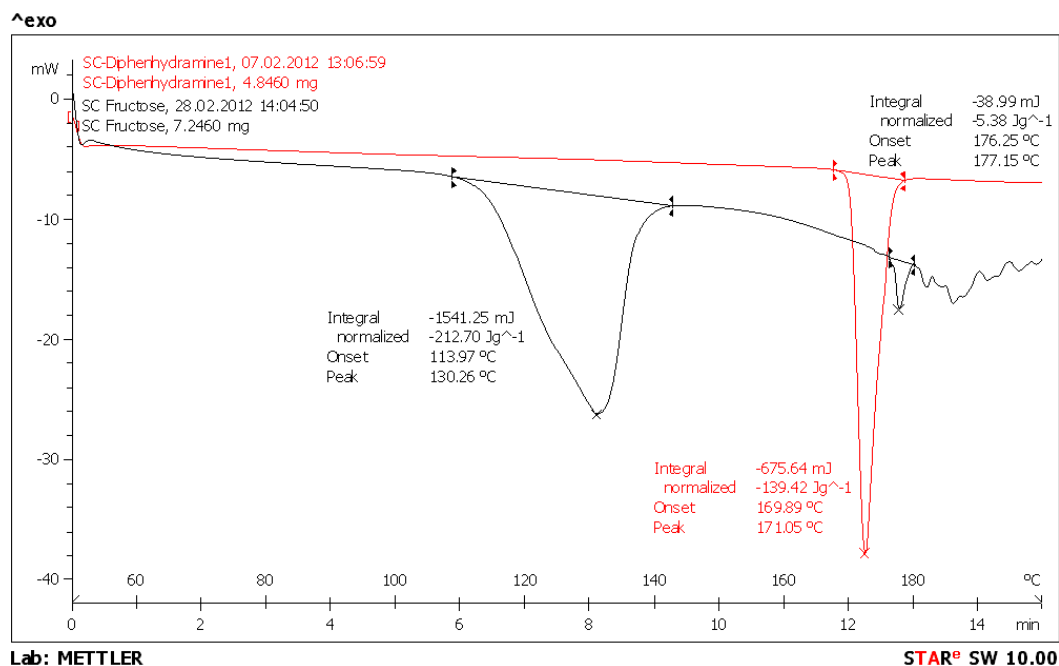


Figure 12.6 DSC Thermogram for Diphenhydramine HCl and Fructose

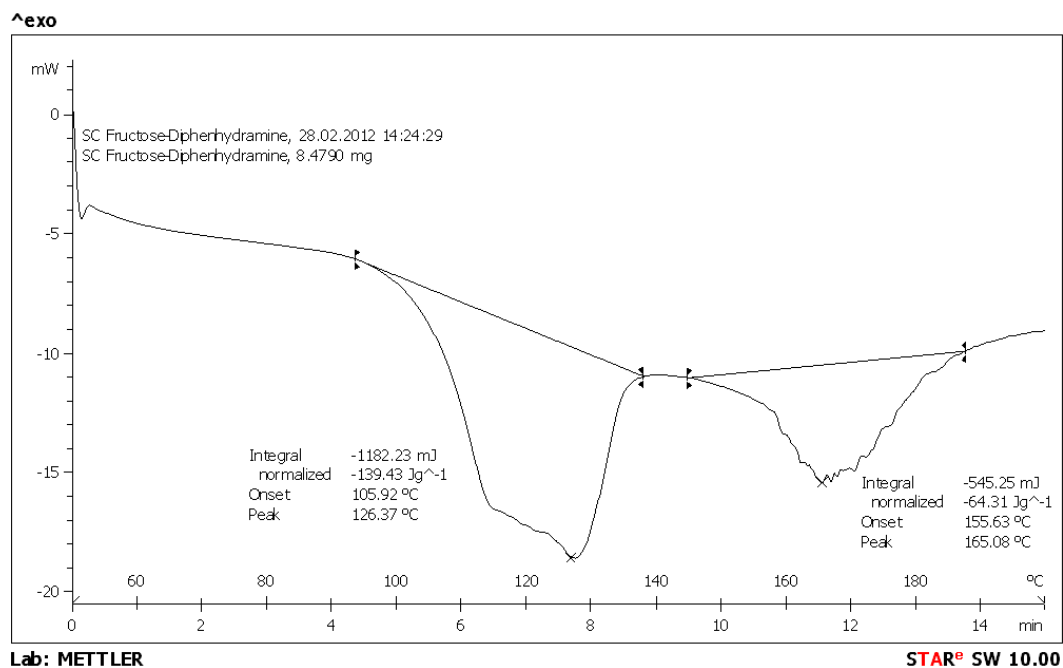


Figure 12.7 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Fructose

The maltodextrin or Maltrin<sup>®</sup> thermogram in Figure 12.8 lacks a distinct peak but indicates a shift in the baseline which suggests a glass transition and amorphous solid. Figure 12.9 for the 1:1 physical mixture illustrates a peak shift and broadening (ca. 15°C while the diphenhydramine HCl alone is 2-3°C at half peak) of the diphenhydramine HCl peak. The change suggests that a chemical reaction is taking place between the maltodextrin and diphenhydramine HCl.

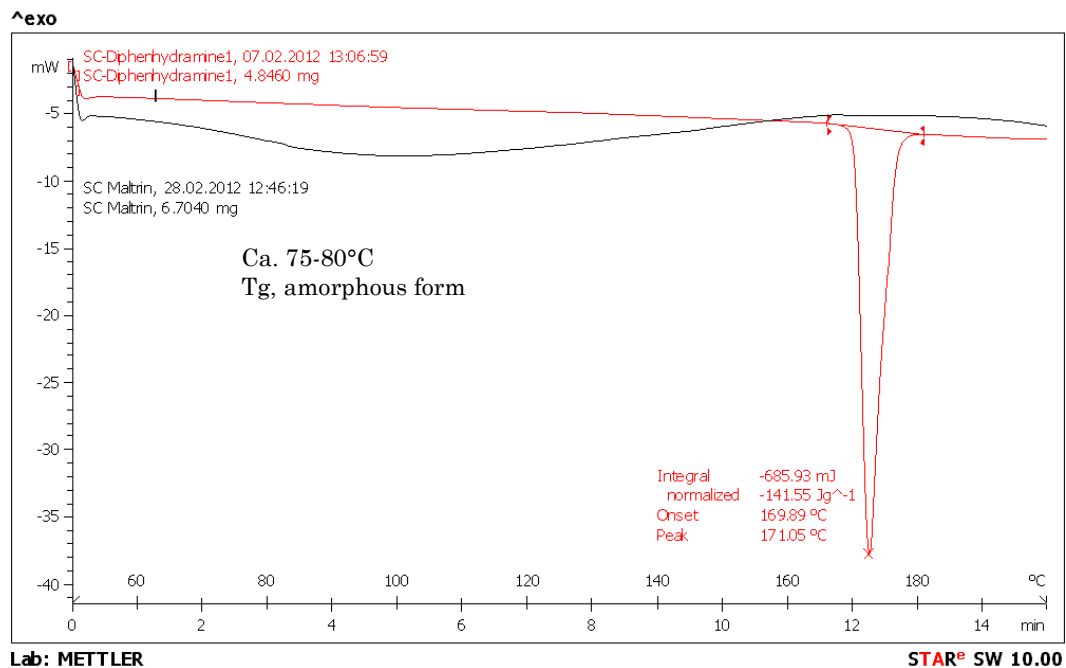


Figure 12.8 DSC Thermogram for Diphenhydramine HCl and Maltodextrin

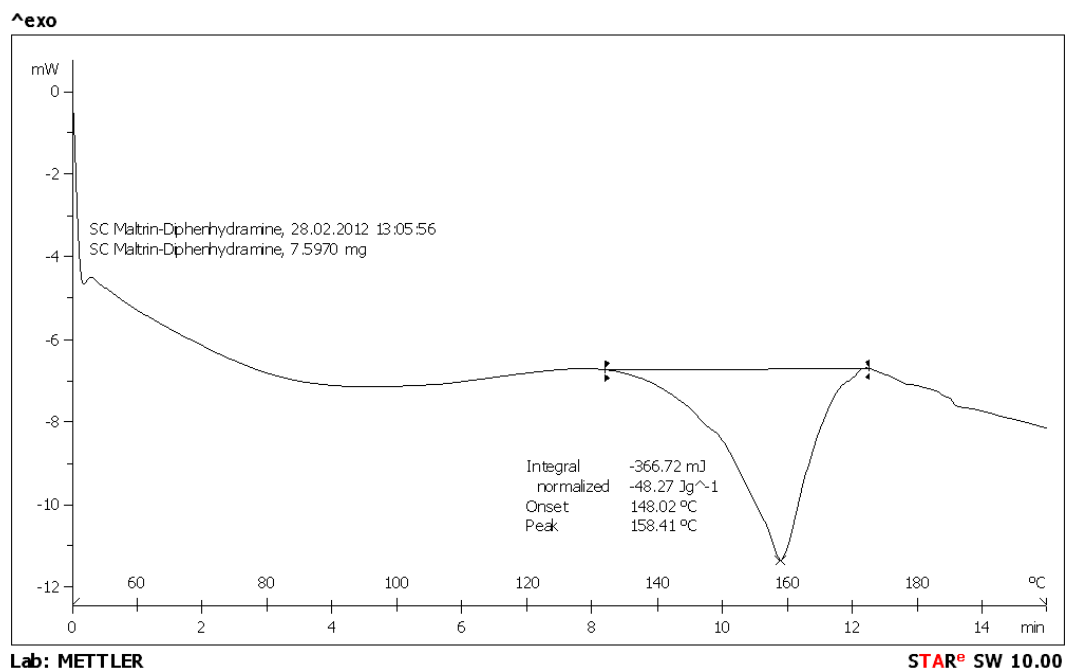


Figure 12.9 DSC Spectra for the 1:1 Physical Mixture of Diphenhydramine HCl and Maltodextrin

Table 12.1 contains all the critical values from the integration of chemical peaks from the DSC analysis. Each blended 1:1 mixture lacks the characteristic diphenhydramine HCl peak at 170°C or has a much lower heat of fusion which suggests a reaction such as the Maillard reaction is occurring.

Table 12.1 The Onset, Peak, and Heat of Fusion ( $\Delta H_F$ ) from DSC Thermal Analysis Critical Values for the Reducing Sugars and Diphenhydramine HCl

	Onset, °C	Peak, °C	Heat of Fusion, J/g
Diphenhydramine HCl	170	171	141
Lactose	146	148	142
Blend	123	127	69
	141	149	73
Diphenhydramine HCl	170	171	141
Dextrose	80	83	87
	148	151	140
Blend	72	81	142
	121	128	65
	168	169	2
Diphenhydramine HCl	170	171	140
Fructose	114	130	213
	176	177	5
Blend	106	126	139
	156	165	64
Diphenhydramine HCl	170	171	142
Maltodextrin	-	-	-
Blend	148	158	48

Due to the non-reducing nature of sucrose, mannitol, isomalt, and trehalose, the Maillard reaction is not a concern with the following physical mixtures, however, other reactions may take place.

