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Disintegration of Tablets and Capsules Measured by Isothermal Thermal Mechanical Analysis and Macrophotography

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DISINTEGRATION OF TABLETS AND CAPSULES MEASURED BY ISOTHERMAL THERMAL MECHANICAL ANALYSIS AND MACROPHOTOGRAPHY

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DISINTEGRATION OF TABLETS AND CAPSULES MEASURED BY ISOTHERMAL THERMAL MECHANICAL ANALYSIS MACROPHOTGRAPHY AND U.V ANALYSIS

VISWESWARARAO BADIPATLA

ABSTRACT

The current United States Pharmacopoeia (USP) test for tablet and encapsulated drug disintegration does not specify the initial disintegration time and provides limited information on the disintegration process itself. An isothermal Thermal Mechanical Analysis (IsoTMA) method is presented to measure the rate and initial time of drug disintegration, that is, the mechanical collapse of the gelatin capsule or the solid tablet. This method monitors changes in the dimensions of the formulated drugs during their disintegration in a liquid. Dimensional changes can be followed as a function of time, temperature, applied stress and pH. Some of the drugs studied were Olanzapine®, Ritalin® Amoxicillin® and .Graphical representations of their dimensional changes over time were compared for tablets and capsules from 25ºC to 37°C and pH 3 to 7. An increase in temperature decreases the overall disintegration time and increases the rate of disintegration (mm/min). For Abilify®, pH had an appreciable effect on the rate of disintegration.

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ABBREVIATIONS

TMA**:** Thermal Mechanical Analysis

Iso TMA : Iso thermal Mechanical Analysis

API: Active Pharmacy Ingredient

ICTAC: International Congress on Thermal Analysis and Calorimetry

FDA: Federal Drug Association

NCDA: National Center for Drug Analysis

NSAID's: Non Steroidal Anti-inflammatory Drugs

BPH: Benign prostatic hyperplasia

SSR I: Selective Serotonin Reuptake Inhibitors

OCD: Obsessive-compulsive disorder

PTSD: Post- traumic stress disorder

GAD: Generalized anxiety disorder

PMDD: premenstrual dysphoric disorder

DBD: Disruptive behavior disorder

SAD: Social anxiety disorder

TCAD: tri cyclic anti depressants

OBJECTIVES

- Develop a New Iso TMA Tablet And Capsule Disintegration Protocol
- Determine Standard Derivation and % Relative error of IsoTMA of Tablets and Capsules
- Determine the effect of Temperature and P^H on drug disintegration rate in um/min or mm/min
- Use Iso TMA Results to Predict drug target organ(oral, stomach,intestine)
- Verify the Iso TMA results with macrophotography and UV

PROTOCOL

Drug Disintegration OF TABLETS AND CAPSULES BY ISO TMA

OVERVIEW:

This document is a over view of drug test procedures in a outlined form so as to include all pertinent steps in a data collection, analysis and interpretation.

SCOPE:

The innovation of using polymer analysis tool, thermal mechanical analysis, to evaluate drug disintegration has led to a higher level of understanding how the drug is solublized and deliverd. This protocol is to guide pharmaceutical scientist to acquire relevant data to enhance their knowledge iin an organized manner.

TERMINOLOGY:

1.Define all significant terms

2. Define all abbreviations

SUMMARY OF TEST METHODS:

1. Brief outline of each method
2. Brief statement of each test method.

SIGNIFICANCE IN USE:

1. Relevance in meaning of each test method
2. Practical use of each test method.

METHODS:

1. TMA
2. UV

PROCEDURE:

1. Describe the successive steps of the procedure for each technique

RESULTS:

1. List all equations
2. Specify the significant figures

REFERENCES:

1. References to publications supporting or providing information
2. Key words: identify words terms phrases

CONCLUSIONS:

1. Summarize all data collected
2. Compare the data from different methods
3. Site all relevant information.

CHAPTER I

INTRODUCTION

A recent paper by Qureshi[1] goes directly to the problem in the development and validation of drug dissolution (disintegration of oral solid dose tablets and capsules). It is pointed out that dissolution tests used as quality control testing (QC) can discover variations in product formulations which are not related directly to drug release in humans i.e. the state of bio-availability. Further observed deviations from expected drug delivery properties do not indicate below average drug release in humans. Quality control tests may also result in false negatives. What is needed is a test based on bio-relevancy. Qureshi recommends a USP Paddle Apparatus[2] to simulate physical activity of gastrointestinal tract physiology. An in vitro method must be product independent. His crescent-shaped paddle test achieved the objective of product independence while simplifying method development and testing[3].

An important feature of drug disintegration is to comprehend the effect of drug-excipient interaction. Drebushchak *et al* used thermo analytical methods TGA and DSC along with X-ray Diffraction analysis to evaluate the dehydration and decomposition of various drugs. It was observed that the crystal structure of cellulose after heating did not

change but Chitosan did contract changing its disintegration properties[4]. Solid dose technology was reviewed by Wesolowski[5] based on DSC and TGA characterization. They studied tablet disintegration and effect of grinding and observed that bioavailability varied. Cracks and altered appearances also caused disintegration variations. Mechanical preparation of drugs was used to vary dispersion properties of drugs with polyvinylpyrrolidone and polyethylene glycol as excipients. Higher apparent solubility and dissolution rates were measured by this innovative mechanical technique, i.e. applied stress caused the observed changes[6]. Gomes, Souza and Macedo studied the thermal and dissolution kinetics of Ampicillin drugs[7]. The dissolution profiles were obtained using USP 23 method. The results of the study showed a good correlation between the Kitazawa rate constant and the thermal decomposition reaction rate constants. This correlation can be used to confirm pharmaceutical equivalence between reference and test products.

There is an ongoing need to develop a better understanding of how solid dose tablets initially disintegrate and proceed to the final state of disintegration in an aqueous medium of known pH. Our new innovative Isothermal Thermal Mechanical Analysis (IsoTMA) method established the relevancy and range of drug dissolution by in vitro examination of Olanzapine®, an "orally disintegrating drug" which disintegrates in 18 seconds at a dimensional rate change of approximately 6 millimeters/min. Conversely Abilify® has an IsoTMA disintegration time of 60-70 minutes and a much slower rate measured in units of microns/min. Dr. Riga and Alexander introduced this IsoTMA method internationally at the International Congress on Thermal Analysis and Calorimetry (ICTAC) Conference

in Denmark[8]. They reported a real world disintegration evaluation that correlated well (R^2=0.92) with the Iso TMA method (Figure 1).

Williams, Alexander and Riga examined a wide variety of rapidly disintegrating tablets by IsoTMA[9-10]. They observed a good correlation between the United States Pharmacopeia (USP) dissolution method[11] and the IsoTMA technique with consistent results for enteric coated tablets. However the USP method[12] only deals with the final disintegration of the tablet while this IsoTMA method reveals the initial time and rate of disintegration. One assumes the dimensional stability, as monitored by IsoTMA, can be correlated to solid dose tablet disintegration in the throat, stomach or intestines. To-date, we are confident that there is a good relationship with this new analytical tool and drug delivery since, in a number of cases, the drug uptake at pH=1 was correlated with IsoTMA and ultraviolet spectroscopy.

The objectives of this study are to evaluate formulated tablet drugs by their disintegration times (min) and dimensional stability rates (millimeters/min = mm/min or microns/min = μm/min). These dimensional stability rates are considered to represent the disintegration rates of the formulated tablets. Initially, we had hoped to observe disintegration mechanisms that might involve swelling in an aqueous fluid ultimately followed by disintegration in one or more steps. Variables in this study were different drug/excipients combinations, different pH and temperature.

Tablets disintegrate and release their active drug while structurally changing. Some tablets expand and thereby allow the active ingredient to be released. Other tablets swell and then disintegrate either rapidly or over a period of time. Measured disintegration times can statistically distinguish between drugs disintegrating in less than 1 minute, 5 to

10 minutes and those disintegrating in more than 30 minutes. The IsoTMA method can identify the drug delivery process as orally occurring over 15-30 seconds, gastrically over 2- 30 minutes and intestinally over 30-90 minutes. The percent relative error for IsoTMA measured disintegration times was approximately10-20% and is probably due primarily to non-uniformity of the tablet surface with its curvature and embossed letters.

The % relative error of the disintegration rate (mm/min) varied more widely than the disintegration time, with a value of 20-30%. Factors to improve the precision and accuracy of TMA (relative to the standard APA method) will be discussed.

TABLETS:

Tablets are solid dosage forms containing one or more active ingredients. They are obtained by single or multiple compression (in certain cases they are moulded) and may be uncoated or coated. They are usually intended for oral administration, but preparations for alternative applications, such as implants, solution-tablets for injections, irrigations, or for external use, vaginal tablets, etc., are also available. These preparations may require a special formulation method of manufacture. The different categories of tablet that exist include soluble tablets, effervescent tablets, tablets for use in the mouth, and modified-release tablets. Unless otherwise specified in the individual monograph, tablets are normally circular in shape, and their surfaces are flat or convex. Tablets may have lines or break-marks, symbols, or other markings. They should be sufficiently hard to withstand handling, including packaging, storage, and transportation, without crumbling or breaking.

Tablets may contain excipients such as diluents, binders, disintegrating agents, glidants, and lubricants, substances capable of modifying the behavior of the dosage forms and the active ingredient in the gastrointestinal tract, coloring matter, and flavoring substances. When such excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

CAPSULES:

Encapsulation refers to a range of techniques used to enclose medicines in a relatively stable shell known as a capsule, allowing them to, for example, be taken orally or be used as suppositories. The two main types of capsules are:

- Hard-shelled capsules, which are normally for dry, powdered ingredients or miniature pellets or tablets;
- Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Both of these classes of capsules are made from aqueous solutions of gelling agents like: Animal protein mainly gelatin; Plant polysaccharides or their derivatives like carrageenans and modified forms of starch and cellulose. Other ingredients can be added to the gelling agent solution like plasticizers such as glycerin and or sorbitol to decrease the capsules hardness, coloring agents, preservatives, disintegrants, lubricants and surface treatment.

DISINTEGRATION:

Disintegration is defined as that state in which no residue of the tablet or capsule remains on the screen of the apparatus or, if a residue remains, it consists of fragments of insoluble coating of the tablets or of capsule shells or is a soft mass with no palpable core. If discs have been used with capsules, any residue remaining on the lower surface of the discs consists only of fragments of shells.

DISSOLUTION:

Dissolution is a standardized method for measuring the rate of drug release from a dosage form. The principle function of the dissolution test may be summarized as follows:

• Optimization of therapeutic effectiveness during product development and stability assessment.

• Routine assessment of production quality to ensure uniformity between production lots.

• Assessment of 'bioequivalence', that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers.

• Prediction of 'in-vivo' availability, i.e. bioavailability

DISSOLUTION TESTING

In a recently published paper in Pharmaceutical Technology, Gene Knapp explains why FDA has become involved in dissolution testing[13] briefly; they feel that in vitro dissolution testing can help the development of formulations that may present potential bioequivalence problems. They further believe that once a formulation has been shown to be bioavailable, dissolution testing is of great value in assuring lot-to-lot bioequivalence.

Many dissolution apparatuses that have been proposed for in vitro testing of solid drug – dosage forms, FDA has chosen to concentrate on three apparatus: The USP rotating basket apparatus, [14] the USP paddle apparatus, [15] and the former two have achieved official recognition by the USP. The National Center for Drug Analysis (NCDA) has been conducting routine dissolution tests with some techniques evolving from the basket method and paddle method and gives good results. In vitro dissolution testing, as applied to solid-dosage drug forms measures the amount of drug dissolved in a known volume of

liquid medium at a predetermined time, using a specified apparatus designed to carefully control the parameters of dissolution testing. The amount of drug dissolved may be determined at one time

DEAERATION:

In our laboratory, deionized water is routinely used to prepare large batches of dissolution medium. Water emerges from the deionizer below room temperature and under pressure, and thus will be supersaturated with air. This medium is used in test under 37^{o}C. During this testing excess air will manifest itself as tiny bubbles and this affects the dissolution rate. Air may be partially removed by boiling and cooling the water, by spraying the water into a large vessel under vacuum. If a large quantity of medium is prepared before it is implemented, then it is best to test the medium and bring the temperature to 37^{o}C and then use the medium.

TEMPERATURE

Temperature of the dissolution medium in the vessels should be checked before the test is started. A dissolution apparatus is used with a constant temperature bath of 37^{o}C. If the temperature of the bath is less than 37^{o}C heat the medium until it attains the required temperature.

VOLUME:

The amount of drug dissolved during testing is determined from its concentration in the dissolution medium, therefore the total volume of dissolution present in the system at a time the sample is withdrawn must be known. Relatively large volumes, in the range of 500-1000 ml. are used in the dissolution test. Certain amounts of the samples are taken at given intervals. we have to be sure the total amount of the dissolution medium must be

constant before and after taking the samples so we have to put the same amount of dissolution medium in the bath after we take sample solution from the bath to test how much amount of the drug dissolved in the medium.

RATE OF AGITATION:

The rate of agitation and times of aliquoting will be specified in the dissolution test methodology. Ideally these parameters will have been selected on the basis of some correlation with in vivo data.

The rate of agitation, usually from 50 to 150 rpm, will govern how quickly a solid dosage form will disintegrate or dissolve in specified volume of dissolution medium. From the time the drug begins to dissolve until dissolution is complete, concentration gradients are present in the dissolution medium. These concentration gradients depend on the rate of agitation: as the rate of agitation increases the gradient becomes less pronounced.

STANDARD SOLUTION:

In the analysis, the filtrate will be compared to standard solution. It is difficult to know the amount of standard solution required to dissolve in the medium. Usually we take large amount of standard solution and dissolve in small amount of water-miscible solvent. An aliquot of this stock solution is diluted to final volume with the dissolution medium. The presence of a small amount of water-miscible solvent in the standard solution should have no effect on the analysis. To confirm this, several standard solutions of different strengths should be prepared each of the standard solutions should be diluted in the dissolution medium such that each final solution has the same amount of drug content.

STIRRING CONTROL:

Apparatus should be adjusted with a variable speed usually 100 rpm speed is preferred in the spindle apparatus method. Initially before we start the experiment the speed must be adjusted to 25 rpm after it attains the speed the speed must be increased to 50 and then to 100 rpm.

USP PADDLE METHOD

In this method usually the solid dosage forms that tend to float should be weighed and the metal paddle that is inert to medium. There should be minimal movement of solid dosage forms under the paddle until the disintegration occurs. Excessive movement of the solid dosage form gives higher dissolution results. The paddle methodology in USP specifies that, ideally the upper portion of the vessel must be cylindrical and bottom would be perfect hemisphere. There are two shafts available for this method, one is a coated stainless steel shaft and other is a glass shaft. Preferred is the stainless steel shaft.

In the USP method the paddle shaft will be centered within 0.2 cm of the center line of the vessel the shaft shall rotate without perceptible wobble, and the bottom of the paddle shall be 2.5cm from the lowest inner surface. Shaft rotation is maintained within the nominal value. Temperature is maintained at $37^{o}C$.

LABORATORY PROCEDURE FOR THE PADDLE METHOD:

Before starting the test, turn the motor and, place the dissolution medium into the vessel and measure the temperature. If the temperature is below 37^{o}C then raise the temperature of the medium to 37^{o}C and the speed of the motor must be 100 rpm. Drop the tablet or capsule into the vessel, one at point near the wall of the vessel. After the specific periods of time withdraw a sample using a glass syringe and membrane filter device for subsequent filtration usually the membrane filter device is attached to a syringe and aliquot are collected. The aliquots are collected at specific time intervals as 1, 5, 10, 15, 20, 25, and 30 min until the whole dosage form is dissolved in the medium the resulted aliquots are tested.

Some of the tablets that are orally disintegrating tablets, for these dosage forms the aliquots are collected at initial start of the experiment, middle and at the end of the experiment eg: Zyprexa tablet dissolves in 18-20 sec so we have take the aliquots at 1, 10, and 20 sec.

Dissolution tests are critical and difficult to carry out properly. If one is to obtain correct results, care and attention must be given to those aspects that have identified as crucial.

THERMAL MECHANICAL ANALYSIS (TMA)

Thermal Mechanical Analysis (TMA) is one of a group of techniques of Thermal Analysis (TA). The terminology of thermal analysis is recommended by the International Confederation of Thermal Analysis and Calorimetry (ICTAC). Terminologies have been redefined to provide consistency amongst the numerous thermal analysis techniques[16]. In particular TMA has been classified as a method of the Thermomechanometry (TM) technique.