The DSC thermogram in Figure 12.10 shows the individual peaks for sucrose and diphenhydramine HCl separately. Figure 12.11 displays a slight shift in the second peak for sucrose and the disappearance of the diphenhydramine HCl peak. These changes indicate a reaction may have taken place or the diphenhydramine HCl became amorphous after melting from its crystalline form.

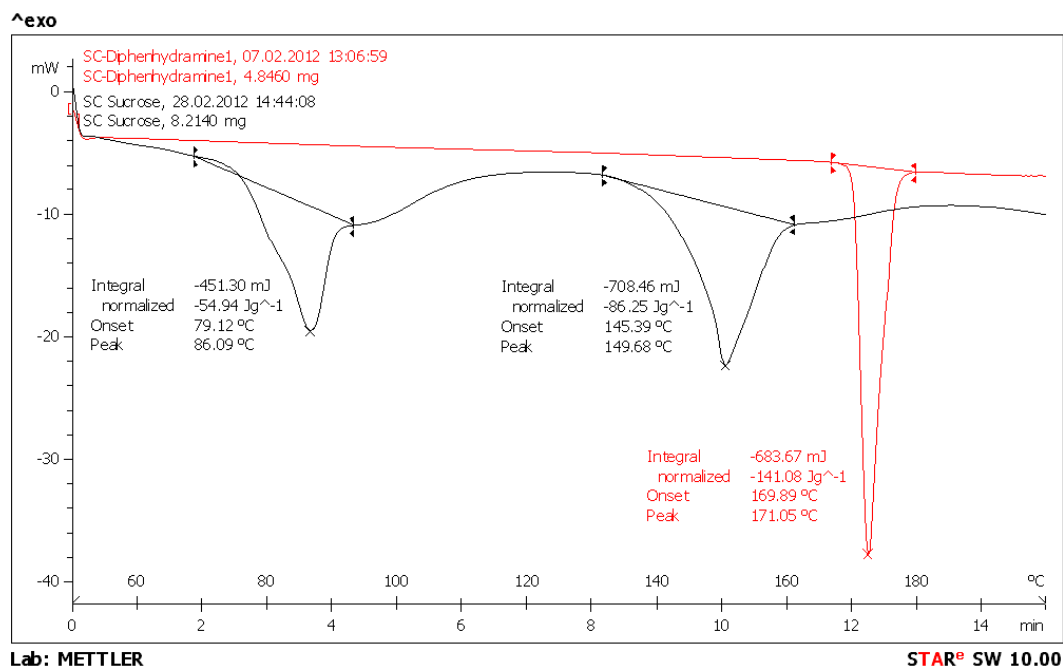


Figure 12.10 DSC Thermogram for Diphenhydramine HCl and Sucrose

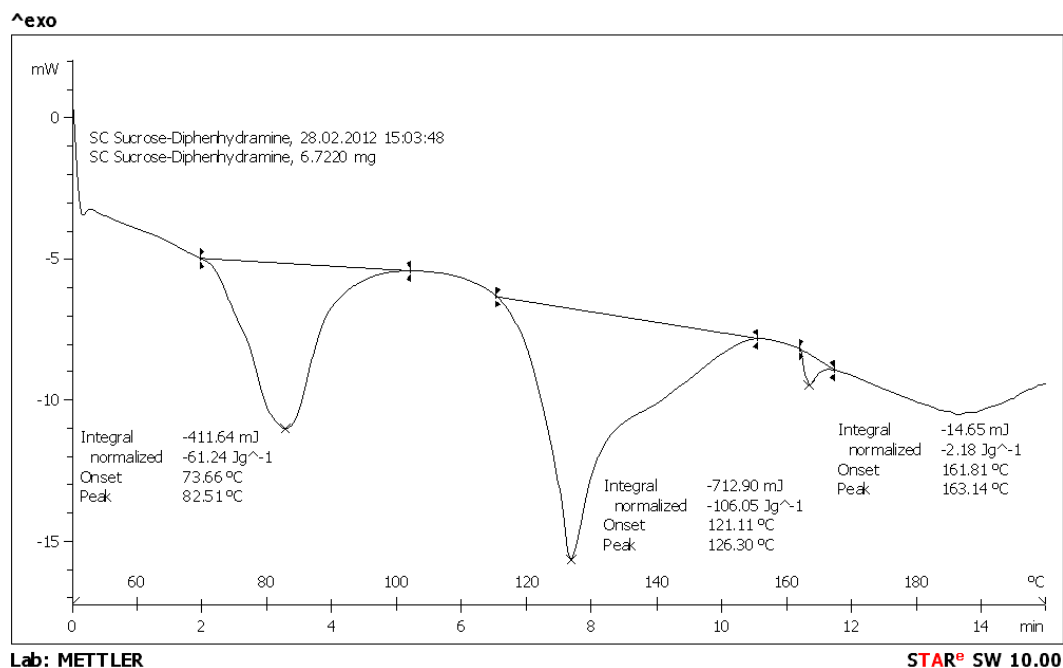


Figure 12.11 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Sucrose

Mannitol and diphenhydramine HCl both exhibit peaks at 170°C in Figure 12.12. The thermogram in Figure 12.13 for the 1:1 physical mixture displays two distinct peaks, neither of which are at 170°C. The changes suggest a reaction which may have occurred with diphenhydramine HCl and mannitol or that the diphenhydramine HCl became amorphous.



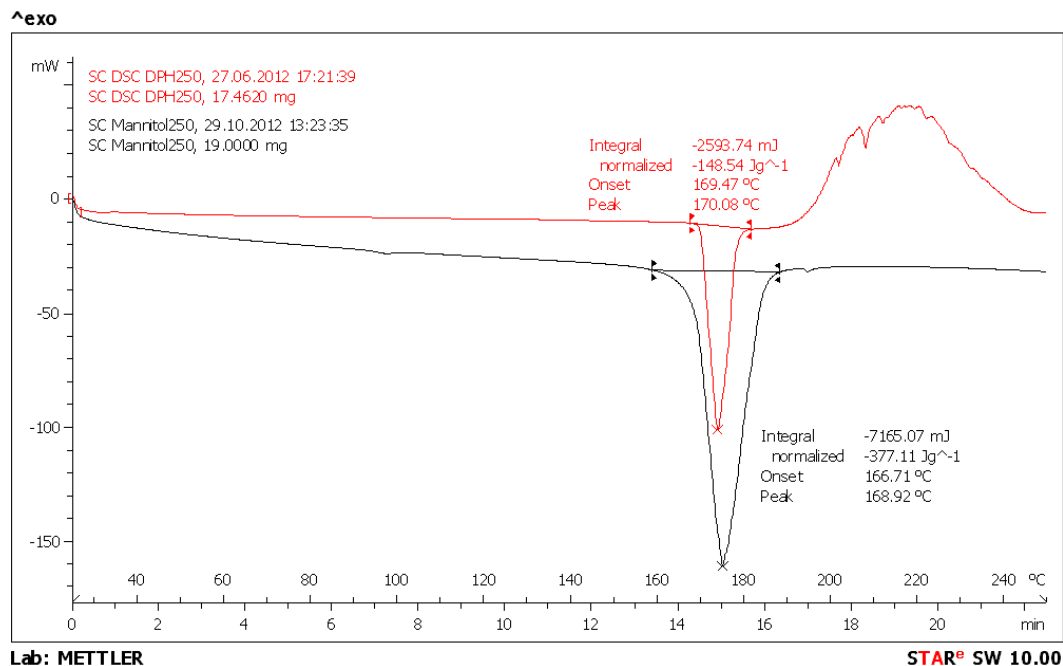


Figure 12.12 DSC Thermogram for Diphenhydramine HCl and Mannitol

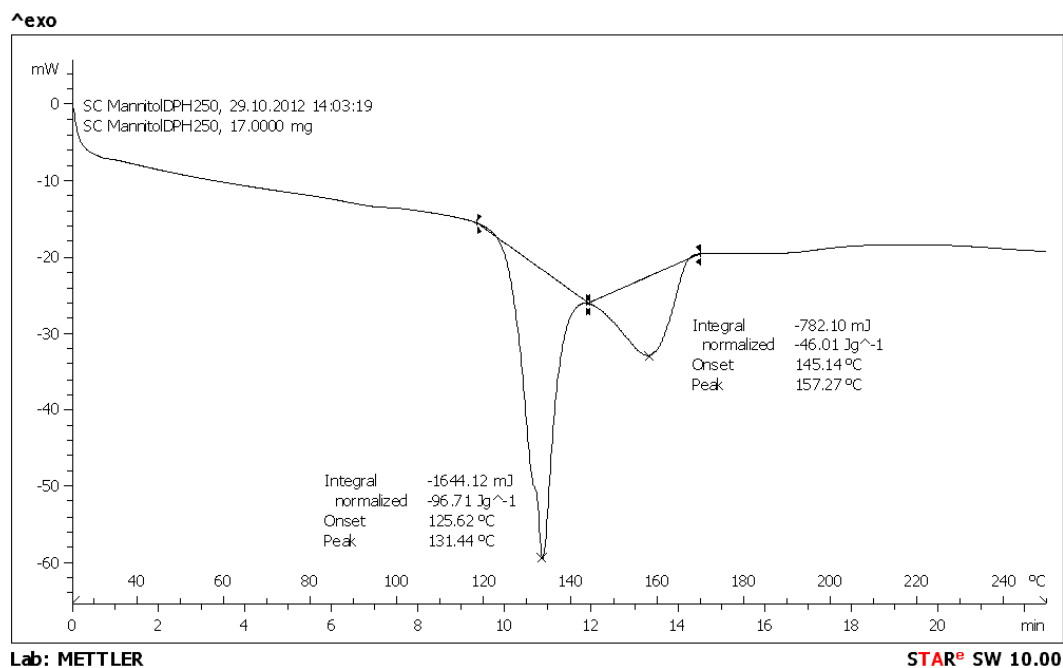


Figure 12.13 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Mannitol

Isomalt has two broad peaks in Figure 12.14 and displays shouldering in Figure 12.15 when combined in a physical mixture with diphenhydramine HCl which indicates another phase is present, such as an amorphous solid. The thermogram for the blended mixture suggests a reaction may have taken place or the diphenhydramine HCl has become amorphous.

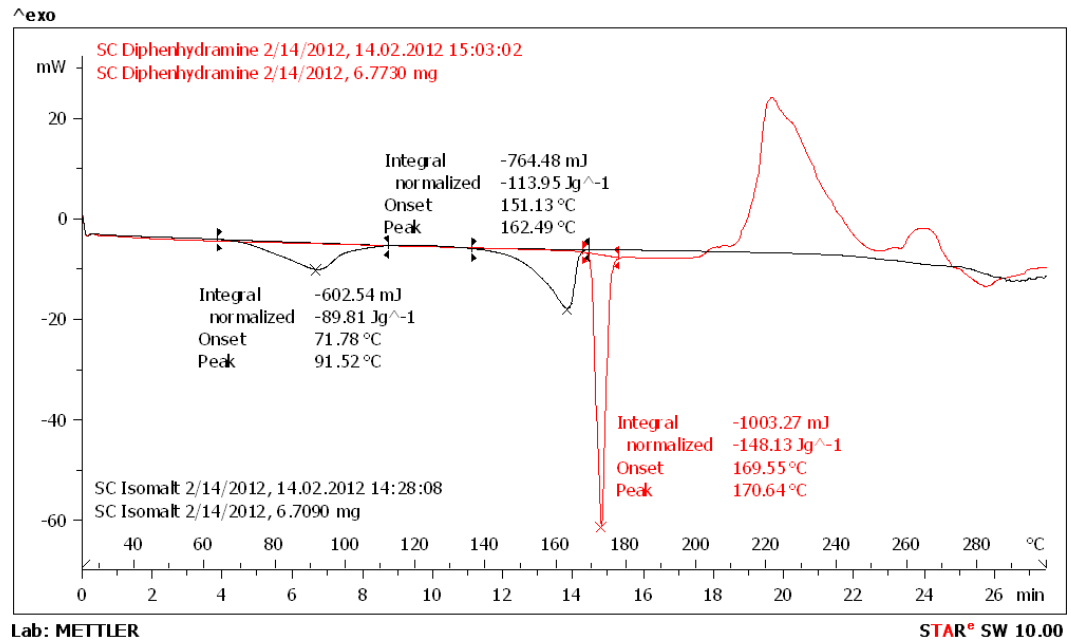


Figure 12.14 DSC Thermogram for Diphenhydramine HCl and Isomalt

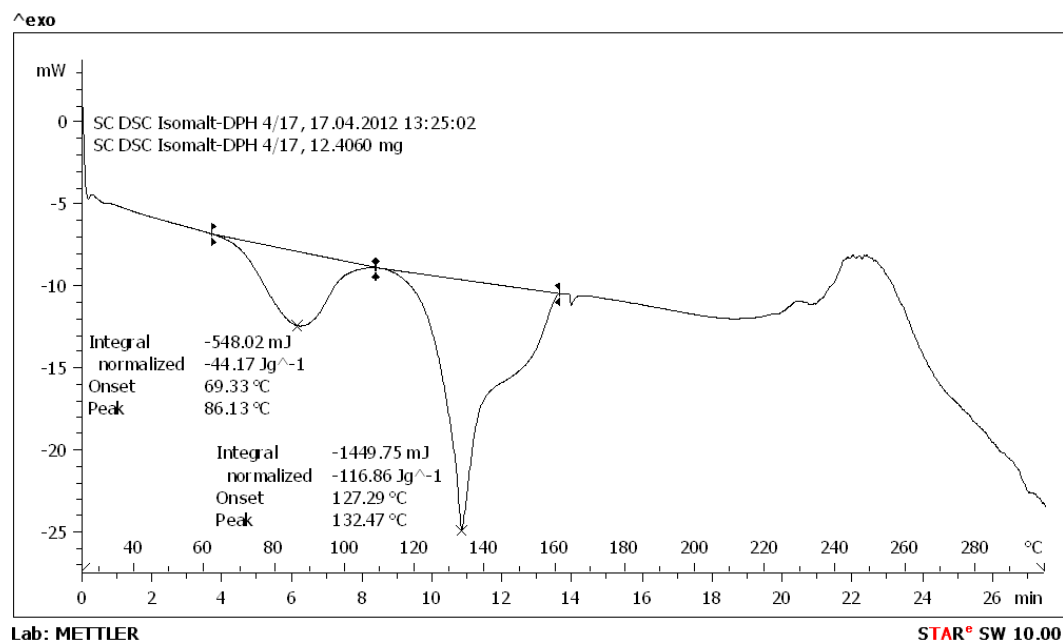


Figure 12.15 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Isomalt

The individual thermograms for trehalose and diphenhydramine HCl are presented in Figure 12.16. The DSC thermogram for the 1:1 physical mixture in Figure 12.17 has one distinct peak which suggests the diphenhydramine HCl became amorphous or a complex was formed.

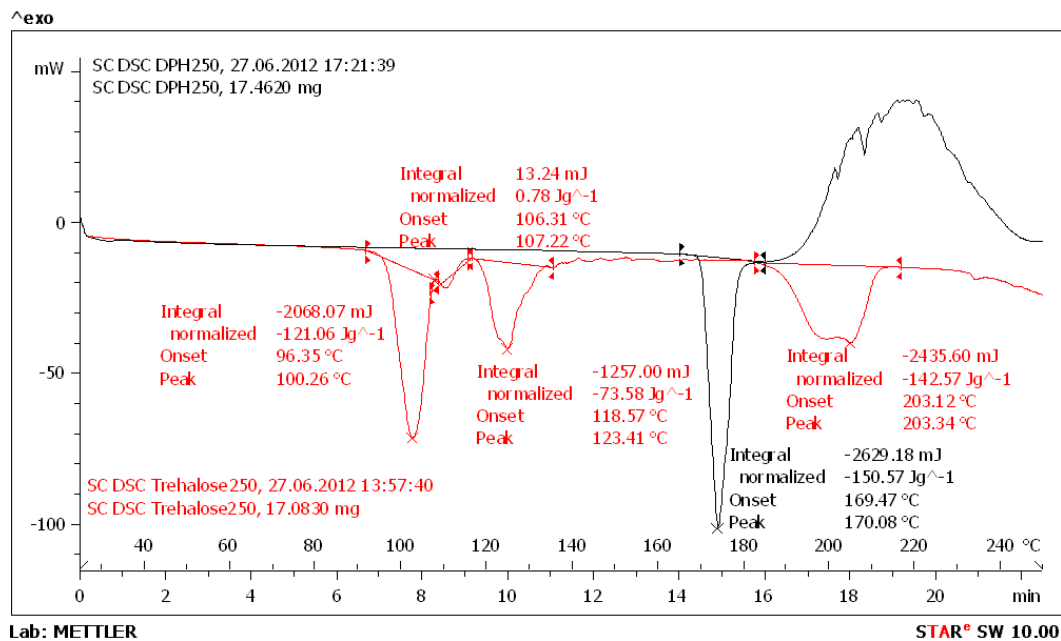


Figure 12.16 DSC Thermogram for Diphenhydramine HCl and Trehalose

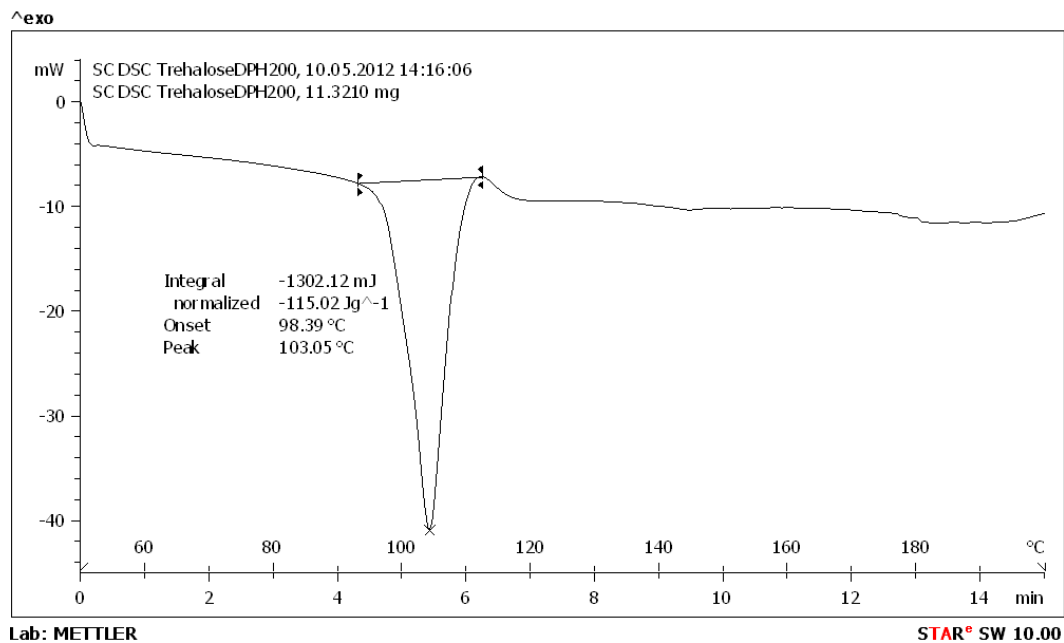


Figure 12.17 DSC Thermogram for the 1:1 Physical Mixture of Diphenhydramine HCl and Trehalose

Table 12.2 contains all the critical values from the integration of all the chemical peaks from the DSC analyses. Each blended 1:1 mixture lacks the

characteristic diphenhydramine HCl peak at 170°C or has a much lower heat of fusion. Due to the non-reducing nature of the sugars given in Table 12.2, the Maillard reaction is not a concern. Other reactions such as complex formation or diphenhydramine HCl becoming amorphous are possible explanations for the changes in DSC spectra of the blended mixtures.

Table 12.2 The Onset, Peak, and Heat of Fusion ( $\Delta H_F$ ) from DSC Thermal Analysis Critical Values for the Non-Reducing Sugars and Diphenhydramine HCl

	Onset, °C	Peak, °C	Heat of Fusion, J/g
Diphenhydramine HCl	169	170	148
Sucrose	75	86	105
	147	150	121
	210	220	66
Blend	174	180	9
	70	80	18
	121	129	120
Diphenhydramine HCl	169	170	150
Mannitol	167	169	380
Blend	126	131	95
	145	157	45
Diphenhydramine HCl	170	171	148
Isomalt	72	93	90
	151	162	114
Blend	69	86	44
	127	132	117
Diphenhydramine HCl	169	170	151
Trehalose	119	123	74
	96	100	121
	106	107	1
	203	204	142
Blend	98	103	115

Trehalose was selected for further analysis to determine if the reaction or complex formation with diphenhydramine HCl affected the available diphenhydramine HCl concentration.

### 12.3 FTIR Analysis of Trehalose and Diphenhydramine HCl

The FTIR spectra of diphenhydramine HCl in Figure 12.18 shows characteristic peaks of aromatic rings around  $3000\text{ cm}^{-1}$ . Additionally, the N-H bond is described by the absorbance at  $1640\text{-}1500\text{ cm}^{-1}$ . C-N is absorbed in the range of  $1360\text{-}1025\text{ cm}^{-1}$ .