Thermomechanometry is the measurement of a change of a dimension or a mechanical property of the sample while it is subjected to a temperature regime. An associated thermo analytical method is thermo mechanical analysis. A special related technique is thermodilatometry (TD), the measurement of a change of a dimension of the sample with negligible force acting on the sample while it is subjected to a temperature regime. The associated thermo analytical method is thermodilatometry analysis (TDA). TDA is often referred to as zero force TMA. The temperature regime may be heating, cooling at a rate of temperature change that can include stepwise temperature changes, linear rate of change, temperature modulation with a set frequency and amplitude, free (uncontrolled) heating or cooling, or maintaining a constant increase in temperature. The sequence of temperatures with respect to time may be predetermined (temperature programmed) or sample controlled (controlled by a feedback signal from the sample response). Thermomechanometry includes several variations according to the force and the way the force is applied. Static force TM (sf-TM) is, when the applied force is constant; previously called TMA with TD as the special case of zero force. Dynamic force TM (df-TM) is, when the force is changed as for the case of a typical stress–strain analysis;

previously called TMA with the term dynamic meaning any alteration of the variable with time, and not to be confused with dynamic mechanical analysis (DMA). Modulated force TM (mf-TM) is when the force is changed with a frequency and amplitude; previously called DMA. The term modulated is a special variant of dynamic, used to be consistent with modulated temperature differential scanning calorimetry (mt-DSC) and other situations when a variable is imposed in a cyclic manner[17]. The paper by Seyler and Earnest gives information about development and testing of a method for TMA temperature calibration. They report on the experimental results of round robin that included seven labs. Although interlaboratory results vary by several degree, the bias (accuracy) in these measurements was less than $0.1^{o}C$ when corrections for temperature linearity in each measurements was included in analysis.

MATERIAL PROPERTIES AND THERMOMECHANICAL MEASUREMENTS:

TMA and TDA are typically used in assigning temperature or determining the coefficient of linear thermal expansion by linear thermal expansion dialometry. The techniques associated with TMA are broadly applicable in material science and are used in characterizing liquids polymers and inorganic materials. Van krevelen's[18] classification of material properties describe the many applications of many thermo mechanical methods. Table provides comprehensive overview of various applications of thermomechanical methods. Some of the materials studied such as polymers and plasticizers are briefly explained in their corresponding plots with different parameters.

TMA Comprises a valuable set of techniques for characterizing a variety of bulk and molecular properties in virtually any material. While Thermomechanical analyzers are most often used in penetration or expansion modes, many instruments can be modified to

execute a variety of far more sophisticated experiments. Three of these techniques have been adopted by ASTM [19, 20-22] while quite sensitive for some applications, Thermomechanical methods [23] appear best suited to a complimentary role in research. They are used in analyzing the materials and data and great care must be taken in applying the TMA techniques. However, TMA serves as testimony to its versatility and utility for characterizing materials from the laboratory to production.

ULTRAVIOLET SPECTROPHOTOMETRY (UV)

Ultraviolet-visible spectroscopy or ultraviolet-visible spectrophotometry (UV-Vis or UV/Vis) refers to absorption spectroscopy in the ultraviolet-visible spectral region. This means it uses light in the visible and adjacent (near-UV and near-infrared (NIR)) ranges. The absorption in the visible range directly affects the perceived color of chemicals involved. In this region of the electromagnetic spectrum, molecules undergo electronic transitions. This technique is complementary to fluorescence spectroscopy, in that fluorescence deals with transitions from the excited state to the ground state, while absorption measures transitions from the ground state to the excited state.[24]

BEER- LAMBERT LAW:

The method is most often used in a quantitative way to determine concentrations of an absorbing species in solution, using the Beer-Lambert law:

$$A = -\log_{10}(I/I_0) = \epsilon \cdot c \cdot L,$$

Where A is the measured absorbance, I_0 is the intensity of the incident light at a given wavelength, I is the transmitted intensity, L the path length through the sample, and c the concentration of the absorbing species. For each species and wavelength, ε is a constant known as the molar absorptivity or extinction coefficient. This constant is a fundamental molecular property in a given solvent, at a particular temperature and pressure, and has units of 1 / *M* * *cm* or often *AU* / *M* * *cm*.

The absorbance and extinction ε are sometimes defined in terms of the natural logarithm instead of the base-10 logarithm.

The Beer-Lambert Law is useful for characterizing many compounds but does not hold as a universal relationship for the concentration and absorption of all substances. A 2nd order polynomial relationship between absorption and concentration is sometimes encountered for very large, complex molecules such as organic dyes (Xylenol Orange or Neutral Red, for example).

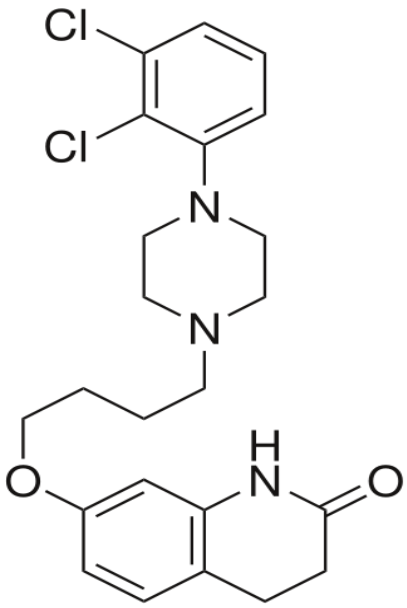
APPLICATIONS:

- UV/VIS spectroscopy is used in the quantitative determination of solutions of transition metal ions and highly conjugated apparatus
- It is used to know the concentration of the sample at desired wave length
- UV can also be used as detector for HPLC
- UV is used to determine the type of the bonds present in the molecule at particular absorption which are valuable in determining functional group in a compound.

DRUGS STUDIED BY TMA:

ABILIFY:

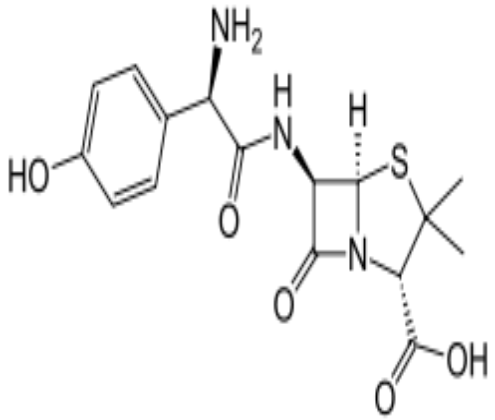
Scientific name of Abilify is (Aripiprazole) which is an Anti Psychotic drug and antidepressant used in the treatment of schizophrenia, bipolar disorder and clinical depression; it is mostly used for acute manic and mixed disorder associated with bipolar disorder in adults [25]. The IUPAC name of Aripiprazole is 7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1*H*)-one.



The Chemical Formula of Abilify is $C_{17}H_{27}Cl_2N_3O_2$ which has molecular mass of 448.35 and has Bio-availability of 87%. Abilify is soluble in water and sulphuric acid

AMOXICILLIN:

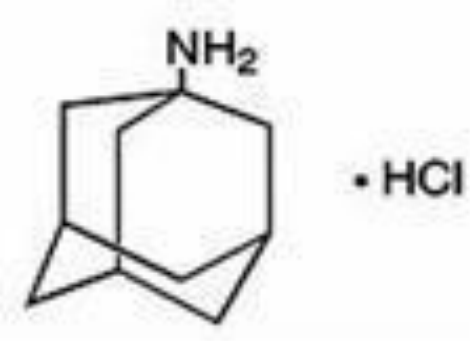
Amoxicillin is a moderate - spectrum, bacteriolytic, β-lactum antibiotic used to treat bacterial infections caused by susceptible microorganisms. It is the drug of choice because it is well absorbed. Amoxicillin in trihydrate form is available in capsule form and tablet, suspension for oral use and sodium salt for intravenous administration. It is one of the most common antibiotics prescribed for children



The IUPAC name of amoxicillin is (2*S*,5*R*,6*R*)- 6-{[(2*R*)-2-amino- 2-(4-hydroxyphenyl)-acetyl]amino}- 3,3-dimethyl- 7-oxo- 4-thia- 1-azabicyclo[3.2.0] heptane- 2-carboxylic acid. The chemical name of Amoxicillin is $C_{16}H_{19}N_3O_5S$ which has a molecular weight of 365.4gm/mol has a bio-availability of 95% which is readily soluble in mouth.

AMANTADINE

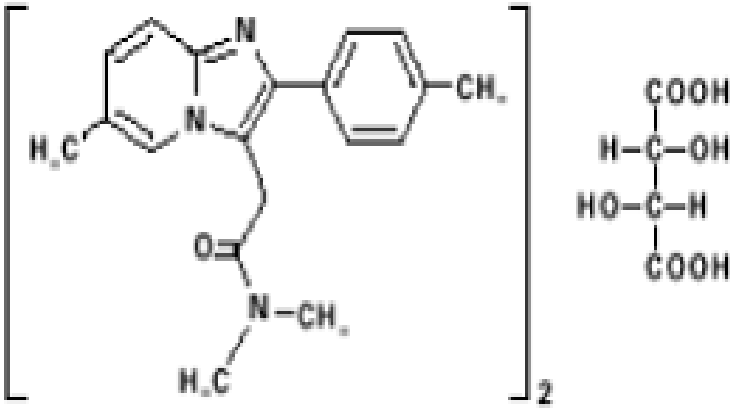
Amantadine is chemically designated as 1-adamantamine hydrochloride. It is available in capsules which are intended for oral use. It is used to treat Parkinson's disease; drug induced extra pyramidal syndromes and Akathisia. It is also used to treat the respiratory infections caused by influenza A virus (flu) [26, 27, 28]



Amantadine is frequently used to treat characteristic fatigue often experienced by patients with Multiple sclerosis; low dose of amantadine is used to treat attention-deficit hyperactivity disorder. It is stable and freely soluble in water and alcohol and in chloroform. The IUPAC name of amantadine is adamantan-1-amine has a chemical formula of $C_{10}H_{17}N$ and has a molecular mass of 151.240gm/mol and is well absorbed. Amantadine has inactive ingredients such as Yellow Iron Oxide, gelatin, glycerin, hydrogenated vegetable oil, lecithin-bleached, soybean oil, sorbitol, sorbitan, mannitol, titanium dioxide, white beeswax, vegetable shortening, simethicone and iron oxide (black imprint ink).

AMBIEN

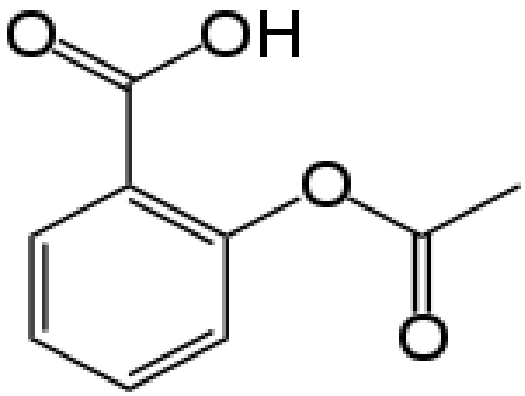
The scientific name of ambien is Zolpidem used for short term treatment of insomnia. It belongs to class called sedative-hypnotics. It is a short acting nonbenzodiapine hypnotic which works by slowing the activity in the brain to sleep. it comes as a tablet which is a extended release tablet taken orally.



Zolpidem is sparingly soluble in water, alcohol and propylene glycol, IUPAC name of Zolpidem is *N*,*N*,6-Trimethyl-2-(4-methylphenyl)-imidazo[1,2-*a*]pyridine-3-acetamide has a chemical formula $C_{19}H_{21}N_3O$ has a molecular weight of 764.88. Each Ambien tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, micro-crystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5 mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80. The bioavailability of Zolpidem is 70% orally and 90% in plasma

ASPIRIN

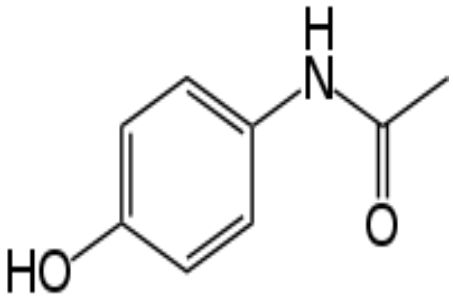
Scientific name of Aspirin is Acetyl salicylic acid is a salycilate drug often used as analgesic to treat minor aches and pains, as an antipyretic to reduce the fever, and as an anti-inflammatory medication. It belongs to class of Non Steroidal Anti-inflammatory Drugs (NSAID's). It is easily soluble in water



The IUPAC name of aspirin is 2-acetoxybenzoic acid has a chemical formula of $C_9H_8O_4$. Its molecular weight is 180.157g/mol. Its melting point is 135^0c. its bioavailability is rapid and completely absorbed. Its solubility in water is 3gm/ml. it is one of the first line drugs used for treatment of migraine and higher amount of aspirin is used for treatment of heart diseases. It is white crystalline acidic compound rapidly decomposes in ammonium acetate and citrates carbonates and hydroxides

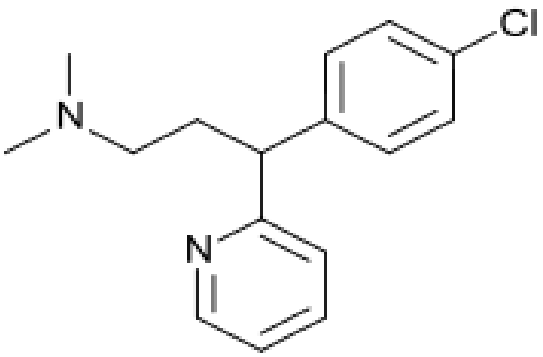
COLDACT

Coldact it comes in capsules which is taken orally, it is a complex capsules which contains three active ingredients Chlorpheniramine Maleate+Acetaminophne+Phenylephrine hydrochloride. it is anti-catahrrhal drug with analgesic, decongestant and antihistaminic actions, effectively prescribed for cold, sneezing, rhinorrhea and any type of rhinitis. It is long acting drug. Acetaminophen: IUPAC name is *N*-(4-hydroxyphenyl)acetamide, chemical formula is $C_8H_9NO_2$



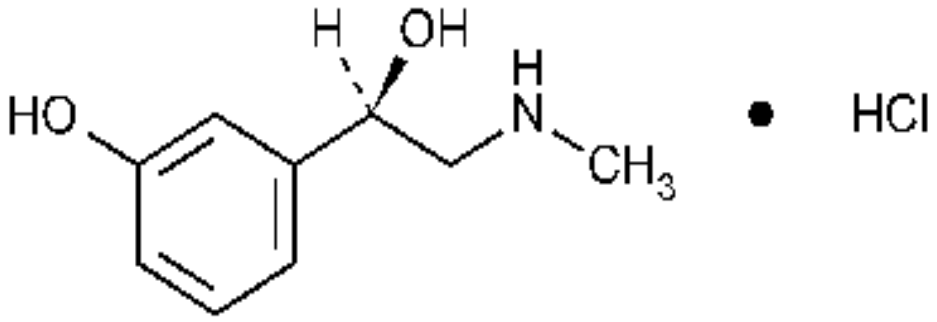
CHLOROPHENIRAMINE MALEATE: IUPAC name is 3-(4-chlorophenyl)-*N*,*N*-dimethyl-

3-pyridin-2-yl-propan-1-amine, chemical formula is $C_{16}H_{19}ClN_2$



PHENYLEPHERNINE HCl

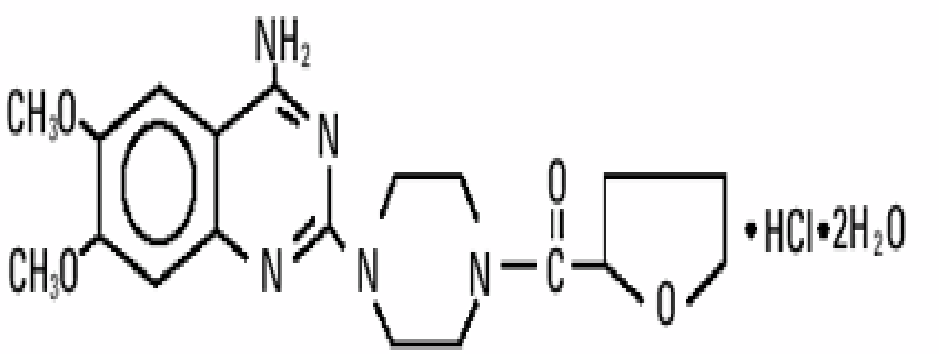
It is used to relieve nasal discomfort caused by cold allergies and hay fever. It is also used to relieve sinus congestion and pressure.