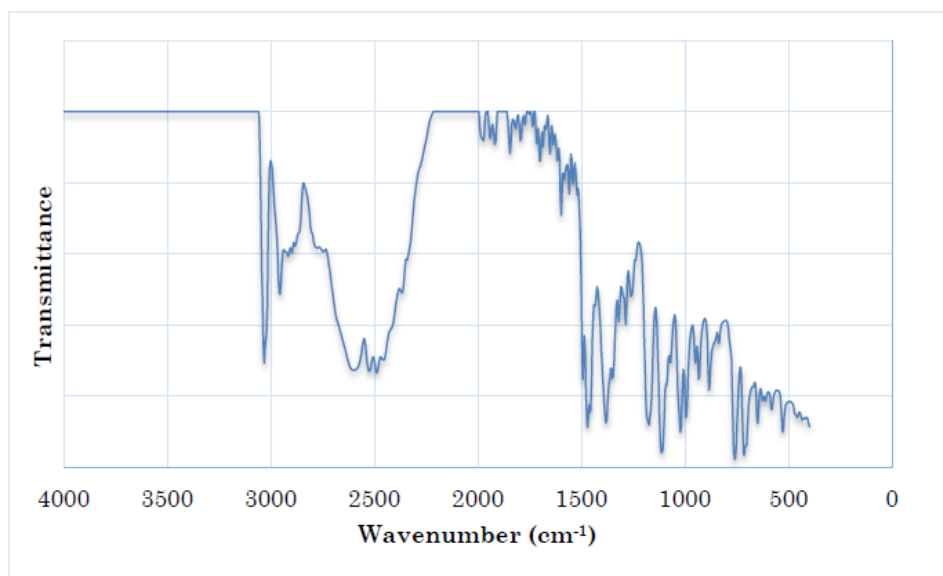


Figure 12.18 FTIR Spectra for Diphenhydramine HCl

The trehalose FTIR spectra in Figure 12.19 illustrates the numerous -OH bonds in a broad strong peak from  $3200\text{-}3500\text{ cm}^{-1}$ .  $\text{CH}_3\text{-CH}_3$  is absorbed at  $1200\text{ cm}^{-1}$  and the C-O bond is absorbed at  $1100\text{ cm}^{-1}$ .

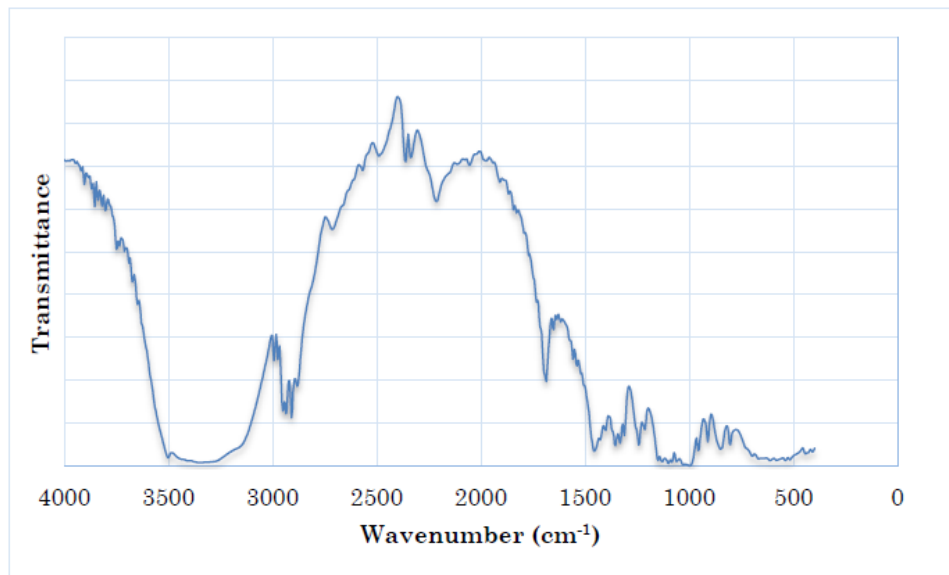


Figure 12.19 FTIR Spectra for Trehalose

The 1:1 physical mixture of diphenhydramine HCl and trehalose in Figure 12.20 illustrates many of the characteristic peaks for diphenhydramine HCl and trehalose individually. The spectra further suggests that diphenhydramine HCl became amorphous and did not undergo a chemical reaction that would affect its bioavailability.

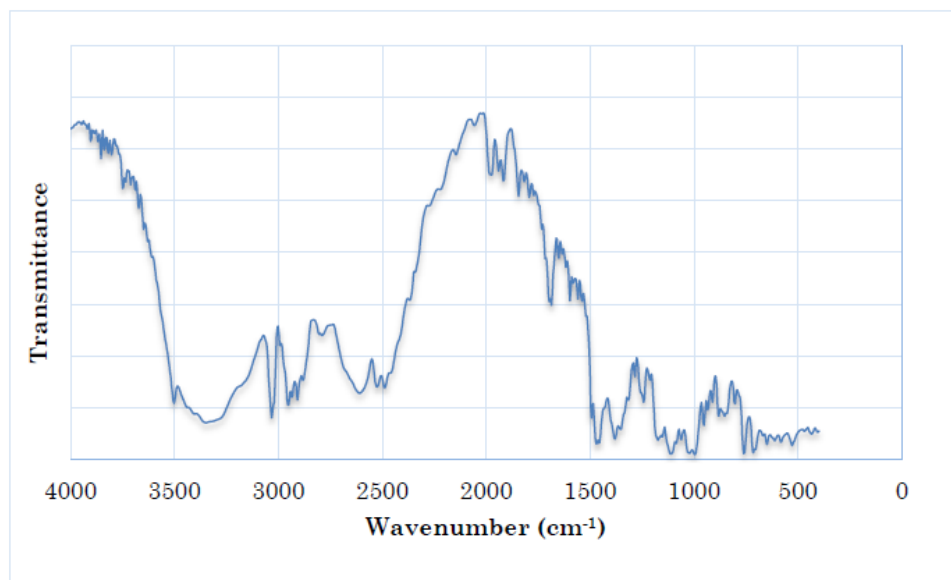


Figure 12.20 FTIR Spectra for the 1:1 Physical Mixture of Diphenhydramine HCl and Trehalose

All three graphs are overlaid in Figure 12.21 to illustrate the characteristic peaks from each analyte and compare them to the 1:1 physical mixture. The blended mixture spectra shows the absorbance of the specific diphenhydramine HCl bonds and supports the DSC results in Figure 12.17 for diphenhydramine HCl becoming amorphous.

Amorphous solids lack long-range order that is often associated with crystalline solids [3]. Solids of this nature are more readily absorbed and consequently are more bioavailable.



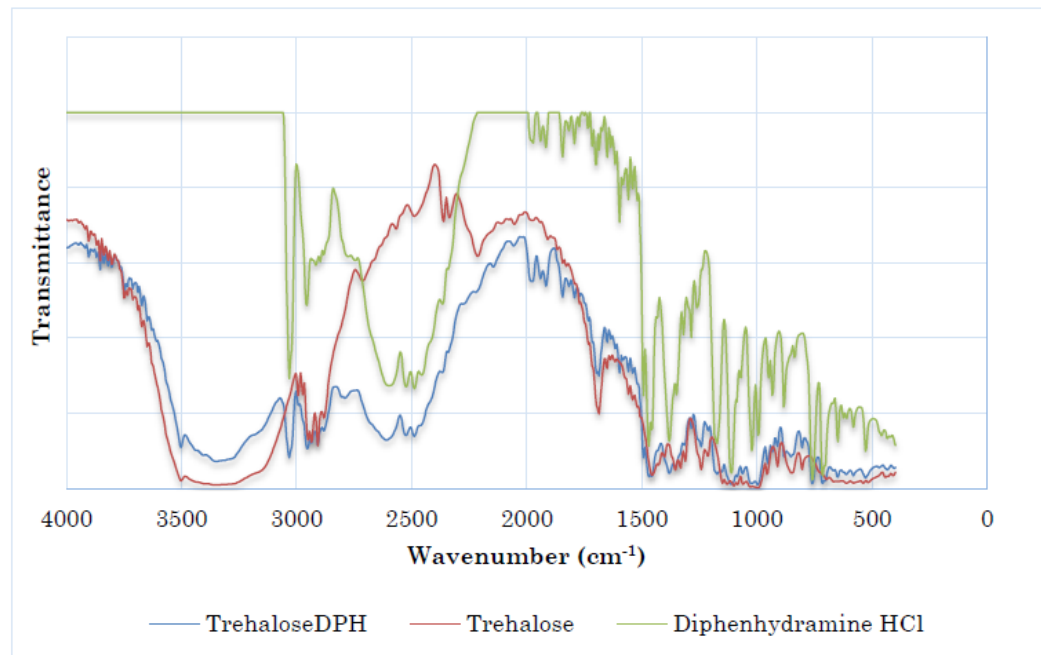


Figure 12.21 FTIR Overlay for the Trehalose, Diphenhydramine HCl, and the 1:1 Physical Mixture

#### 12.4 UV-Vis Analysis of Trehalose and Diphenhydramine HCl

The wavelength ( $\lambda_{\max}$ ) where diphenhydramine HCl has the highest absorption was determined by scanning the dissolved sample of pure diphenhydramine HCl in deionized water from 200 to 300 nanometers. The  $\lambda_{\max}$  for diphenhydramine HCl is 258 nm. Trehalose was evaluated at 258 nm and displayed no significant absorption. Polyplasdone XL®, talc, and magnesium stearate are all insoluble in deionized water and were filtered out before evaluation. None of the excipients registered a UV absorption at 258 nm. This wavelength will be used for the quantitative analysis of diphenhydramine HCl.

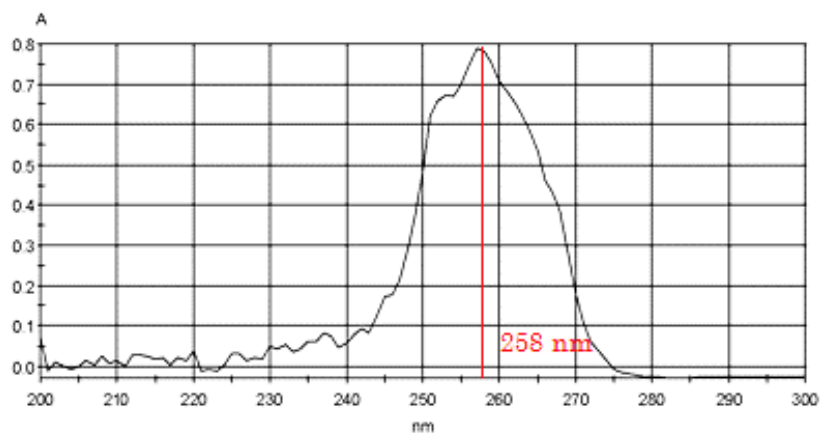


Figure 12.22 UV-Vis Spectral Scan for Diphenhydramine HCl

A 1:1 physical mixture of diphenhydramine HCl and trehalose was blended using a mortar and pestle. The mixture was dissolved in 100 mL of deionized water and analyzed at 258 nm. The absorbance of the mixture was 0.210 A. Using the calibration curve of diphenhydramine HCl in deionized water, the theoretical concentration of diphenhydramine HCl is 0.0005217 M. The percent error of diphenhydramine HCl in the 1:1 mixture is 0.0687%. Therefore, no degradation of diphenhydramine HCl has occurred when physically mixed with trehalose in a mortar and pestle. Trehalose can be used as the primary excipient in the orally disintegrating tablets of diphenhydramine HCl because there is no negative reaction occurring between the two components.

Calibration curves for diphenhydramine HCl were prepared according to the Beer-Lambert Law using both deionized water and simulated gastric fluid without enzymes. Figure 12.23 illustrates the linear relationship that was found and used to quantify diphenhydramine HCl in deionized water,

while Figure 12.24 illustrates the calibration curve which will be used for the simulated gastric fluid without enzymes.

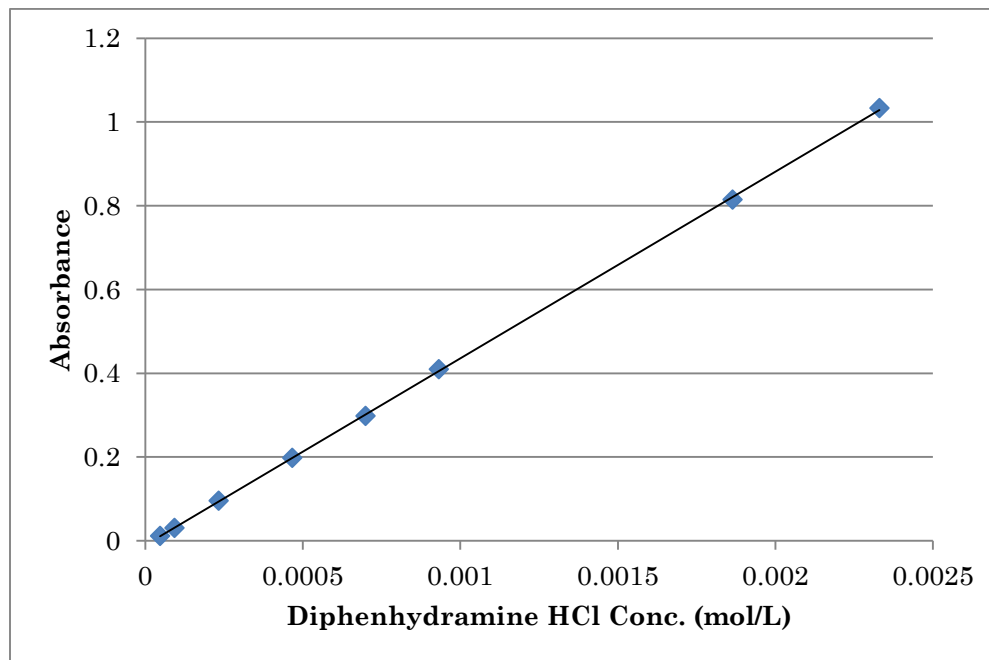


Figure 12.23 Diphenhydramine HCl UV Calibration Curve in Deionized Water at 258 nm where slope = 445.61; intercept = -0.0096; and  $R^2 = 0.9999$

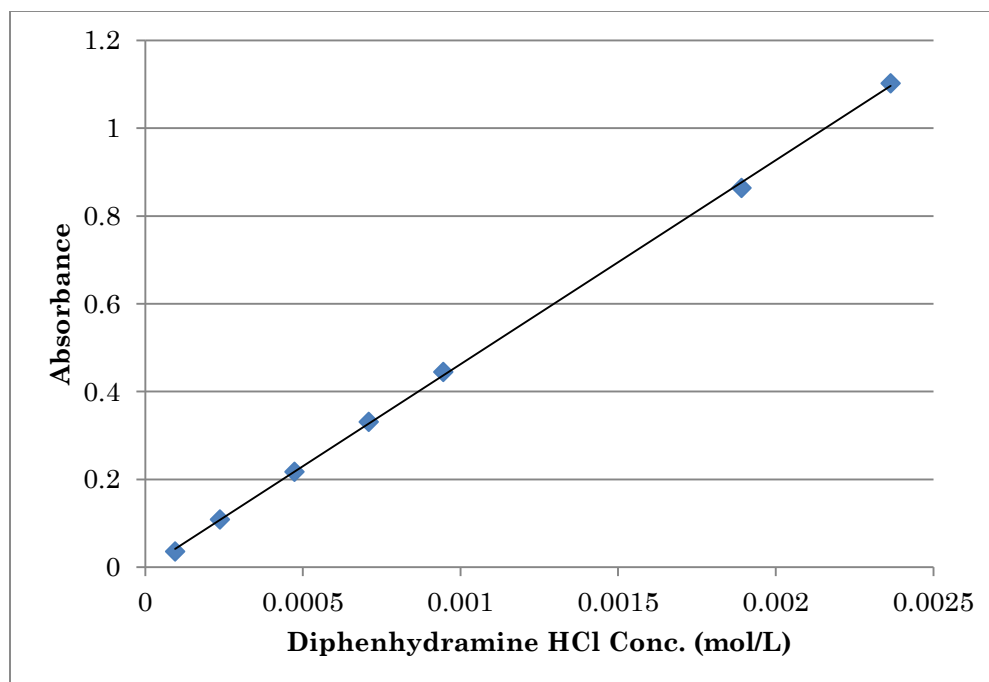


Figure 12.24 Diphenhydramine HCl UV Calibration Curve in Simulated Gastric Fluid without Enzymes at 258 nm where slope = 464.47; intercept = -0.0021; and  $R^2 = 0.9997$

### 12.5 Superdisintegrant Tablet Testing

Tablets prepared according to Sections 11.2.5 Preparation of Superdisintegrant Powder Mixtures and 11.2.6 Superdisintegrant Tableting and were analyzed for weight variation; friability; thickness; hardness; disintegration time and wetting time [4]. Table 12.3 includes the average weight of ten tablets, the average hardness of six tablets, and the average thickness of six tablets.

Table 12.3 Superdisintegrant Tablet Weights, Hardness, and Thickness for the Various Percentages Used

<b>Kollidon CL-SF®</b>			
	Weight Variation, g	Hardness, N	Thickness, mm
3%	0.0986 ± 0.0018	18.2 ± 2.8	3.46 ± 0.01
4%	0.1010 ± 0.0028	23.8 ± 1.9	3.58 ± 0.01
5%	0.1025 ± 0.0016	17.3 ± 3.1	3.59 ± 0.02
6%	0.1012 ± 0.0022	16.0 ± 2.8	3.61 ± 0.01
<b>Ac-Di-Sol®</b>			
	Weight Variation, g	Hardness, N	Thickness, mm
2%	0.1035 ± 0.0020	22.3 ± 1.8	3.51 ± 0.01
3%	0.1129 ± 0.0011	21.2 ± 1.9	3.77 ± 0.01
4%	0.1119 ± 0.0010	22.5 ± 4.2	3.77 ± 0.01
5%	0.1117 ± 0.0017	20.2 ± 3.1	3.78 ± 0.01
<b>Polyplasdone XL®</b>			
	Weight Variation, g	Hardness, N	Thickness, mm
2%	0.1021 ± 0.0009	19.7 ± 2.6	3.53 ± 0.02
3%	0.0995 ± 0.0010	20.5 ± 1.8	3.46 ± 0.01
4%	0.0986 ± 0.0013	20.2 ± 1.9	3.41 ± 0.01
5%	0.0951 ± 0.0010	18.3 ± 2.0	3.40 ± 0.01
<b>Primojel®</b>			
	Weight Variation, g	Hardness, N	Thickness, mm
2%	0.1476 ± 0.0014	26.3 ± 5.4	2.29 ± 0.04
3%	0.1504 ± 0.0050	28.7 ± 2.9	2.28 ± 0.06
4%	0.1486 ± 0.0028	24.8 ± 2.2	2.27 ± 0.05
5%	0.1492 ± 0.0037	21.3 ± 8.2	2.25 ± 0.09
6%	0.1506 ± 0.0054	24.0 ± 6.2	2.36 ± 0.05
7%	0.1532 ± 0.0076	24.7 ± 5.8	2.36 ± 0.06

The disintegration times for the four different types of superdisintegrants are illustrated in Figure 12.25 [5]. Primojel® has significantly longer disintegration times than Kollidon CL-SF®, Ac-Di-Sol®,

Polyplasdone XL®. 5% Polyplasdone XL® has the shortest average disintegration time of 5.83 seconds.

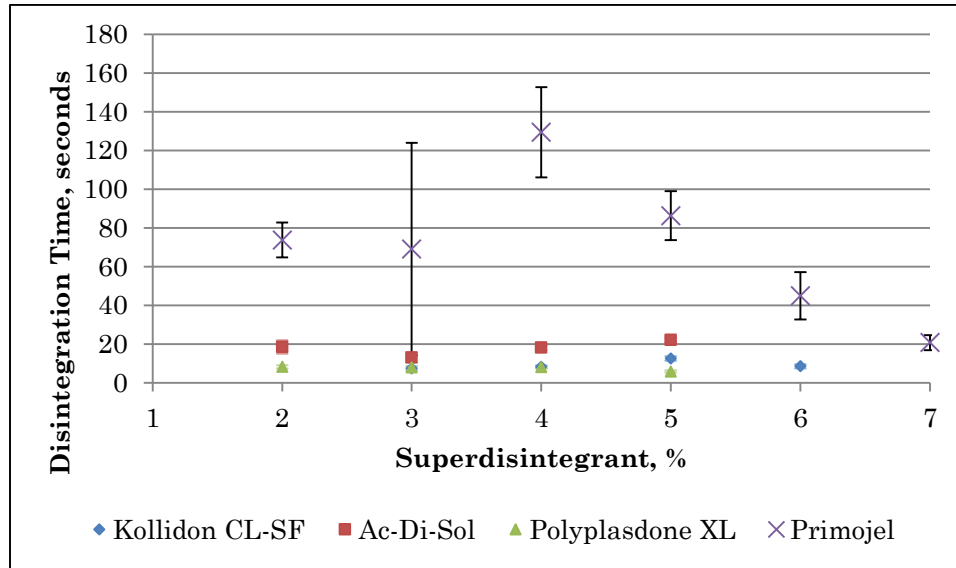


Figure 12.25 Disintegration Time and Variance for the Superdisintegrant Tablets containing (♦) Kollidon CL-SF; (■) Ac-Di-Sol; (▲) Polyplasdone XL; and (X) Primojel

The wetting times for superdisintegrant tablet selection are shown in Figure 12.26. Primojel® and Ac-Di-Sol® have longer wetting times than Kollidon CL-SF® and Polyplasdone XL®. The 5% Polyplasdone XL® has the shortest average wetting time of 31.1 seconds.