IUPAC name of phenylephernine hydrochloride is Benzenemethanol,3-hydroxy-a-[(methylamino)methyl]-,hydrochloride(*R*)-. (-)-*m*-Hydroxy-a-[(methylamino)methyl]benzyl alcohol hydrochloride [*61-76-7*]. It s chemical formula is $C_9H_{13}NO_2$. It has a molecular mass of 167.205gm/mol. Its bioavailability is 38% in GI tract. Its melting point range is from 140^0-145^0

HYTRIN

The scientific name of hytrin is Terazosin Hydrochloride is a selective alpha antagonist used for the treatment of enlarges prostate gland, benign prostatic hyperplasia (BPH) which includes difficulty in urination and painful urination and urinary frequency and urgency and hypertension. So it is the drug of choice for men with hypertension and enlarged prostate gland. It belongs to class alpha-andrenergic blockers.



The IUPAC name of Hytrin is RS)-Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate. hytin is a white crystalline powder which is readily soluble in water and isotonic solutions and has a molecular weight of 459.93. These tablets are supplied in different strength 1mg, 2 mg, 5mg, 10 mg. the inactive ingredients are vary depend on the weight of the tablet.

1 mg tablet: corn starch, lactose, magnesium stearate, povidone and talc.

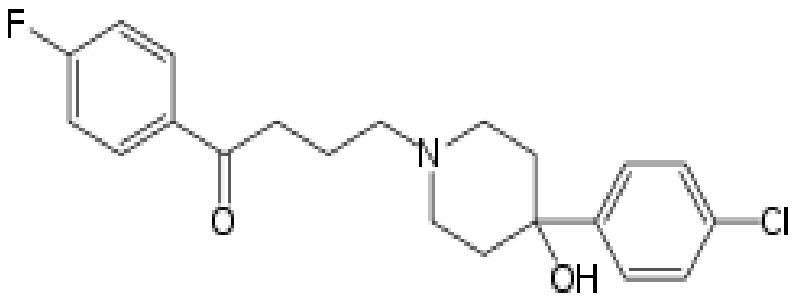
2 mg tablet: corn starch, FD&C Yellow No. 6, lactose, magnesium stearate, povidone and talc.

5 mg tablet: corn starch, iron oxide, lactose, magnesium stearate, povidone and talc.

10 mg tablet: corn starch, D&C Yellow No. 10, FD&C Blue No. 2, lactose, magnesium stearate, povidone and talc.

HALOPERIDOL

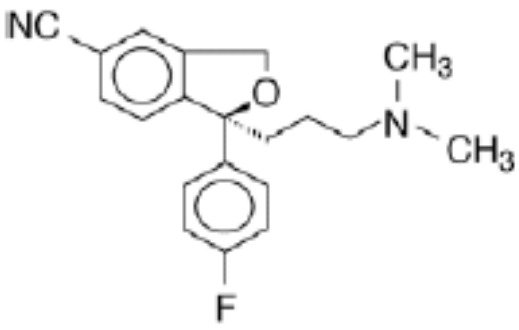
Haloperidol is a typical Anti psychotic drug belongs to class of bytrophenone. It is used to treat schizophrenia and acute psychotic states and delirium. It is also used to control motor tics. Verbal tics and tourette's disorder. It also used to treat explosive behavior and hyper activity in children.



The IUPAC name of haloperidol is 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one, chemical formula is $C_{21}H_{23}ClFNO_2$ which has a molecular weight of 375.9g/mol. The bioavailability of haloperidol is 60%-70%. The melting point of Haloperidol is 151.5^0c. its solubility is 14mg/l and it is bioavailability is 60% orally.

LEXAPRO

The scientific name of lexapro is Escitalopram Oxalate. Lexapro is mainly used as antidepressant which belongs to class Selective Serotonin Reuptake Inhibitors (SSRI). It is used to treat major disorders depression

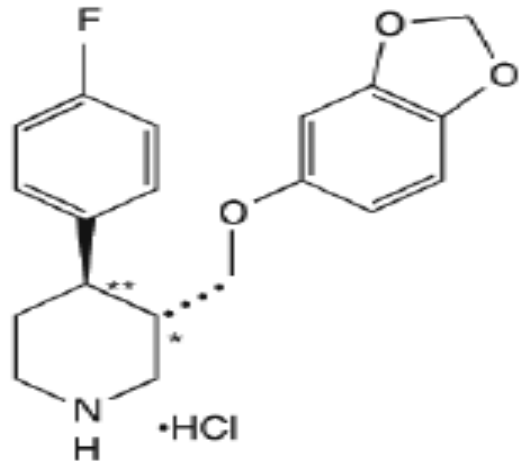


$\bullet C_2H_2O_4$

The IUPAC name of Lexapro is S-(+)-1-[3-(dimethyl-amino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate, chemical formula is $C_{20}H_{21}FN_{20}.C_2H_2O_4$, and its molecular weigh is 414.40 gm/mol. lexapro occurs as white-yellow powder which is soluble in methanol, isotonic saline solution and slightly soluble in water , and its bioavailability is 80%. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.

PAROXETINE HYDROCHLORIDE

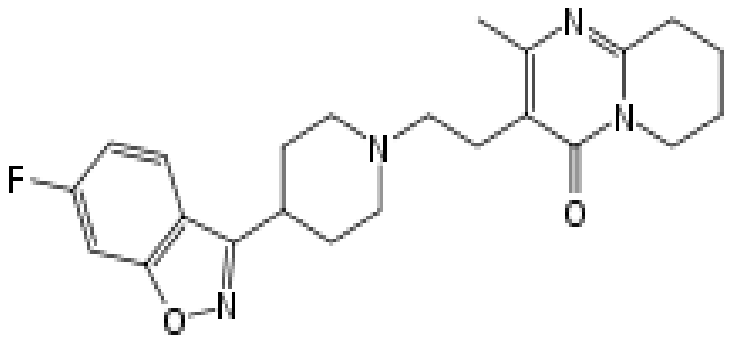
Paroxetine is a anti depressant which belongs to class SSRI. Paroxetine is used to treat major depression, obsessive-compulsive disorder (OCD), and panic, social anxiety, general anxiety, post- traumic stress disorder (PTSD), generalized anxiety disorder (GAD), premenstrual dysphoric disorder (PMDD).



The IUPAC name of Paroxetine is (-)-*trans*-4*R*-(4'-fluorophenyl)-3*S*-[(3',4'-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate. Its empirical formula is C19H20FNO3**.** HCl• 1/2H_2O. It has a molecular weight of 374.80gm/mol. The melting point of Paroxetine ranges from 120^0-138^0c. the solubility of Paroxetine is 5.4mg/ml. the bioavailability is completely absorbed in GI tract . the inactive ingredients of Paroxetine consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

RISPERDAL

Risperidone is a typical antipsychotic drug belongs to class of benzisoxazole used for treatment of schizophrenia, shizo affective disorder, bipolar disorder, autism. It is also used as control drug for treatment of tourett syndrome, obsessive compulsive disorder, eating disorder, disruptive behavior disorder, depression.



The IUPAC name of Risperidone is 4-[2-[4-(6-fluorobenzo[*d*]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one. Its empirical formula is $C_{23}H_{27}FN_4O_2$ has a molecular weight of 410.485gm/mol. The bioavailability of the drug 70% orally.for the orally disintegrating tablets the bioavailability is 90%. It is insoluble in water and soluble in 0.1 HCl, methylene chloride and methanol. RISPERDAL® Tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths.

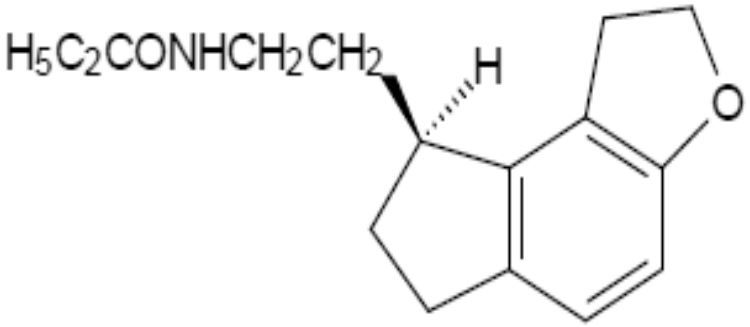
Risperdal® tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). The 0.25 mg, 0.5 mg, 2 mg, 3 mg, and 4 mg tablets also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake. RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (coral), 3 mg (coral), and 4 mg (coral) strengths.

Risperdal® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 2 mg, 3 mg, and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

The melting point of Risperidone is 170^0c. The Experimental solubility of Risperidone is 2.8mg/ml.

ROZEREM

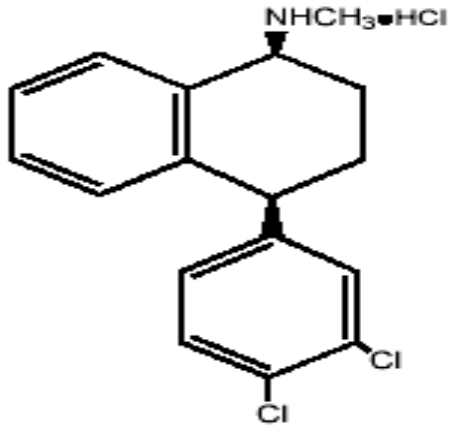
Rozerem (ramelton) is a sedative which causes sleep it is mostly used for insomnia. It belongs to class melatonin receptor agonist. Rozerem (ramelteon) is an orally active hypnotic chemically designated as (S)-N-[2-(1,6,7,8-tetrahydro 2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide



The chemical formula of Rozerem is $C_{16}H_{21}NO_{2,}$ has a molecular weight of 259.34gm/mol. Rozerem is freely soluble in organic solvents, such as methanol ethanol. Soluble in 1-octanol, acetonitrile and very slightly soluble in water. The melting point of Rozerem is 113-115^{0}c. each Rozerem tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.

SERTRALINE

Sertraline hydrochloride is an antidepressant of selective serotonin reuptake inhibitor (SSRI). Sertraline is used to treat major depression obsessive compulsive disorder, panic disorder, posttraumatic stress disorder and social anxiety disorder.

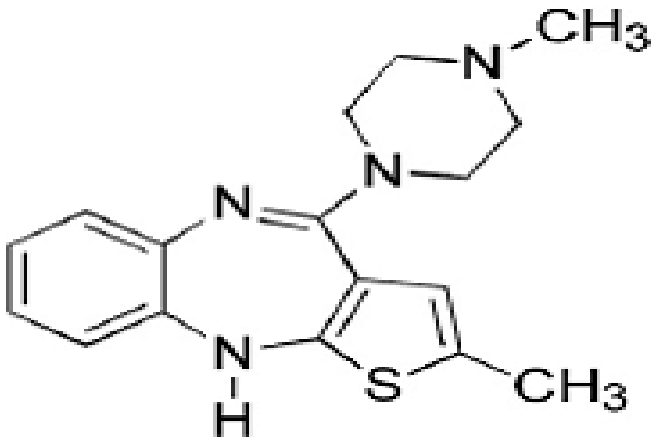


The IUPAC name if Sertraline is (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The chemical formula is $C_{17}H_{17}NCl_2$.HCl. the molecular weight of Sertraline is 342.70gm/mol. Sertraline is a white crystalline powder which is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. The bioavailability of Sertraline is 44% and melting point of Sertraline is 246-249^{0}c. the inactive ingredients of Sertraline is dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet),

FD & C Red #40 aluminum lake (in 25 mg tablet), FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.

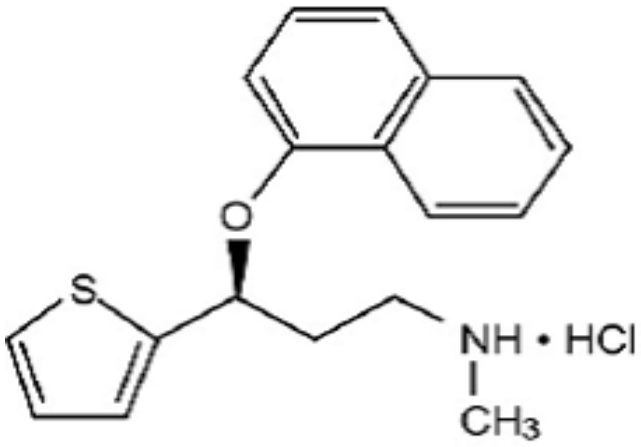
ZYPREXA

Zyprexa (Olanzapine) is a typical antipsychotic used for the treatment of schizophrenia and bipolar disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, posttraumatic stress disorder it belongs to class thienobenzodiazopene.



CYMBALTA

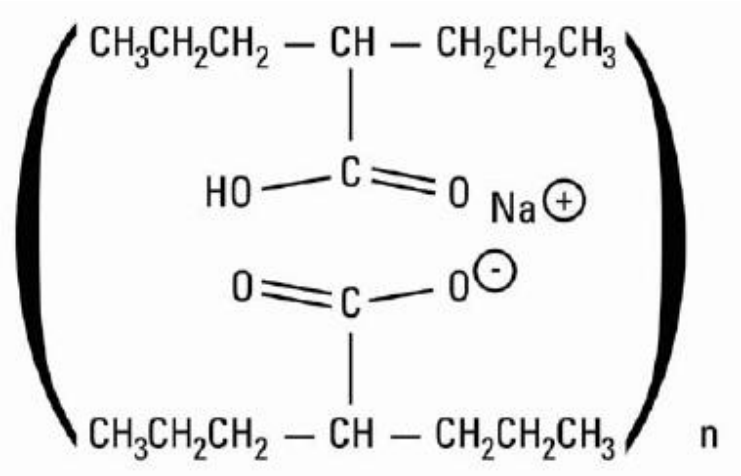
Cymbalta (duloxetine) is a anti-Psychotic drug is a serotonin-norepinephrine reuptake inhibitor it is effective for major depression disorder and general anxiety disorder and it also treats chronic pain disorder. It belongs to class tri cyclic anti depressants



The IUPAC name of Cymbalta is (+)-(S)-N-methyl-β-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The chemical formula is $C_{18}H_{19}NOS$•HCl. The molecular weight of Cymbalta is 333.88gm/mol. Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water. Each capsule is enteric coated tablets. The inactive ingredients of Cymbalta are FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate.

DEPAKOTE

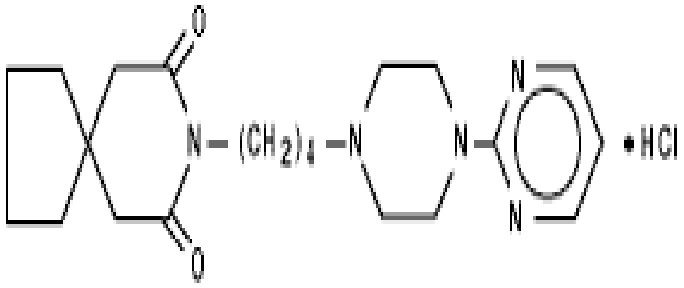
Depakote (valproic acid) it is used in mood stabilizing disorder epilepsy bipolar disorder major depression. It is also used to treat migraine and schizophrenia.



The IUPAC name of Depakote is sodium hydrogen bis(2-propylpentanoate). The chemical formula of Depakote is $NaC_8H_{16}O_2$. The molecular weight of Depakote is 144.211gm/mol. The bioavailability of Depakote is 90%. The melting point is 222^0c. the inactive ingredients of Depakote are cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains corn starch), silica gel, talc, titanium dioxide, and vanillin.

BUSPIRONE

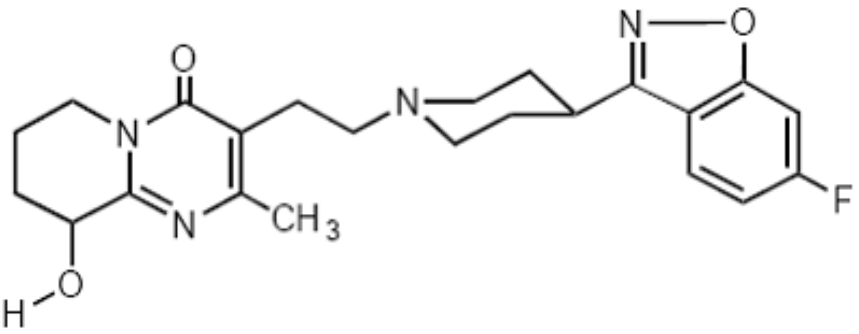
Buspirone is a psychoactive drug which belongs to class piperazine it is used for general anxiety disorder



The IUPAC name of Buspirone is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro [4.5]decane-7,9-dione monohydrochloride. The chemical formula is $C_{21}H_{31}N_5O_2$•HCl. The molecular weight of buspirone is 422mg/mol. Buspirone is white crystalline which is soluble in water. The inactive ingredients present in buspirone are colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The melting point of buspirone is 201.5-202.5^{0}c. the experimental solubility of buspirone is 24mg/l.

PALPERIDOL

Palperidol is a typical anti psychotic drug belong to class benzisoxazole which is extended release tablet. It is mainly used to treat schizophrenia



The IUPAC name of Palperidol is (±)-3-[2-[4-(6-fluoro-1,2benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4Hpyrido[1,2-a]pyrimidin-4-one. The chemical formula is $C_{23}H_{27}FN_4O_3$ and its molecular weight is 426.69. Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; practically insoluble in water, 0.1N NaOH, and hexane; and slightly soluble in N,N-dimethylformamide. The inactive ingredients of Palperidol are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The bioavailability of Paliperidone is 28%.

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CHAPTER II

INSTRUMENTATION AND METHODS

THERMAL MECHANICAL ANALYZER (TMA)

The IsoTMA procedure uses a TA Instruments 942 Thermal Mechanical Analyzer. A schematic of this instrument is shown in Figure 2. This TMA measures the displacement of a quartz probe that rests on the surface of the sample. As the sample changes dimensions due to swelling or dissolution, the position of the probe rises or falls accordingly. This probe displacement is measured electronically by a transformer and, after calibration, is recorded as height changes of the probe per unit time.

To perform these experiments, the 2 mm diameter probe is initially zeroed on the empty quartz sample stage. Then the tablet is placed on the stage, the probe lowered onto the surface of the tablet and the tablets initial thickness is measured. After waiting about 2.0 minutes for equilibrium and a steady signal to be achieved, a time base scan is begun. The tablet is then immersed in a fluid of interest (ex. water) by raising a beaker underneath the sample that sits on a small laboratory jack. The pH of the deionized water

that we used was adjusted to 3, 4, and 7 with pH = 7 being typical. A weight can also be placed on top of the probe to improve contact with the surface of the tablet and to minimize probe slippage. The applied loads during our tests varied from 0.5 to 10 grams, with 1.0 gram being typical. If desired, the beaker of fluid can be placed on a hot plate to raise its temperature. For our experiments, the fluid temperature was either 24 or 37^{o}C. Figure 3 shows a Ritalin tablet, and the quartz probe, before disintegration and while disintegrating in the fluid.

CHAPTER III

ULTRA VISIBLE SPECTROPHOTOMETER

Tablet disintegration was studied using TMA, in a 0.1N sulphuric acid as the media. After the tablet disintegration the media is collected and filtered using a filter paper so that we can see clear solution. The UV spectrophotometer used for the analysis was ___. Before performing the uv analysis of the desired solution we have take blank solution 0.1 N sulphuric acid in the clean cuvet calculate the absorbance of the blank solution. Then we have take 1ml of filtered zyprexa solution (stock solution) perform the uv analysis and we have calculate the absorbance and wavelength of the solution if the absorbance is more then we have to dilute the solution and again perform the uv analysis of the diluted stock solution until we desired absorbance range. The maximum disintegration of the tablet occurs at the maximum absorbance. The energy is calculated by equation

$$E=hc/\lambda$$

E= energy.

H= planck's constant.

C =concentration.,λ = wavelength.