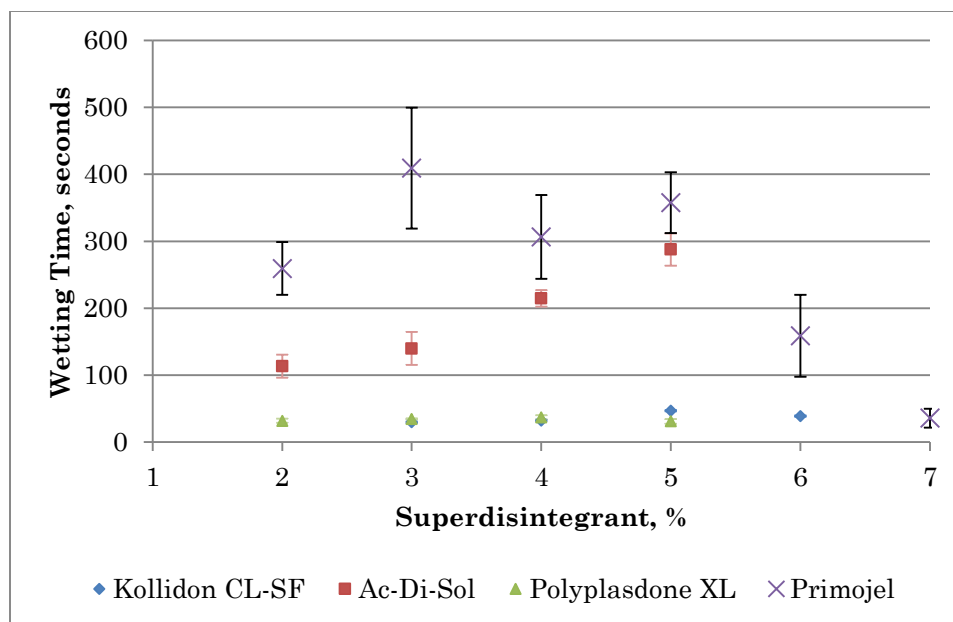


Figure 12.26 Wetting Time and Variance for the Superdisintegrant Tablets containing (♦) Kollidon CL-SF; (■) Ac-Di-Sol; (▲) Polyplasdone XL; and (X) Primojel

Disintegration in the oral cavity would likely require more time than the disintegration test described in Section 11.2.7 Superdisintegrant Tablet Testing and less time than the wetting test. The disintegration test incorporates agitation in a large volume of water while the wetting test more closely resembles the oral cavity but lacks the closed environment and agitation the tongue would contribute. Both parameters illustrate specific qualities of the orally disintegrating tablet that allow it to uptake water and disintegrate in the presence of aqueous fluid.

Primojel® failed the friability test for all concentrations analyzed by resulting in tablet capping and breakage. All concentrations of Kollidon CL-SF®, Ac-Di-Sol®, Polyplasdone XL® passed the friability test with less than

1% weight loss [6]. These superdisintegrants also possess binding properties that are essential to forming a rigid tablet that can withstand the rigors of manufacturing and shipping stress.

Polyplasdone XL<sup>®</sup> was selected as the ideal superdisintegrant because it out performed Primojel<sup>®</sup>, Kollidon CL-SF<sup>®</sup>, Ac-Di-Sol<sup>®</sup> in the disintegrating and wetting tests. The optimal concentration of Polyplasdone XL<sup>®</sup> is 5% in the 100 mg tablets.

## **12.6 Powder Properties for the Optimal Choice of Superdisintegrant and its Concentration**

The following powder mixture was analyzed for its flow properties:

5% Polyplasdone XL<sup>®</sup>  
91% Trehalose  
3% Talc  
1% Magnesium Stearate

Table 12.4 contains the angle of repose data for the optimal concentration of superdisintegrant, namely 5% Polyplasdone XL<sup>®</sup> [7]. The average angle of repose for this mixture is 32.56° and has good flow properties based on the USP 30 standard method [7].



Table 12.4 Results for five trials for 5% Polyplasdone XL®  
Angle of Repose

Height (cm)	Width (cm)	Angle (degree, °)	Flow
3.3	9.3	35.36	Good
2.9	8.9	33.24	Good
3.4	10.9	31.96	Good
3.0	9.8	31.48	Good
3.6	12.1	30.75	Excellent

The densities were calculated according to Equations 12.1 and 12.2. Compressibility index was calculated according to Equation 11.2. The average compressibility index was 17.450 and classified as fair flowing properties [7]. The Hausner ratio was calculated according to Equation 11.3. The average Hausner ratio was 1.211 and classified as fair flowing properties [7].

$$\rho_{tapped} = \frac{mass}{volume_{tapped}} \quad (\text{Equation 12.1})$$

$$\rho_{bulk} = \frac{mass}{volume_{bulk}} \quad (\text{Equation 12.2})$$

Table 12.5 Compressibility Index and Hausner Ratio for three trials for 5% Polyplasdone XL®

Trial	$\rho_{tapped}$ (g/mL)	$\rho_{bulk}$ (g/mL)	Compressibility Index $= 100 \times \left( \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \right)$	Flow	Hausner Ratio $= \left( \frac{\rho_{tapped}}{\rho_{bulk}} \right)$	Flow
1	0.9017	0.7469	17.164	Fair	1.207	Fair
2	0.9092	0.7408	18.519	Fair	1.227	Fair
3	0.9087	0.7572	16.667	Fair	1.200	Fair

The Flowratex® apparatus was used to determine the smallest orifice that allowed the 5% Polyplasdone XL® powder mixture to freely flow through

the opening. The 7 mm orifice was the smallest opening that allowed free flowing powder to pass through on three consecutive attempts.

### **12.7 Diphenhydramine HCl Tablet Testing**

Since the addition of diphenhydramine HCl in 100 mg tablets using 5% Polyplasdone XL<sup>®</sup> slowed the disintegration time and wetting time for the tablets by hindering the water uptake capacity, the concentration of the superdisintegrant had to be increased. Further studies were performed to optimize the superdisintegrant concentration used with diphenhydramine HCl.

Tablets prepared according to Sections 11.2.9 Preparation of Diphenhydramine HCl Powder Mixture with Polyplasdone XL<sup>®</sup> and 11.2.10 Diphenhydramine HCl Tableting were analyzed for weight variation; friability; thickness; hardness; disintegration time and wetting time [4]. Table 12.6 includes the average weight of ten tablets, the average hardness of six tablets, and the average thickness of six tablets.

Table 12.6 The Weight Variation, Hardness, and Thickness for Diphenhydramine HCl Tablets Containing Polyplasdone XL®

<b>12.5 mg Diphenhydramine HCl Tablets with Polyplasdone XL®</b>			
	Weight Variation, g	Hardness, N	Thickness, mm
5%	0.1017 ± 0.0018	24.8 ± 3.7	3.56 ± 0.04
6%	0.0983 ± 0.0018	20.0 ± 2.1	3.53 ± 0.02
7%	0.1052 ± 0.0011	19.7 ± 1.8	3.74 ± 0.01
8%	0.1016 ± 0.0016	22.2 ± 2.3	3.67 ± 0.03
9%	0.1021 ± 0.0014	17.7 ± 1.2	3.69 ± 0.01
10%	0.1024 ± 0.0012	16.2 ± 1.6	3.71 ± 0.01
11%	0.1013 ± 0.0021	21.3 ± 4.0	3.67 ± 0.04
12%	0.1025 ± 0.0011	22.8 ± 2.8	3.64 ± 0.02

The disintegration times for each concentration of Polyplasdone XL® in diphenhydramine HCl tablets are illustrated in Figure 12.27 [5]. The 10% Polyplasdone XL® has the shortest average disintegration time of 10.3 seconds.

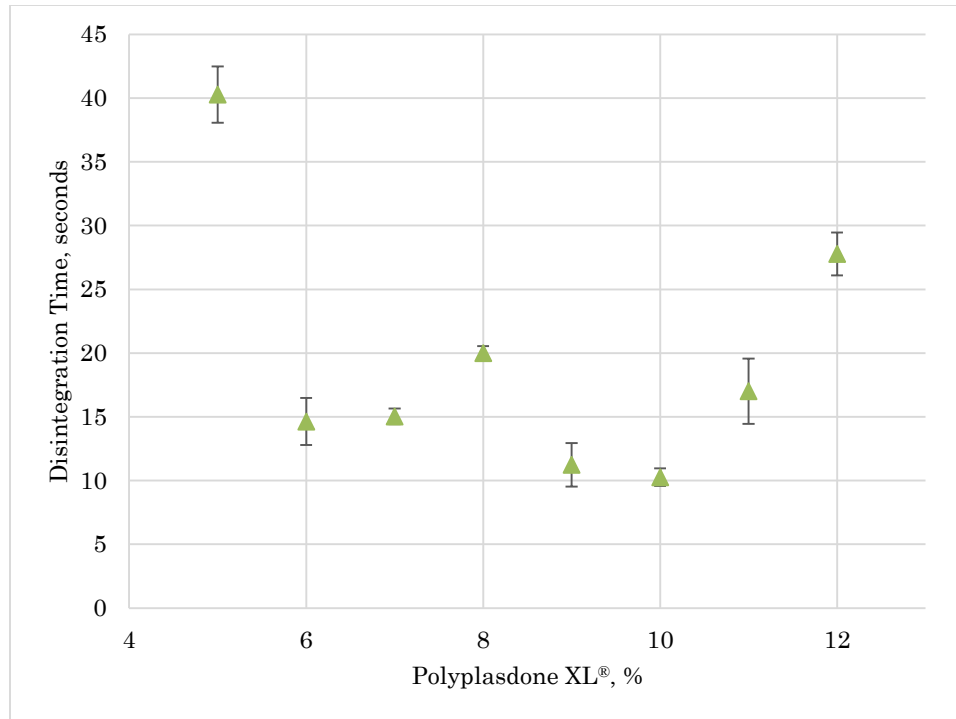


Figure 12.27 Disintegration Time and Variation for Tablets of 12.5 mg Diphenhydramine HCl with Polyplasdone XL<sup>®</sup>

The wetting times for diphenhydramine HCl tablets containing Polyplasdone XL<sup>®</sup> are shown in Figure 12.28. The 10% Polyplasdone XL<sup>®</sup> has the shortest average wetting time of 234.6 seconds in the presence of diphenhydramine HCl.

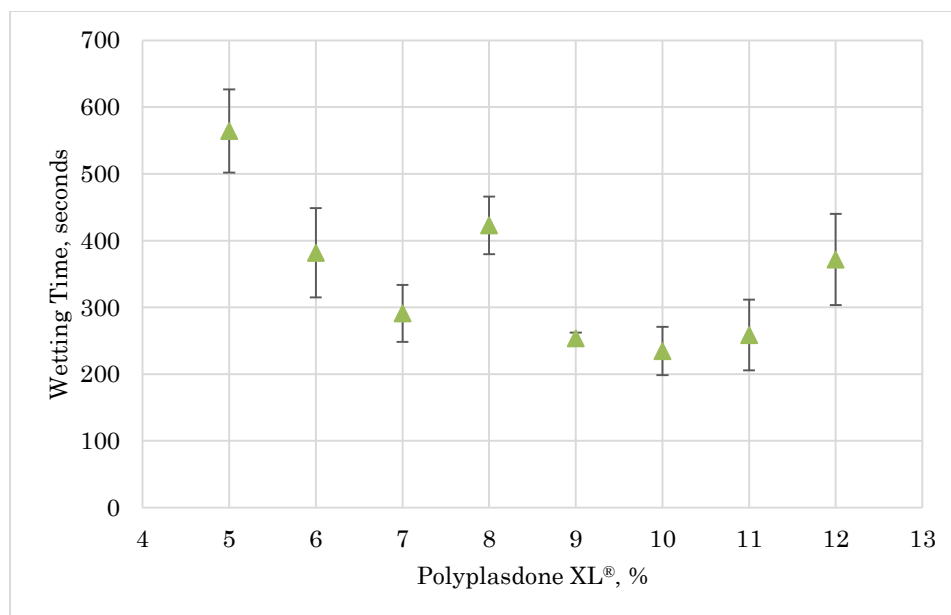


Figure 12.28 Wetting Time and Variation for Tablets of 12.5 mg Diphenhydramine HCl with Polyplasdone XL®

All concentrations greater than 5% Polyplasdone XL® with diphenhydramine HCl passed the friability test with less than 1% weight loss [6].