TMA vs. Real World Disintegration Measurements

A. Riga and M. Williams, Pharmacy Technology Conference, Joao Pessoa, Brazil 2003

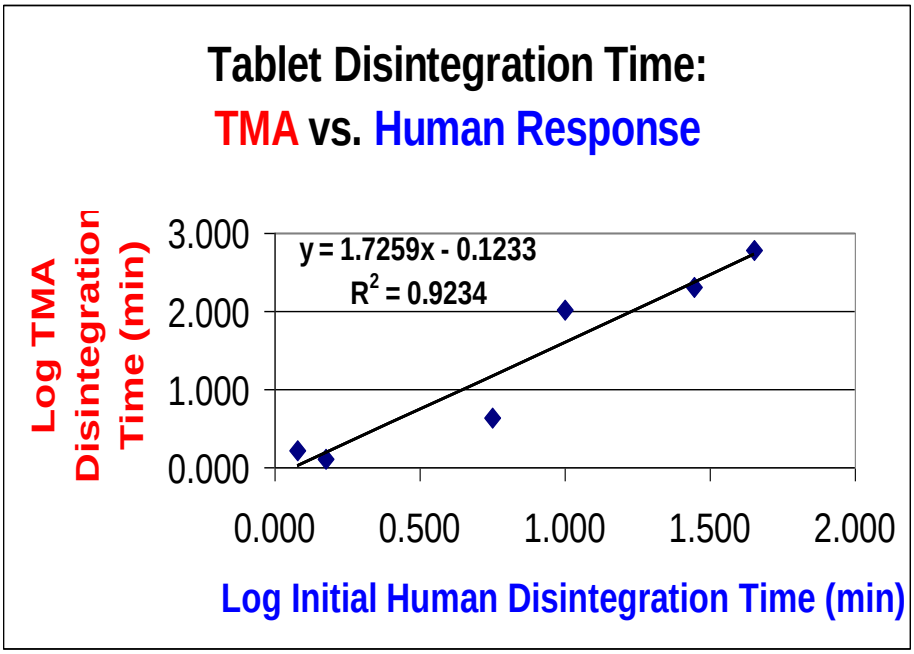


Figure 1 TMA vs Real World Disintegration Measurements

SCHEMATIC DIAGRAM OF TMA

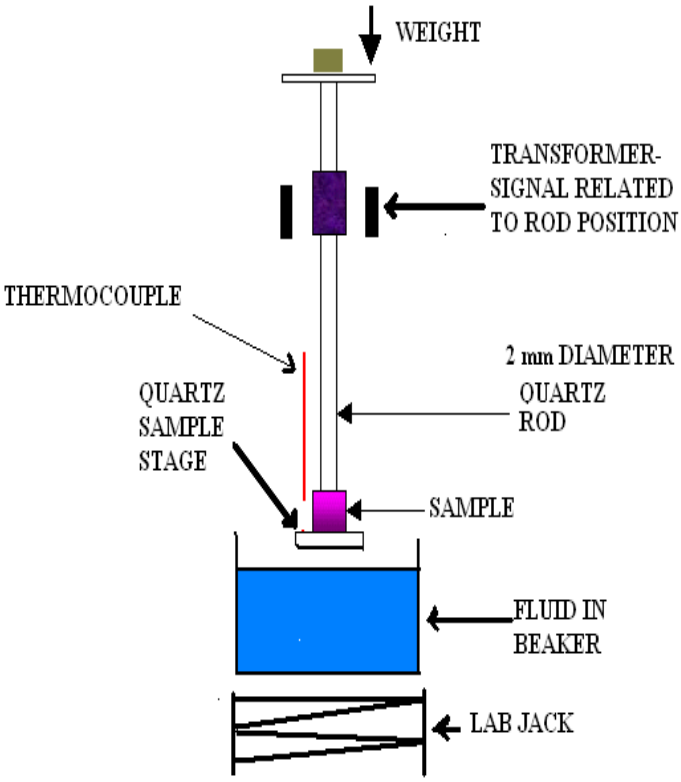


Figure 2 Schematic Diagram of TMA

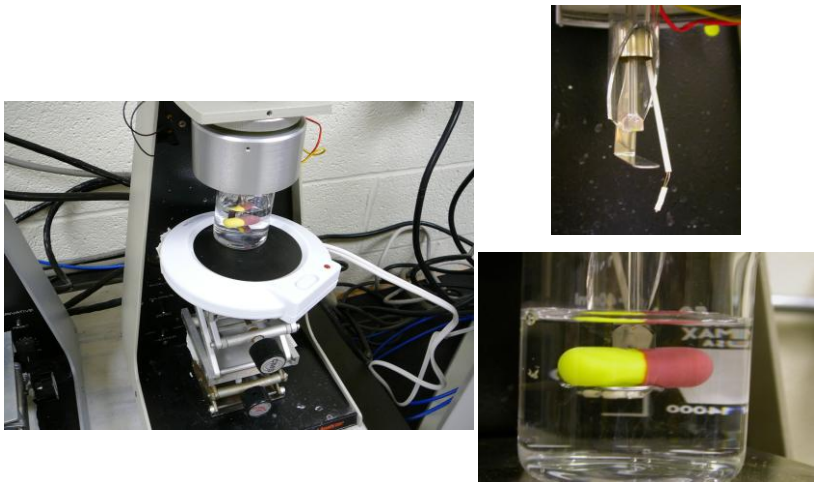


Figure 3 Modified TMA Apparatus

RITALIN TABLET BEFORE AND AFTER DISINTEGRATION

Figure 4 Ritalin Tablet Before and After Disintegration

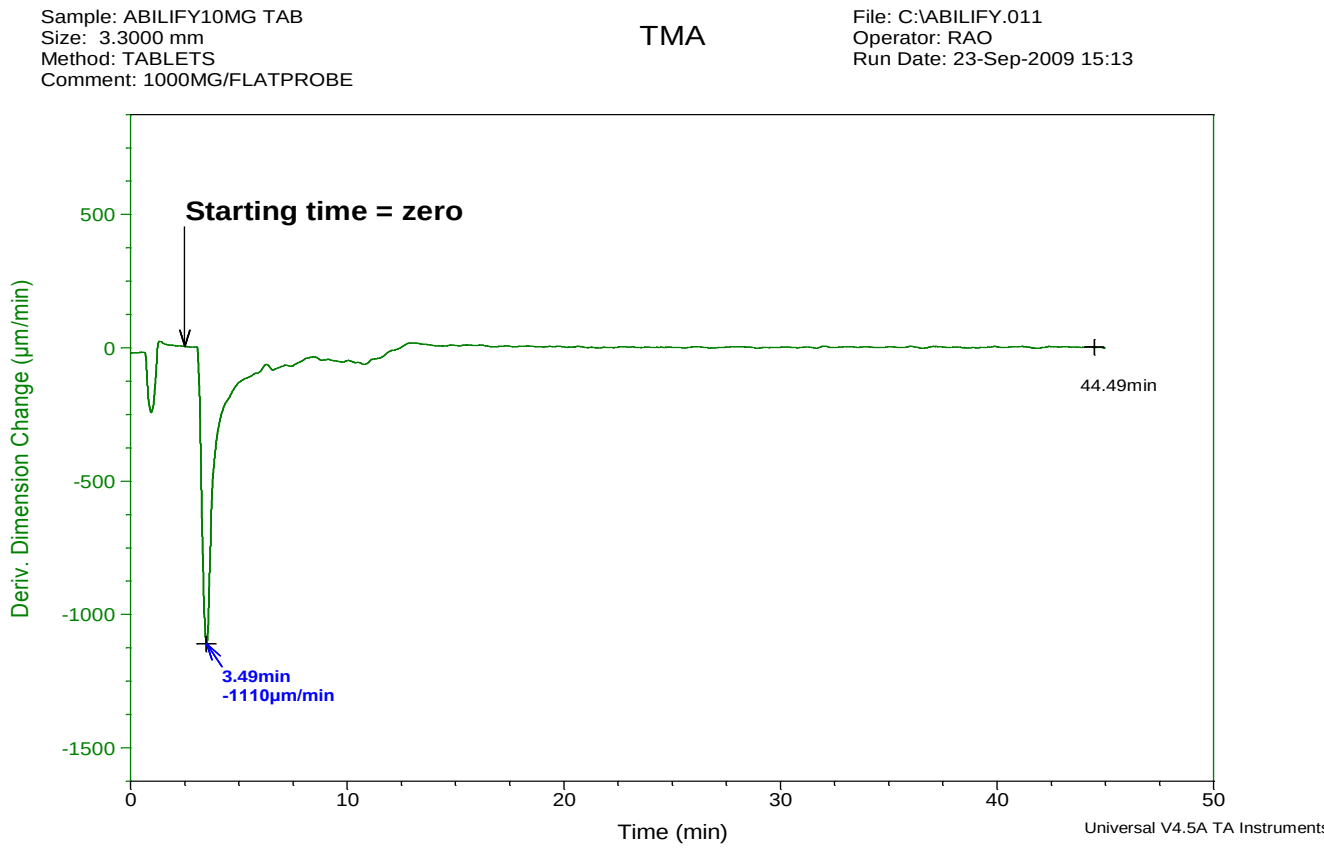


Figure 5 Drug Disintegration of Abilify by Iso TMA

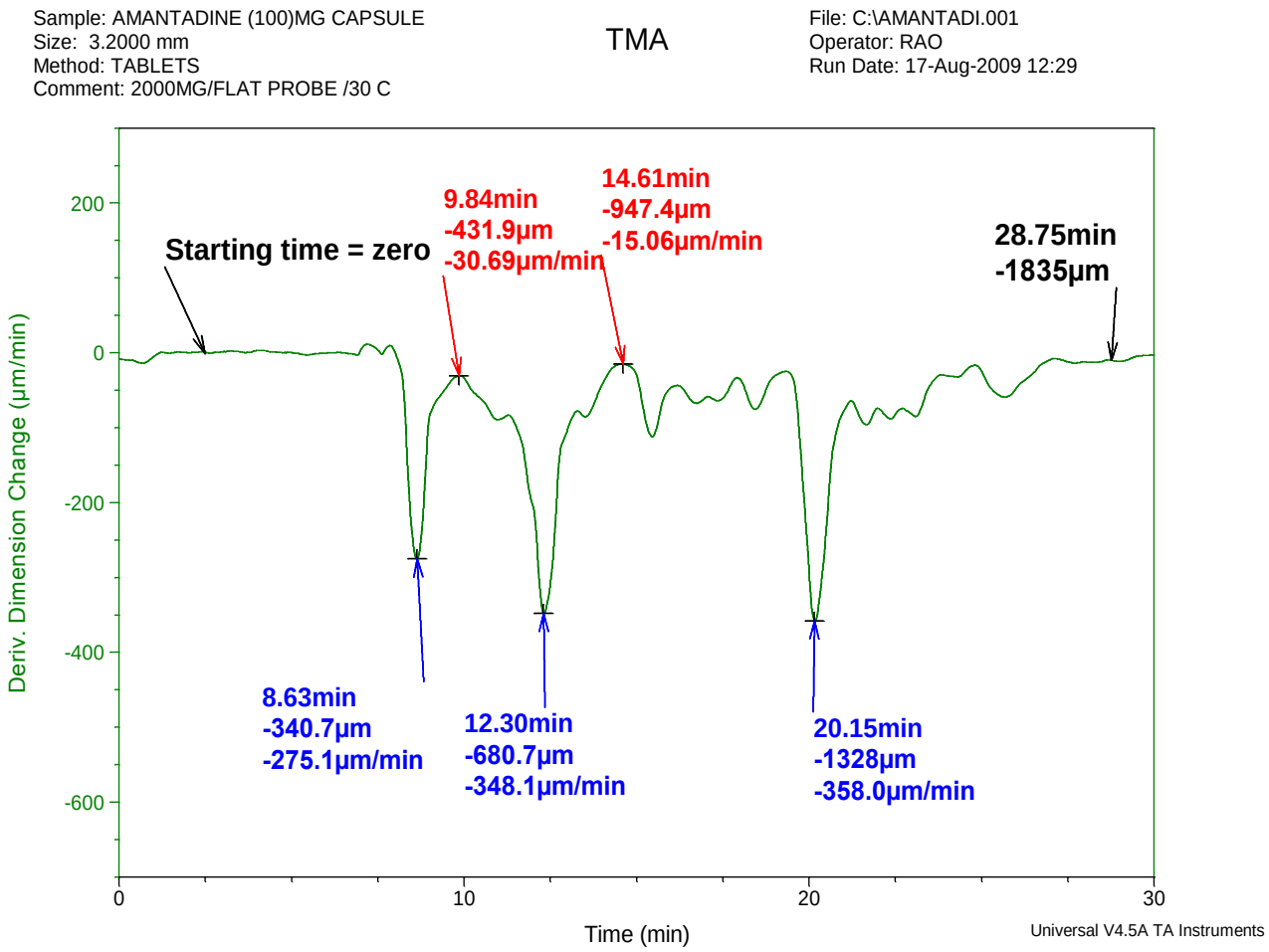


Figure 6: Drug Disintegration of Amantadine Capsule by Iso TMA