Larger concentrations of the ideal superdisintegrant were used to account for the change caused by the addition of diphenhydramine HCl to the blank formulation and optimized the disintegration and wetting time for the tablets while passing friability standards.

## 12.8 Powder Properties for the Optimal Polyplasdone XL<sup>®</sup> Concentration with Diphenhydramine HCl

The following powder mixture was analyzed for its flow properties:

10% Polyplasdone XL<sup>®</sup>  
73.5% Trehalose  
3% Talc  
1% Magnesium Stearate  
12.5% Diphenhydramine HCl

Table 12.7 contains the angle of repose data for the optimal concentration, namely 10% Polyplasdone XL<sup>®</sup> in the diphenhydramine HCl tablet mixture [7]. The average angle of repose for this mixture is 31.87° and has good flow properties based on the USP 30 standard method [7].

Table 12.7 Angle of Repose for five trials of powder containing 10% Polyplasdone XL<sup>®</sup> and Diphenhydramine HCl (12.5 mg/100 mg tablet)

Height (cm)	Width (cm)	Angle (degree, °)	Flow
3.7	11.2	33.45	Good
3.3	10.6	31.91	Good
3.5	11.0	32.47	Good
3.0	10.3	30.22	Excellent
3.1	10.2	31.29	Good

The densities were calculated according to Equations 12.1 and 12.2. Compressibility index was calculated according to Equation 11.2. The average compressibility index was 20.705 and classified as fair flow properties [7]. The

Hausner ratio was calculated according to Equation 11.3. The average Hausner ratio was 1.262 and classified as passable flowing properties [7].

Table 12.8 Compressibility Index and Hausner Ratio for three trials of the 10% Polyplasdone XL<sup>®</sup> and Diphenhydramine HCl Powder Mixture

<b>Trial</b>	$\rho_{tapped}$ (g/mL)	$\rho_{bulk}$ (g/mL)	<i>Compressibility Index</i> = 100 $\times \left( \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \right)$	<b>Flow</b>	<i>Hausner Ratio</i> = $\left( \frac{\rho_{tapped}}{\rho_{bulk}} \right)$	<b>Flow</b>
1	0.8265	0.6712	18.792	Fair	1.231	Fair
2	0.8547	0.6623	22.517	Passable	1.291	Passable
3	0.8475	0.6712	20.805	Passable	1.263	Passable

The Flowratex<sup>®</sup> apparatus was used to determine the smallest orifice that allowed the 10% Polyplasdone XL<sup>®</sup> powder mixture containing diphenhydramine HCl to freely flow through the opening. The 12 mm orifice was the smallest opening that allowed free flowing powder to pass through on three consecutive attempts.

### 12.9 Stability Testing

The final formulation containing 10% Polyplasdone XL<sup>®</sup> and 12.5 mg of diphenhydramine HCl per tablet was analyzed for weight variation; friability; thickness; hardness; disintegration time; wetting time and dissolution of the active ingredient. Table 12.9 contains the average data of ten tablets for each parameter.

Table 12.9 Tablet Parameters for the Final ODT Diphenhydramine HCl Formulation

Weight Variation, g	$0.0995 \pm 0.0012$
Friability	Pass
Thickness, mm	$3.57 \pm 0.02$
Hardness, N	$18.1 \pm 3.9$
Disintegration Time, s	$20.1 \pm 4.4$
Wetting Time, s	$242.3 \pm 30.3$

Dissolution of the tablets at time-zero was assessed in both deionized water dissolution medium and simulated gastric fluid without enzymes [8]. Both sets of dissolution data provided the same release profile. Deionized water dissolution medium was selected for subsequent studies because USP 30 recommends deionized water as the dissolution medium for diphenhydramine HCl tablets and capsules (since there is no protocol in place for diphenhydramine HCl orally disintegrating tablets). Furthermore, the log P value for diphenhydramine HCl is greater than 1 and diffuses into the epithelium of the upper gastrointestinal tract or the oral cavity where water is the primary dissolution medium [9, 10].

Accelerated stability studies using extreme environmental conditions were implemented to determine how the orally disintegrating tablets would perform over time. The percent diphenhydramine HCl dissolved was calculated by adjusting the volume after each sample until the tablets disintegrated completely (12 min).\* Additionally, the filter paper used to



remove solid particulates affected the UV-Vis absorption and was corrected in the percent dissolved evaluation.\*

The dissolution of the tablets kept under refrigerated conditions (3°C) is illustrated in Figure 12.29. The dissolution profile was consistent over the nine week testing period and suggests the final formulation of 12.5 mg diphenhydramine HCl orally disintegrating tablets are viable in similar conditions for at least nine weeks.

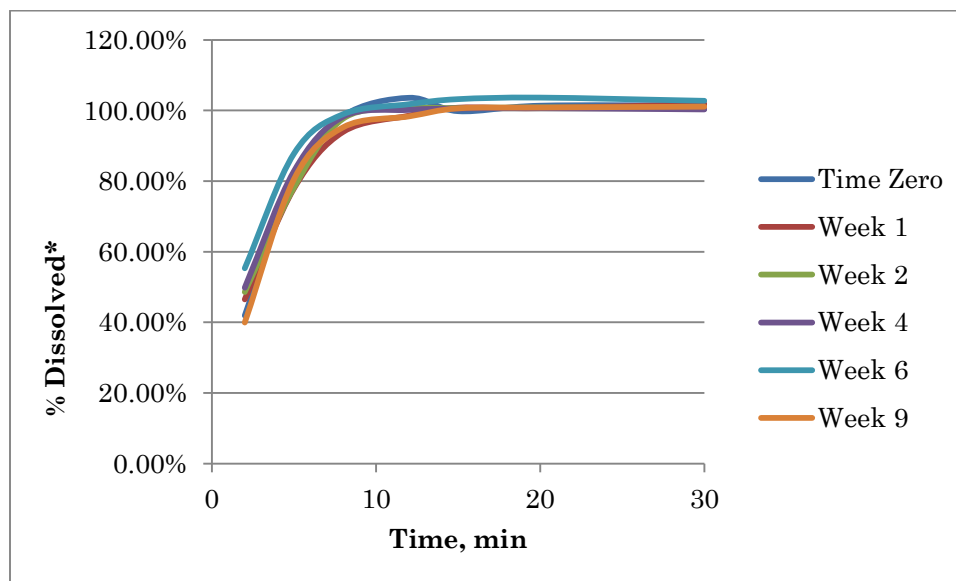


Figure 12.29 Dissolution Testing for the Refrigerated (3°C) 12.5 mg Diphenhydramine HCl Tablets

The dissolution of tablets kept at room temperature (21°C) is illustrated in Figure 12.30. The dissolution profile showed slight variation over the nine week testing period but remained consistent in the final percent diphenhydramine HCl dissolved. Tablets of the final formulation kept in a comparable environment are suitable for up to and perhaps beyond nine weeks after manufacture.

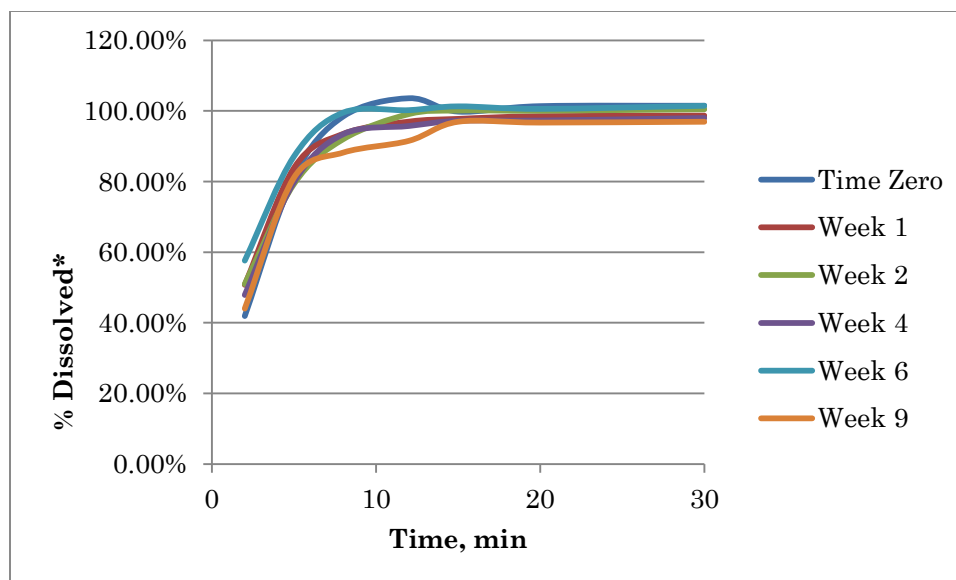


Figure 12.30 Dissolution Testing for the 12.5 mg Diphenhydramine HCl Tablets at Room Temperature (21°C)

Figure 12.31 displays the results for the dissolution testing for tablets stored at an elevated temperature (40°C) for nine weeks. The dissolution profile showed some variation over time, however the percent of diphenhydramine HCl dissolved remained within acceptable limits defined in USP 30 standards. This indicates that tablets stored under less thermal stress would be viable for a longer period of time.

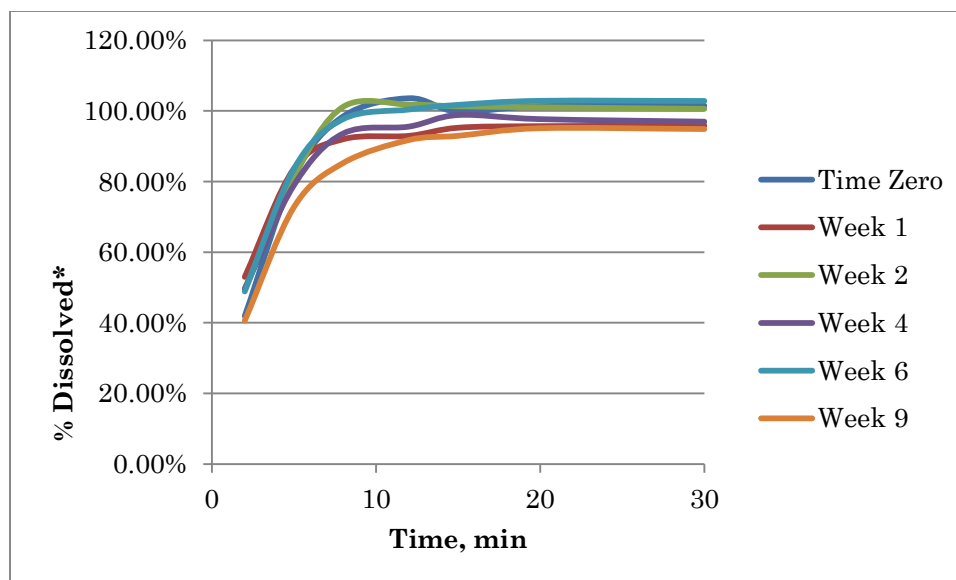


Figure 12.31 Dissolution Testing for the 12.5 mg Diphenhydramine HCl Tablets under Oven (40°C) Conditions

The final percent of diphenhydramine HCl dissolved for each dissolution test is represented in Figure 12.32. All parallels for each temperature condition remained within the specified limits outlined in USP 30. The percent of drug dissolved was between 90 and 110% for each determination.