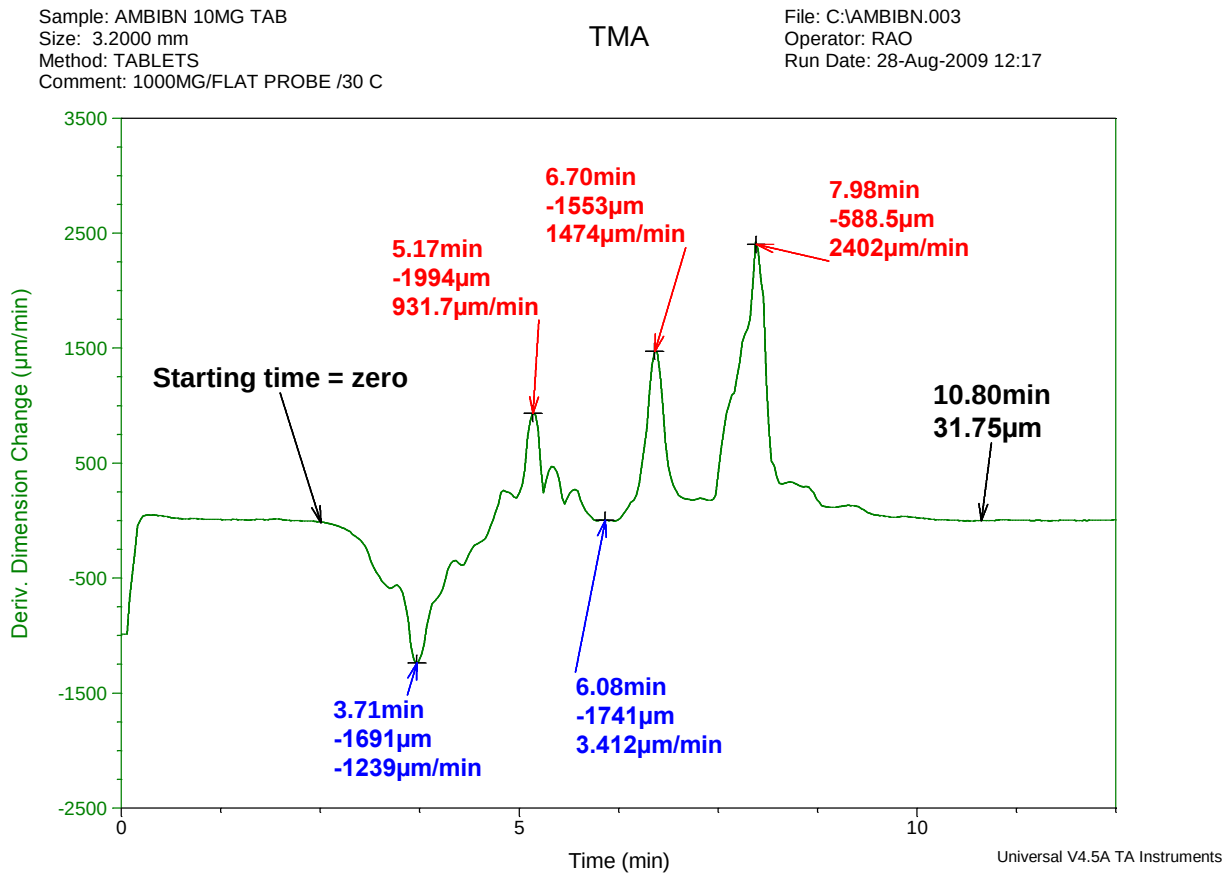


Figure 7: Drug Disintegration of Ambien tablet by Iso TMA

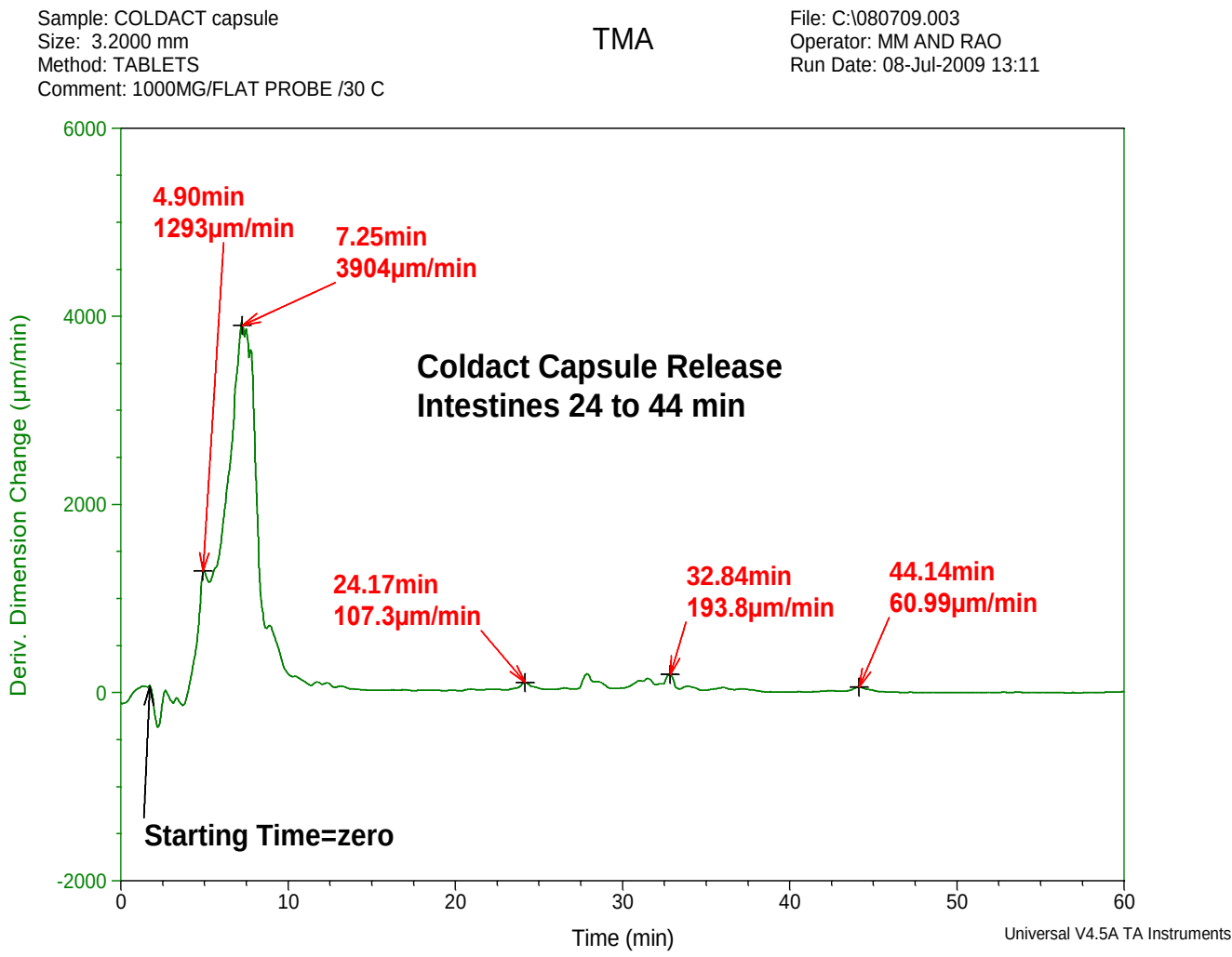


Figure 8: Drug Disintegration of Coldact Capsule by Iso TMA

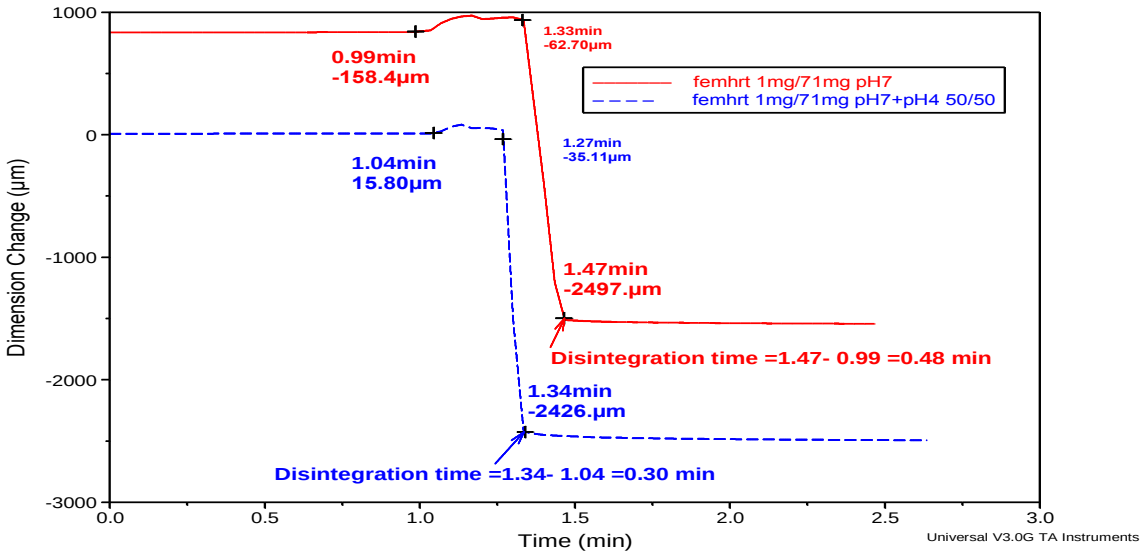


Figure 9: Drug disintegration of Femhrt tablet by IsoTMA under different ph 5, 7

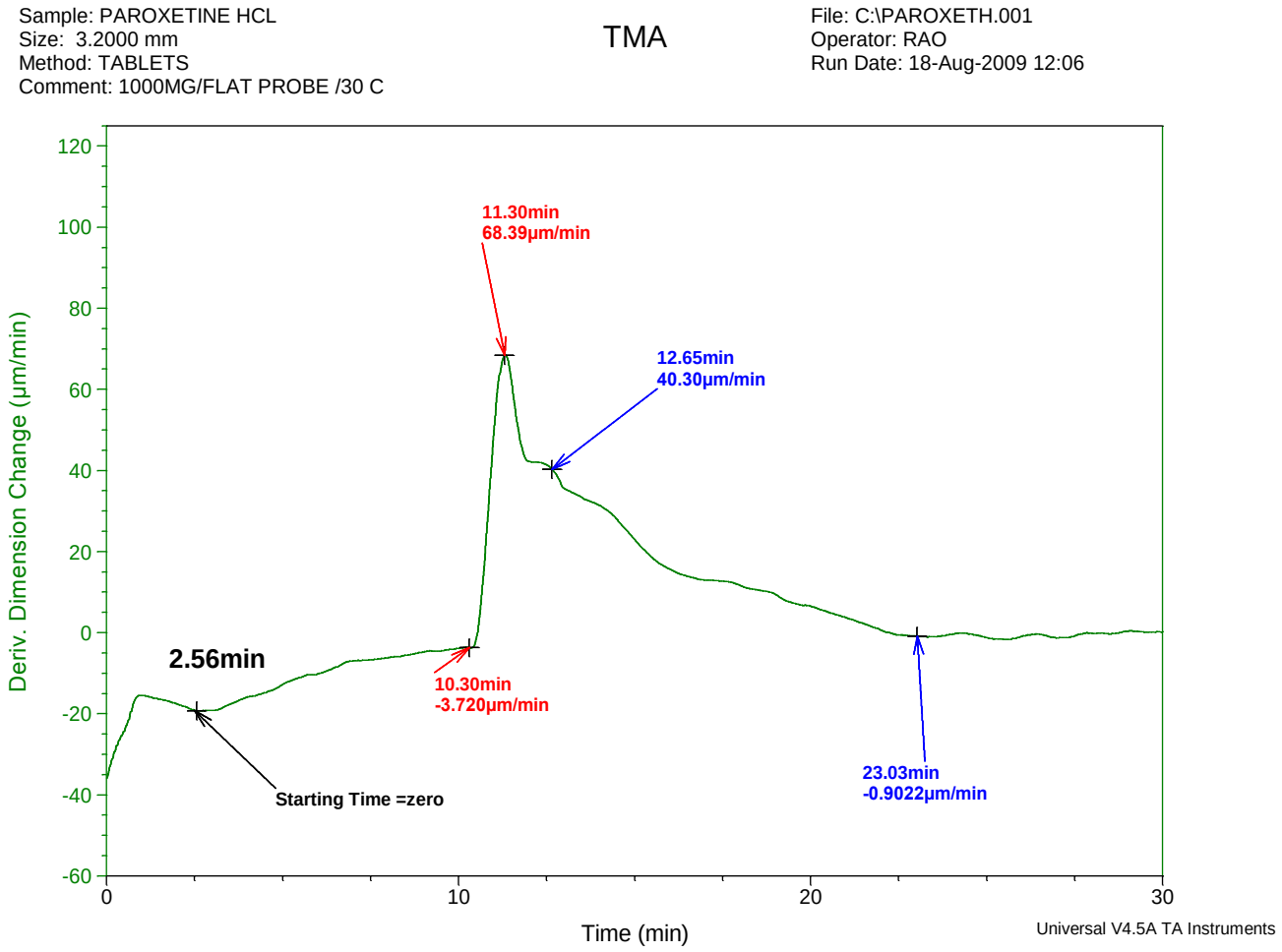


Figure 10: Drug disintegration of Paroxetine HCl by IsoTMA

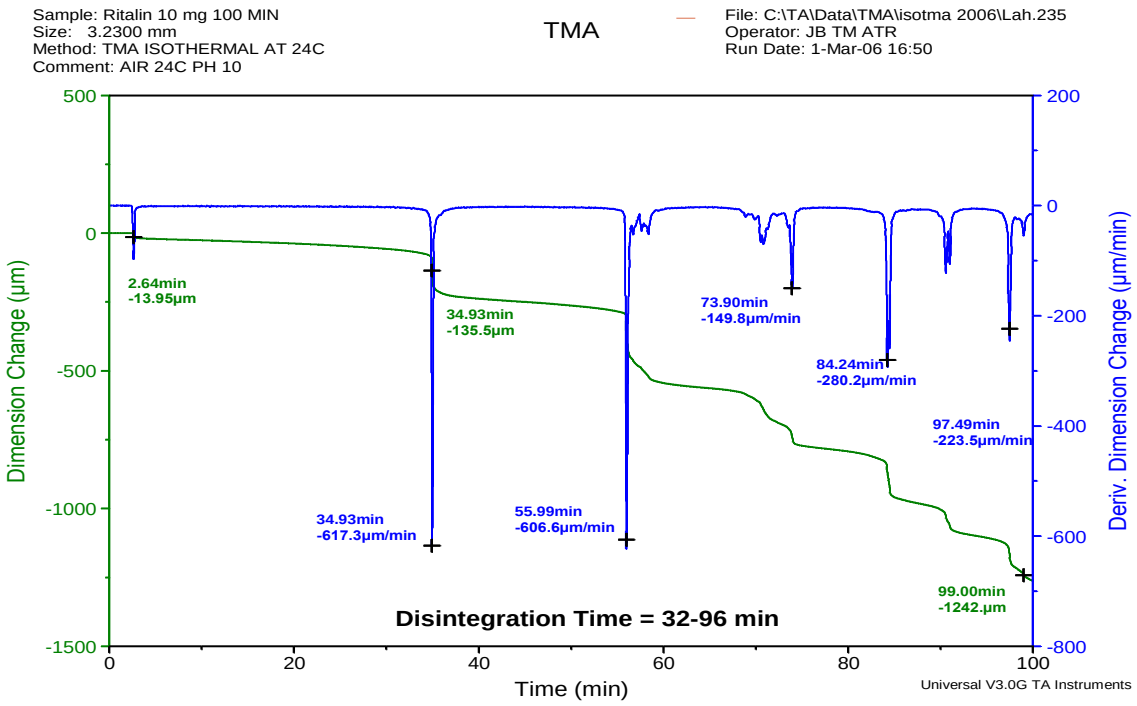


Figure 11: Drug Disintegration of Ritalin Tablet by ISOTMA

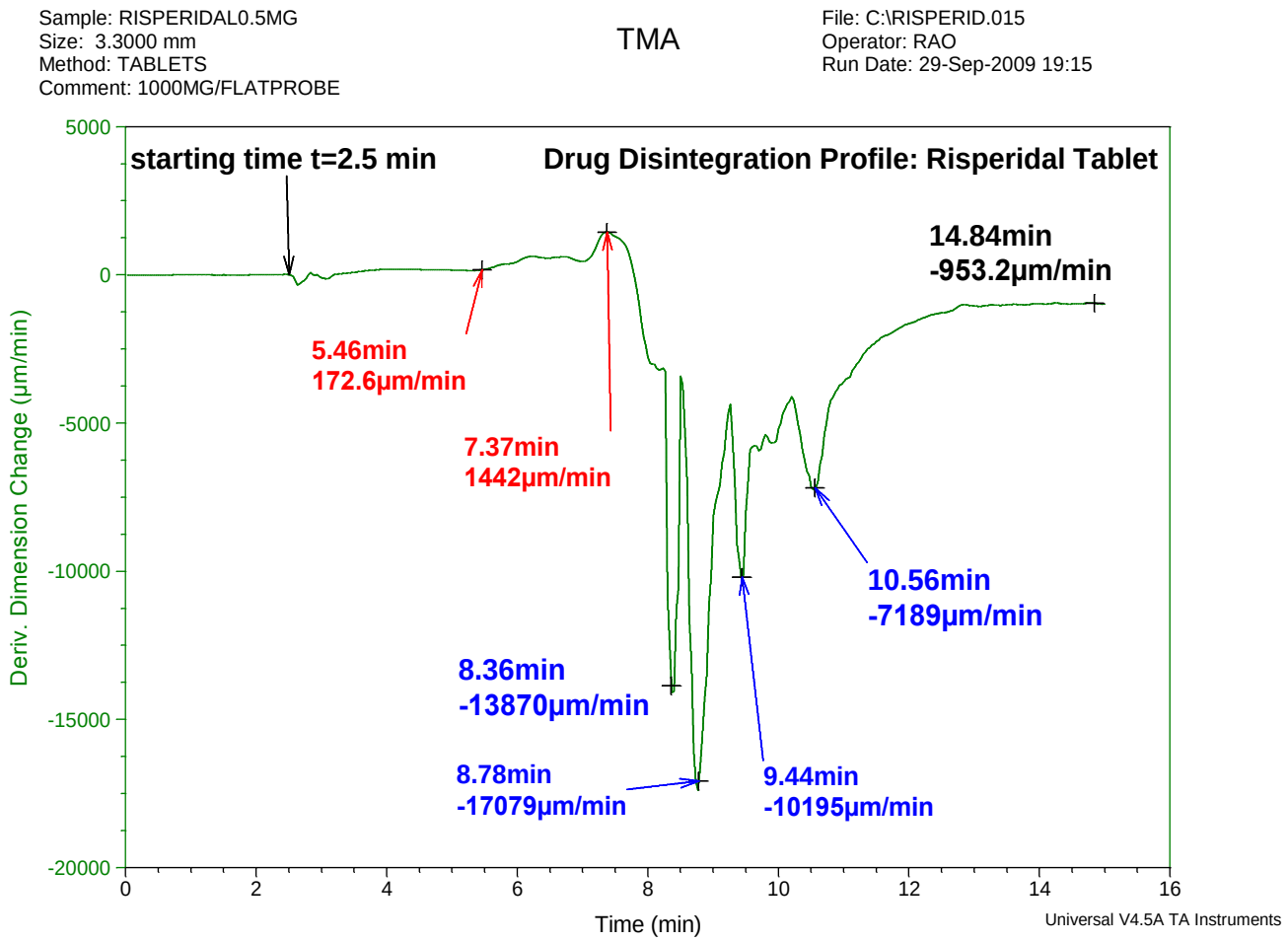


Figure 12: Drug Disintegration of Risperdal tablet by Iso TMA

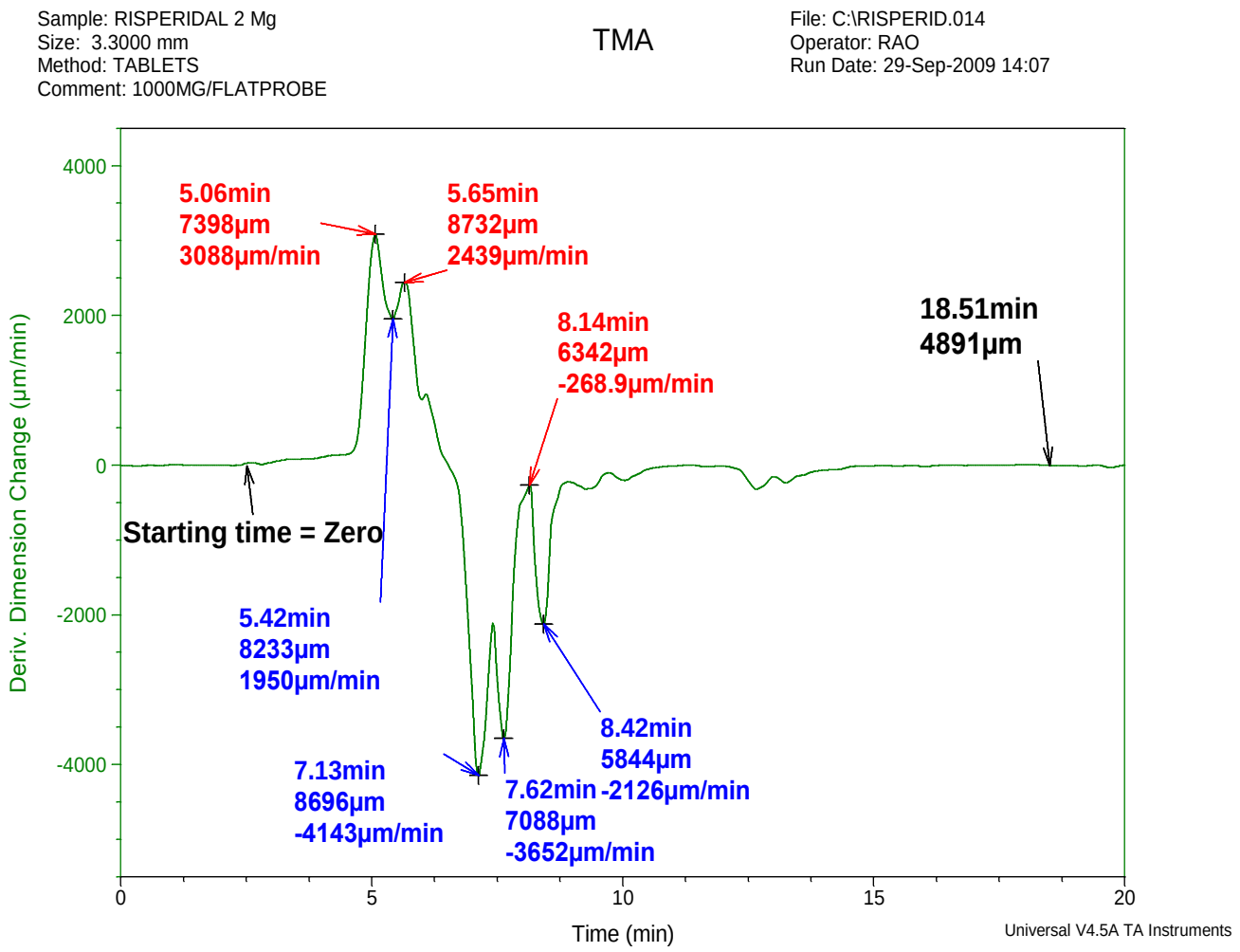


Figure 13: Drug Disintegration of Risperdal 2mg tablet BY IsoTMA

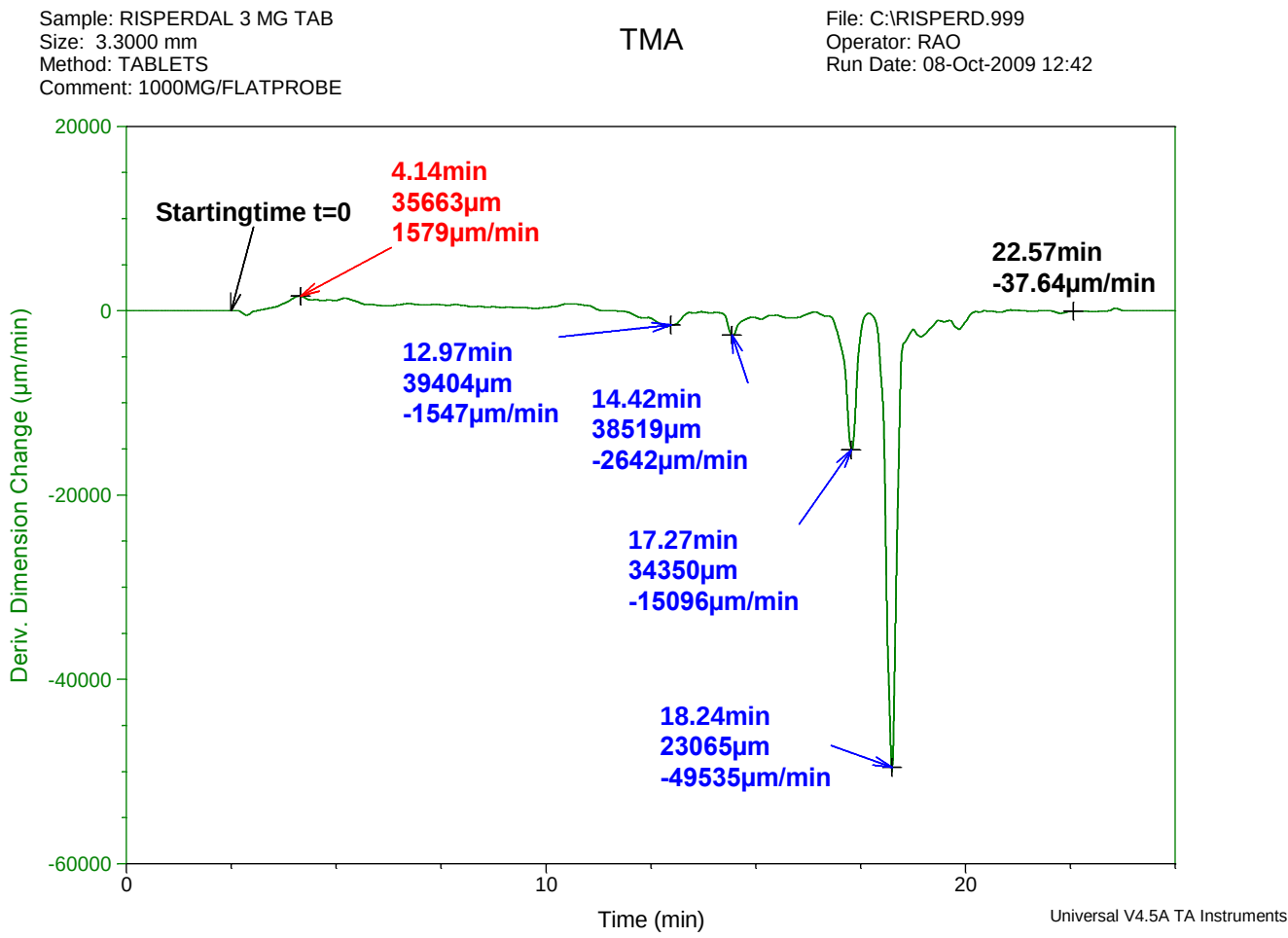


Figure 14: Drug Disintegration of Risperdal 3mg tablet by Iso tma

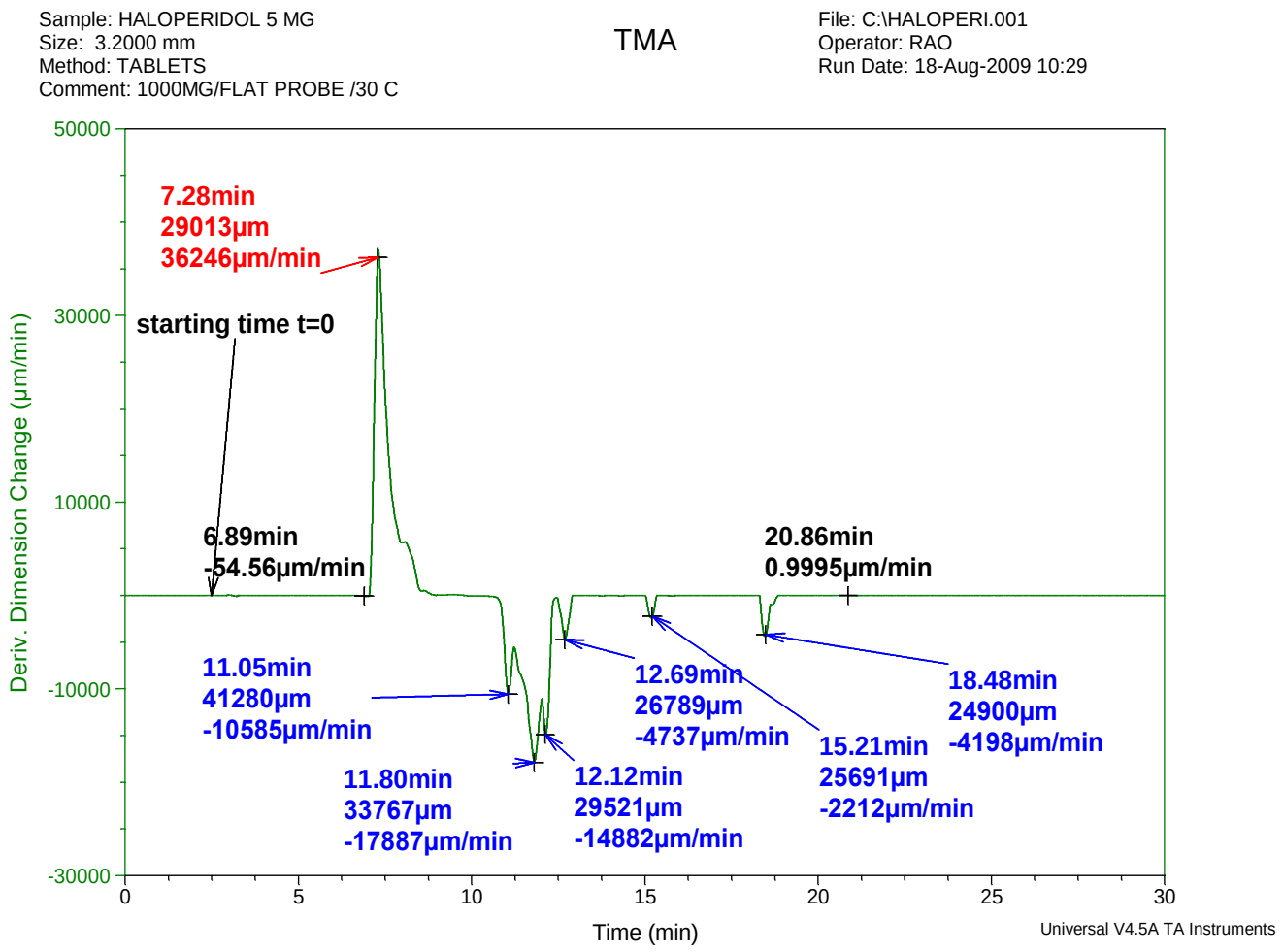


Figure 15: Drug Disintegration of haloperidol tablet by Iso tma

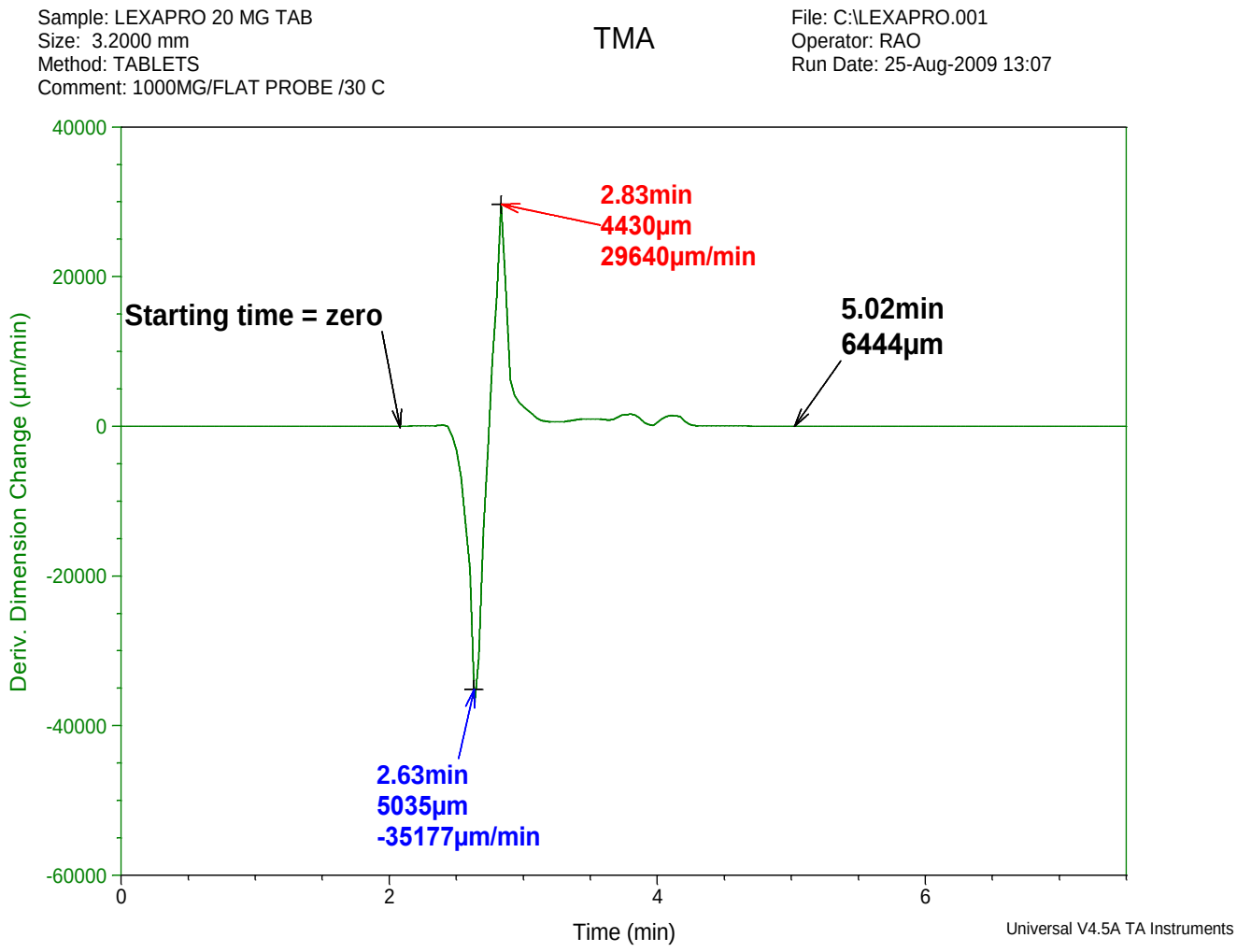


Figure 16: Drug Disintegration of lexapro tablet by Iso TMA

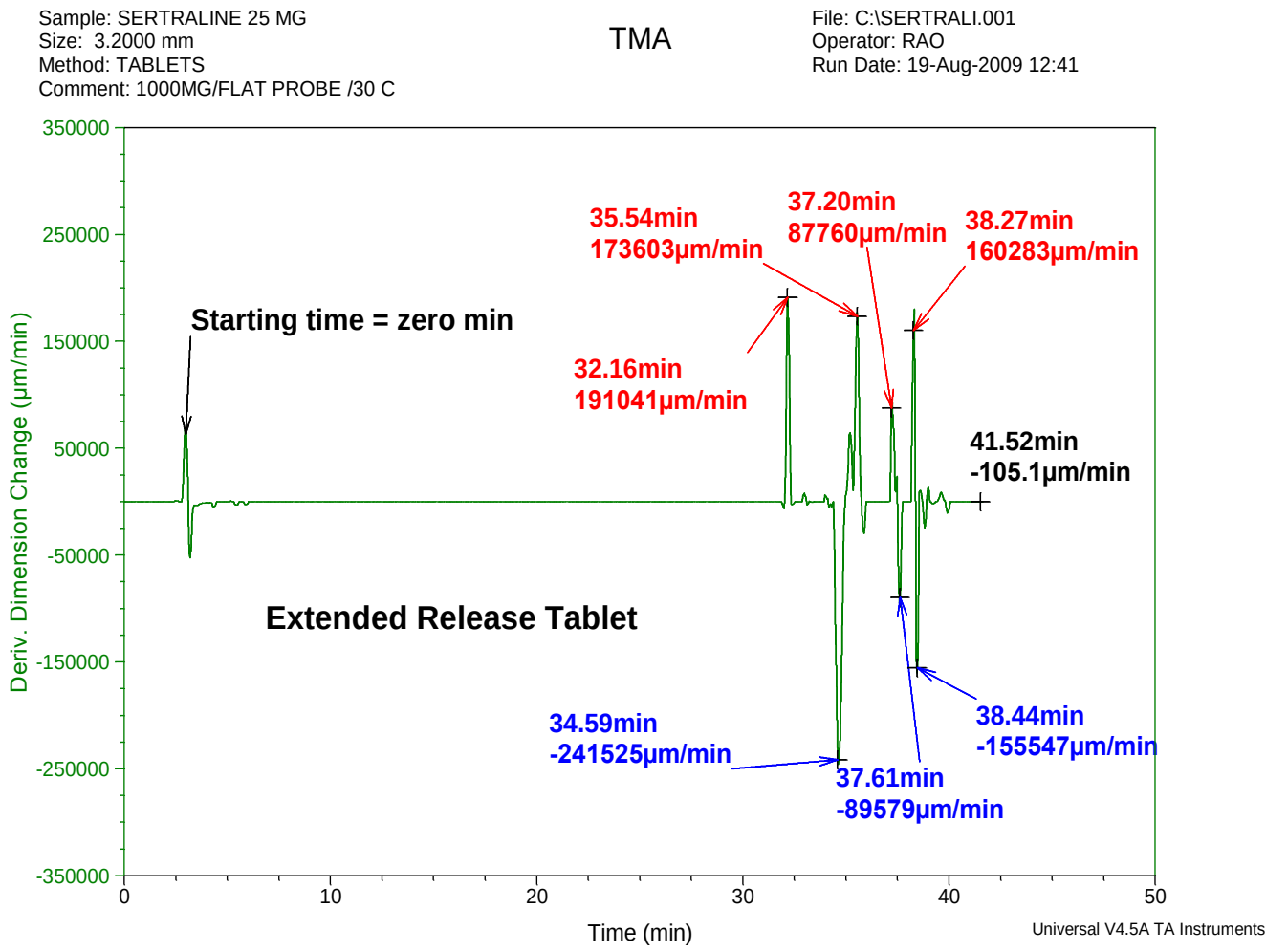


Figure 17: Drug Disintegration of Sertraline tablet by Iso tma

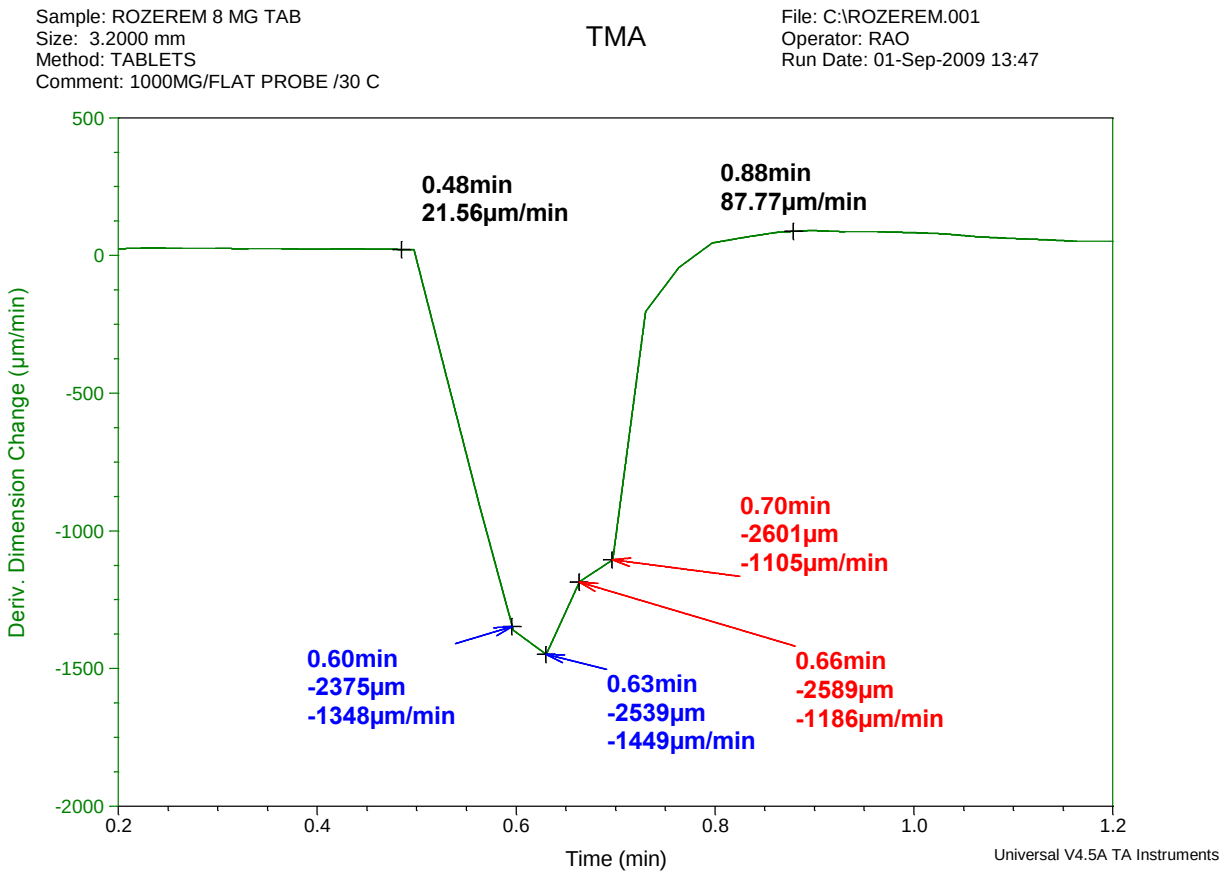


Figure 18: drug disintegration of Rozerem tablet by Iso tma

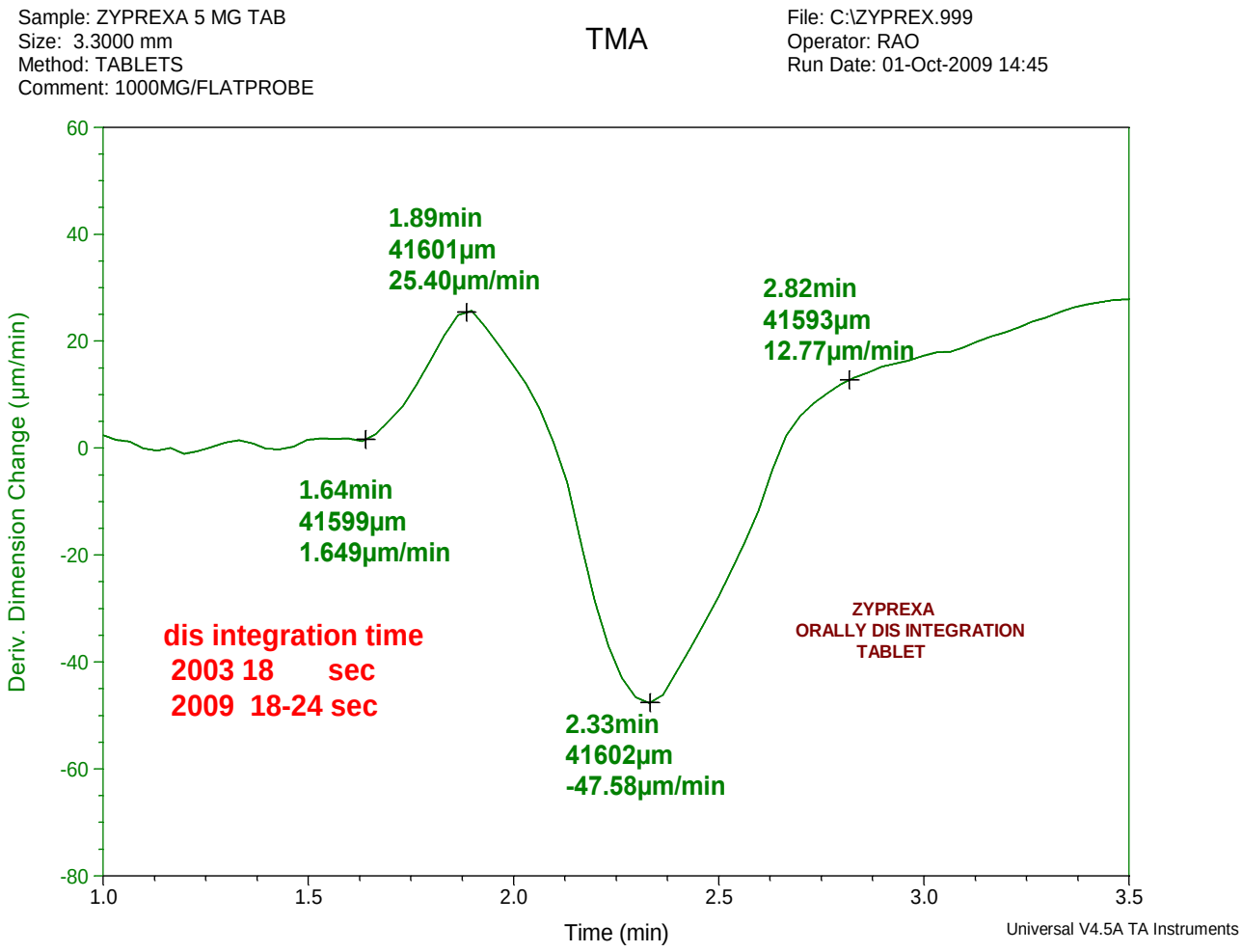


Figure 19: Drug disintegration of Zyprexa tablet by Iso tma

Figure 20: Drug Disintegration of Amoxicillin capsule by tma under different temperatures