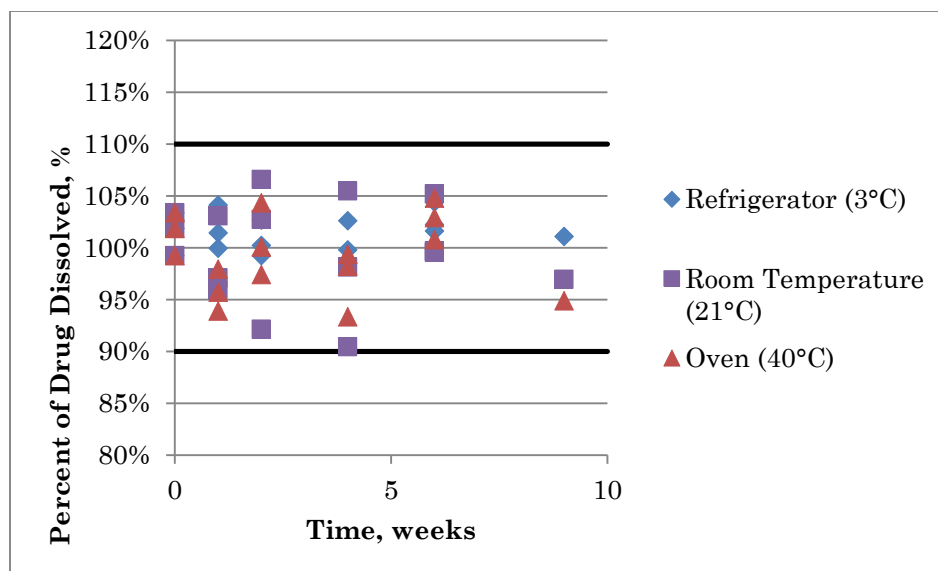


Figure 12.32 Combined Stability Testing Results for the 12.5 mg Diphenhydramine HCl ODT

### 12.10 Humidity Testing

Tablets were weighed prior to and after specific humidity conditions. The percent weight change of diphenhydramine HCl tablets is illustrated in Figure 12.33. Tablets stored in 16% and 33% relative humidity chambers maintained the same weight throughout the duration of the study with acceptable error of the electronic balance. Tablets kept at 75% relative humidity swelled over the eight week study and experienced around 2% weight gain throughout the stability testing period.

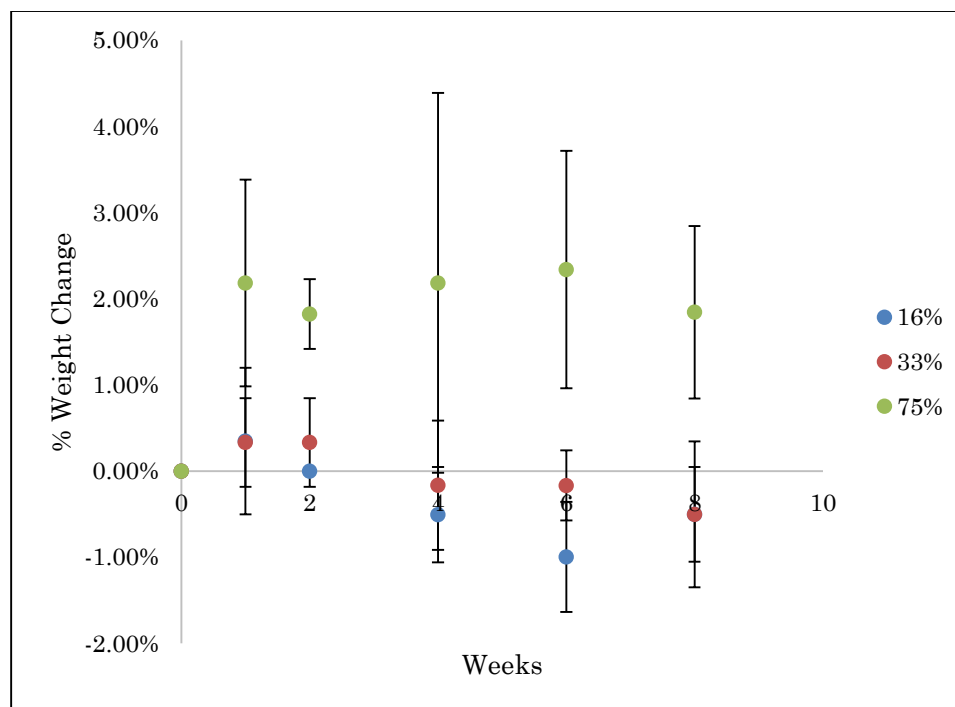


Figure 12.33 Percent Weight Change and Variance of the 12.5 mg Diphenhydramine HCl ODT during Humidity Stability Testing

The same tablets were evaluated for hardness and compared to the average hardness of the final formulation at time-zero in Figure 12.34. Tablets stored at 16% and 33% relative humidity experienced little change in hardness over the course of the study except for the Week 2 tablets kept at 33% relative humidity. This deviation suggests experimental error such as a non-sealed vessel. Tablets stored in 75% relative humidity had zero Newton hardness and fell apart with minimal effort. As a result, the orally disintegrating tablets of Diphenhydramine HCl are not stable under elevated humidity conditions and easily uptake water from the environment to swell and diminish their structural integrity. The tablets are stable and capable of being stored at or below 33% relative humidity.

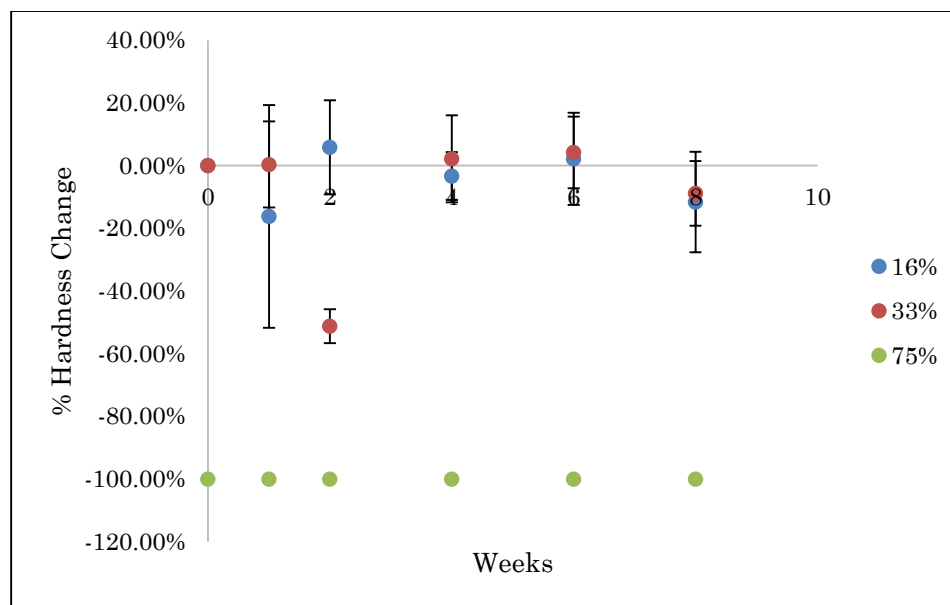


Figure 12.34 Percent Hardness Change and Variance in Humidity Stability Testing for 12.5 mg Diphenhydramine HCl ODT

### 12.11 Physical and Mechanical Testing of Currently Available Diphenhydramine HCl Orally Dissolving Tablets

Commercially available orally disintegrating tablets of diphenhydramine HCl were tested for weight variation; thickness; hardness; disintegration time and wetting time. Table 12.10 contains the average data for six tablets giving their weight variation, hardness, and thickness. The average disintegration time and wetting time were calculated using three tablets. The wetting test was stopped if complete saturation did not occur within 20 minutes. The tablets available over the counter each contained 12.5 mg of diphenhydramine HCl as with our final formulation; however, the total tablet weight was around 580 mg as opposed to the 100 mg tablets manufactured for our study. The three commercial products required

significantly more time to disintegrate completely and did not achieve complete wetting using our testing parameters. Therefore, the final formulation of 12.5 mg diphenhydramine HCl tablets containing 10% Polyplasdone XL® will disintegrate in the oral cavity more quickly than commercially available orally disintegrating tablets of diphenhydramine HCl.

Table 12.10 Source, Weight Variation, Hardness, Thickness, Disintegration Time, and Wetting Time for Commercially Available 12.5 mg Diphenhydramine HCl Orally Disintegrating Tablets

	Weight Variation, g	Hardness, N	Thickness, mm	Disintegration Time, s	Wetting Time, min
Target®	0.5827 ± 0.0052	57.7 ± 4.7	4.86 ± 0.02	236.8 ± 1.4	>20min
Walmart®	0.5880 ± 0.0049	52.7 ± 4.8	4.89 ± 0.04	201.1 ± 17.4	>20min
Rite Aid®	0.5770 ± 0.0033	55.8 ± 8.0	4.96 ± 0.02	163.9 ± 12.2	>20min
Final Formulation	0.0995 ± 0.0012	18.1 ± 3.9	3.57 ± 0.02	20.1 ± 4.4	4.04 ± 0.51

### 12.12 Future Studies

Due to limited resources and legal restrictions, the orally disintegrating tablets of diphenhydramine HCl could not be evaluated for taste. The addition of flavoring agents, sweetener, and use of coated diphenhydramine HCl particles can be used to create a palatable tablet for pediatric use in future studies.

We have learned that the tablets remain viable when stored at 33% relative humidity or less when stored for eight weeks. The tablets can also be stored between 3 - 40°C for up to nine weeks. Additional batches of the final

formulation can be analyzed further to gain a better stability estimate for the shelf life of the product.



## Chapter Thirteen

### CONCLUSION

An orally disintegrating tablet of diphenhydramine HCl was successfully formulated for pediatric and geriatric use. Trehalose was selected as the diluent for 100 mg tablets containing 12.5 mg diphenhydramine HCl. The DSC and FTIR spectra suggest diphenhydramine HCl becomes amorphous when combined with trehalose. The amorphous API lacks rigidity, but can be absorbed readily and has increased bioavailability. Trehalose, talc, and magnesium stearate were used in addition to diphenhydramine HCl and the ideal superdisintegrant. Polyplasdone XL<sup>®</sup> outperformed the other superdisintegrants in nearly all the concentrations and all of the testing parameters. The ideal concentration was 5% Polyplasdone XL<sup>®</sup> for the orally disintegrating tablets before the API, diphenhydramine HCl was added. 10% Polyplasdone XL<sup>®</sup> was selected for the final formulation. The tablets remained stable and within the acceptable range of drug release (90%-110%) at the three temperatures analyzed. The final formulation of diphenhydramine HCl tablets was stable between 3-40°C and at 33% relative humidity or less for eight weeks.

Future research can be done to effectively taste mask the bitter diphenhydramine HCl particles and create a suitable orally disintegrating tablet for pediatric and geriatric use. Additional testing can also be done to further confirm the notion that diphenhydramine HCl becomes amorphous when combined with trehalose.

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## Chapter Six

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