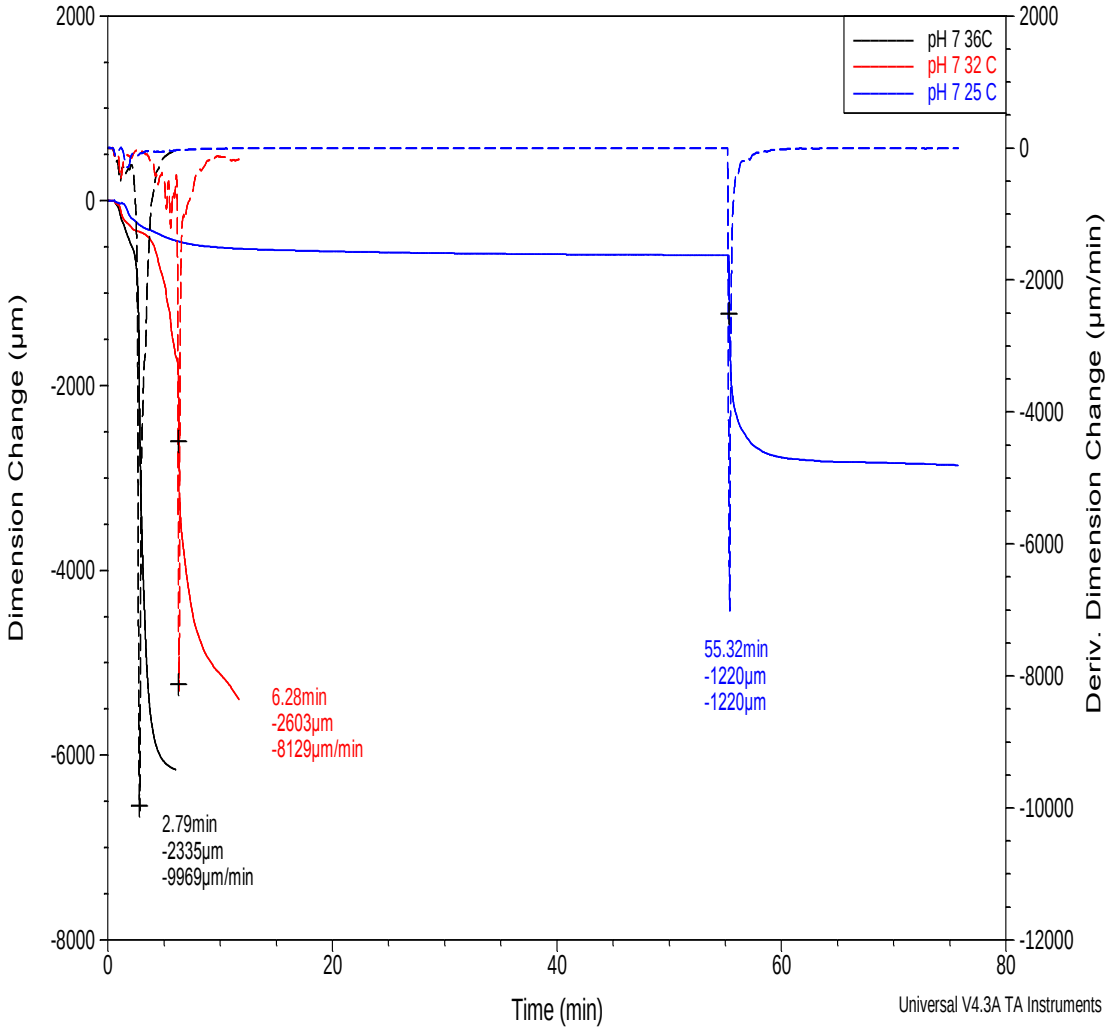


Figure 21: Drug disintegration of Amoxicilin capsule with different pH 3,4,7

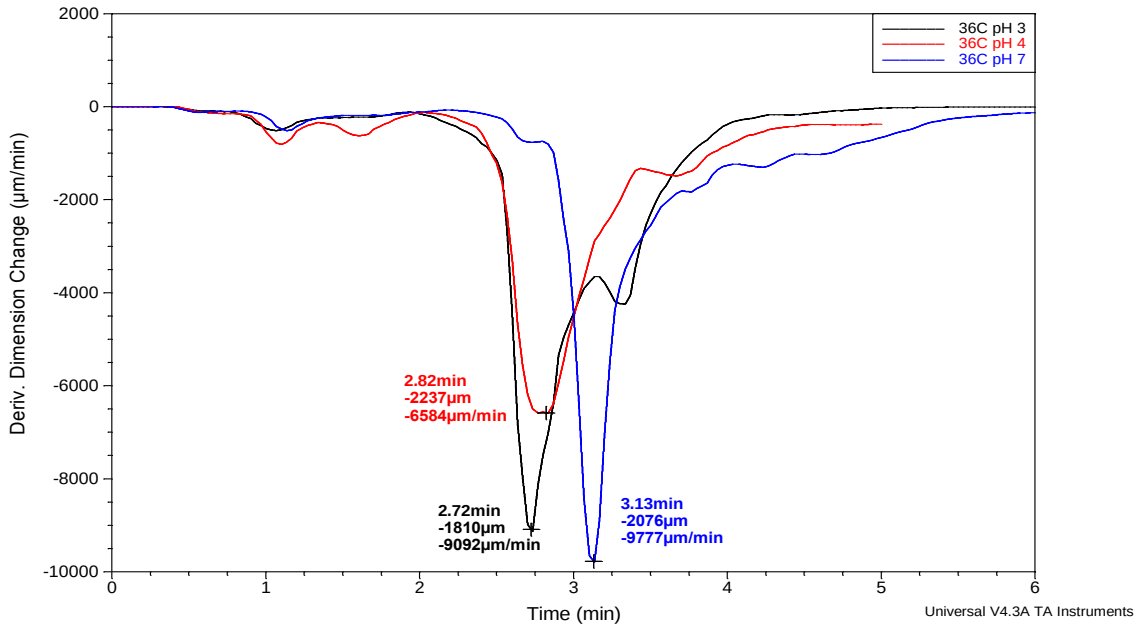


figure 22: Drug Disintegration of Amoxicillin Capsule by Iso tma and visual photographic methods

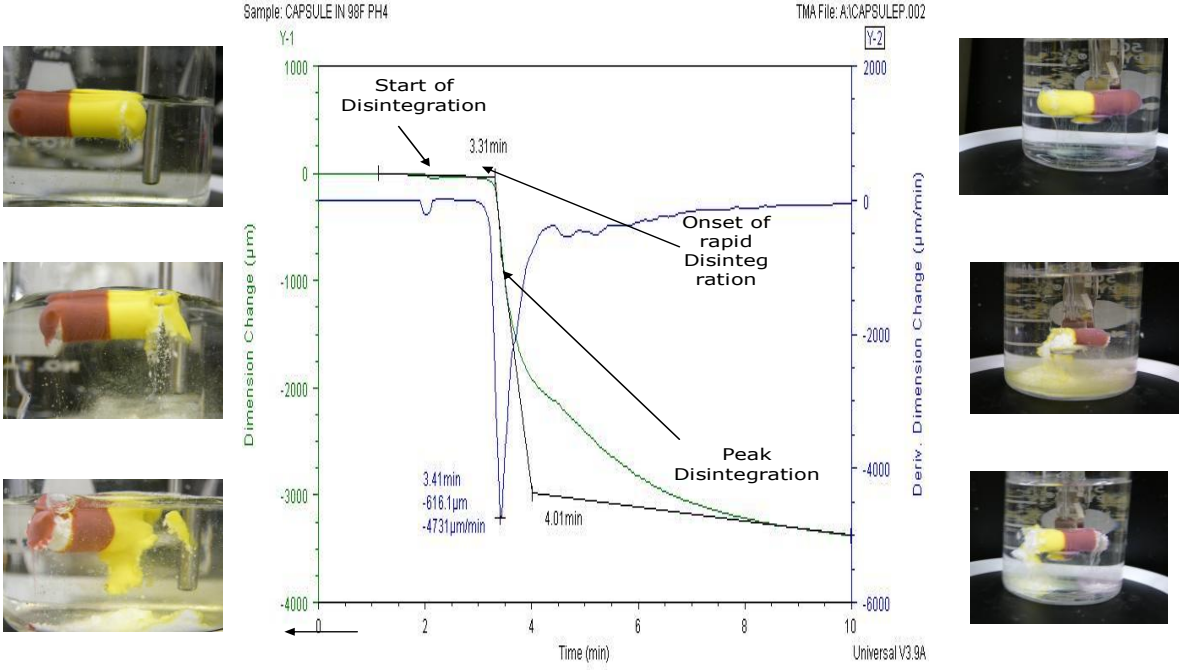


Figure 23: Drug Disintegration of Amoxicillin capsule and their corresponding photographs

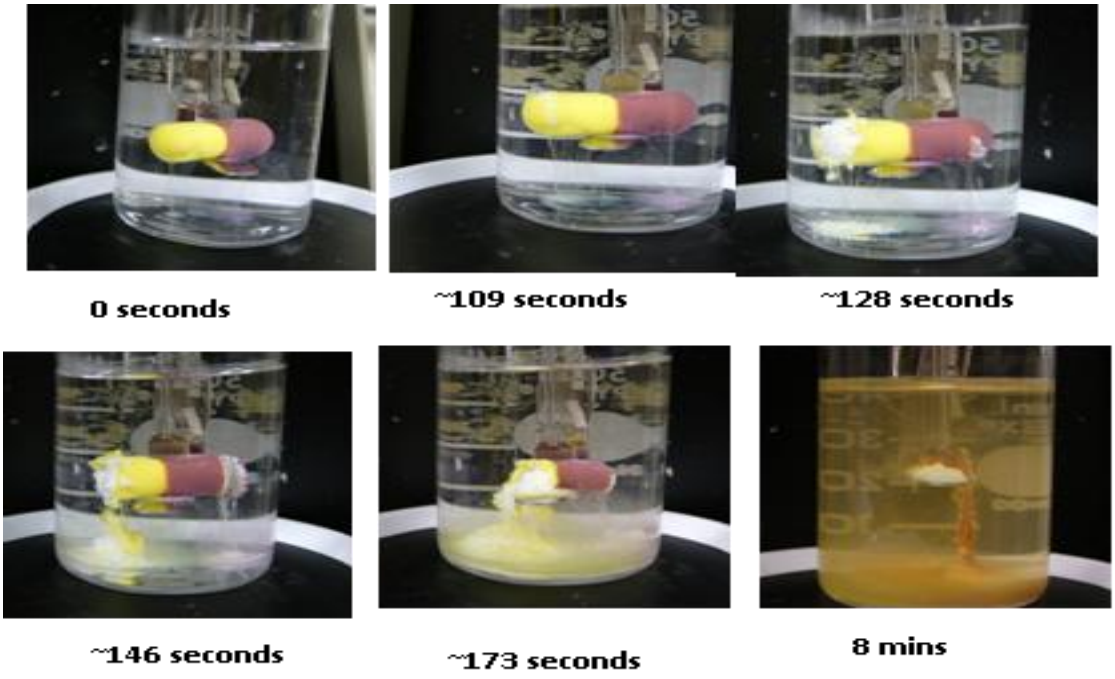
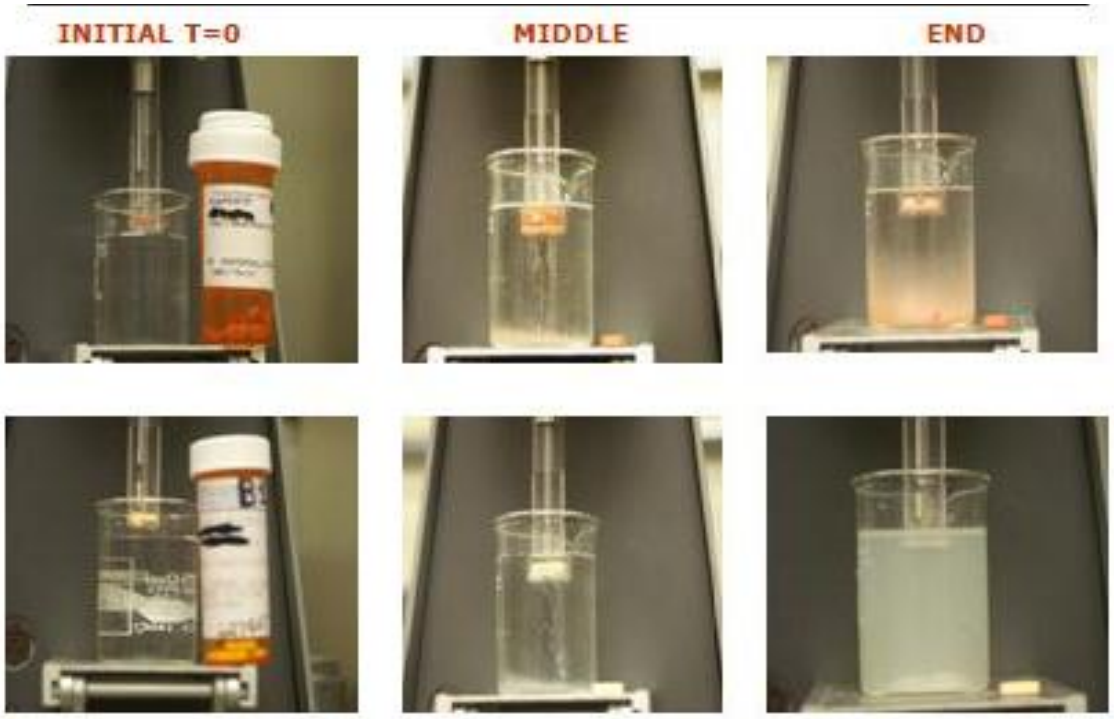


Figure 24: Photographic method of Risperdal



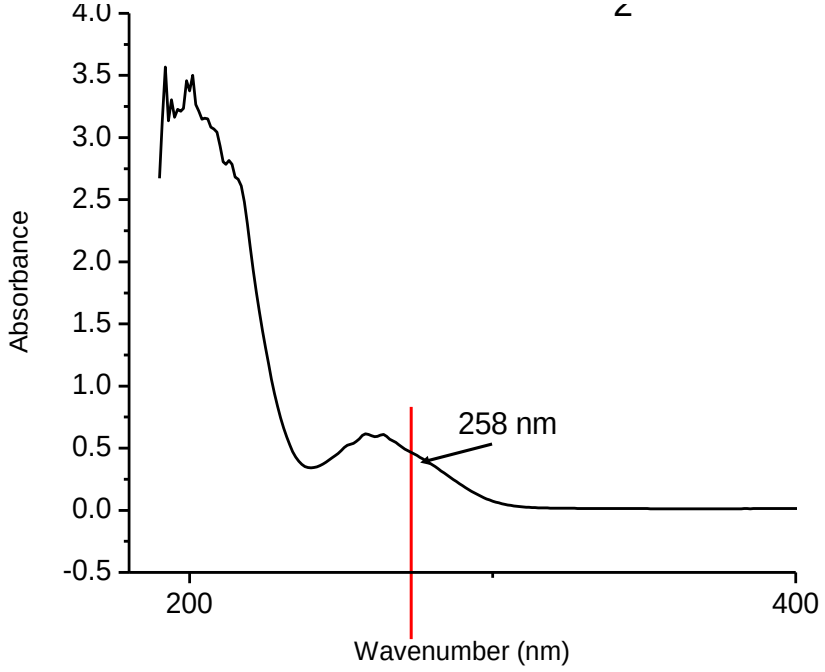


Figure 25: UV Analysis of Ritalin Tablet

Figure 26: UV ANALYSIS OF RISPERIDAL

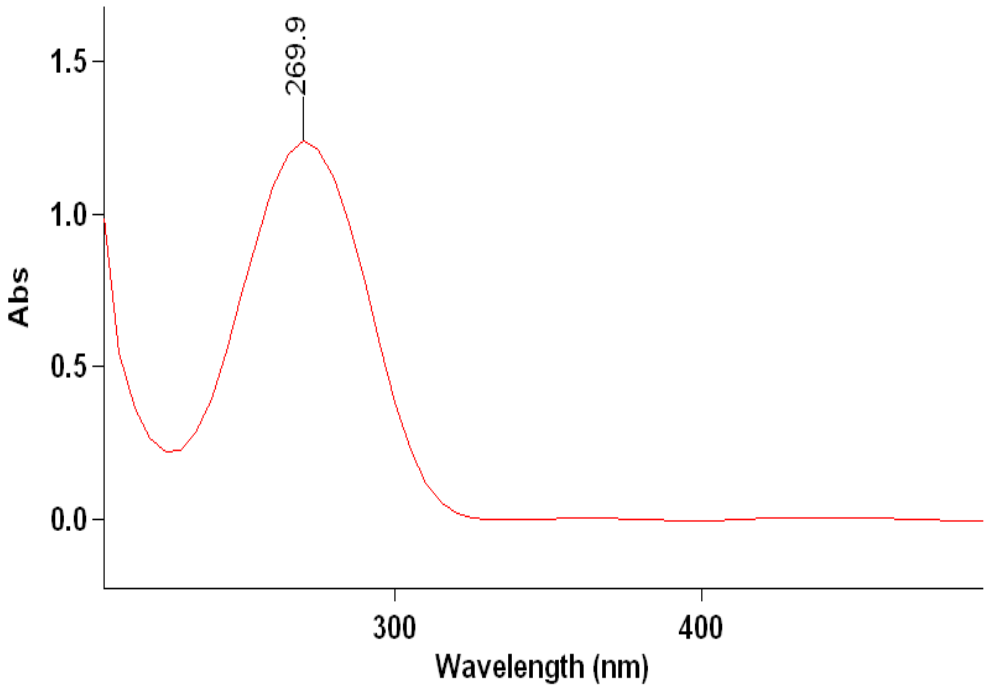


Figure 27: UV Anlysis OF Zyprexa Tablet

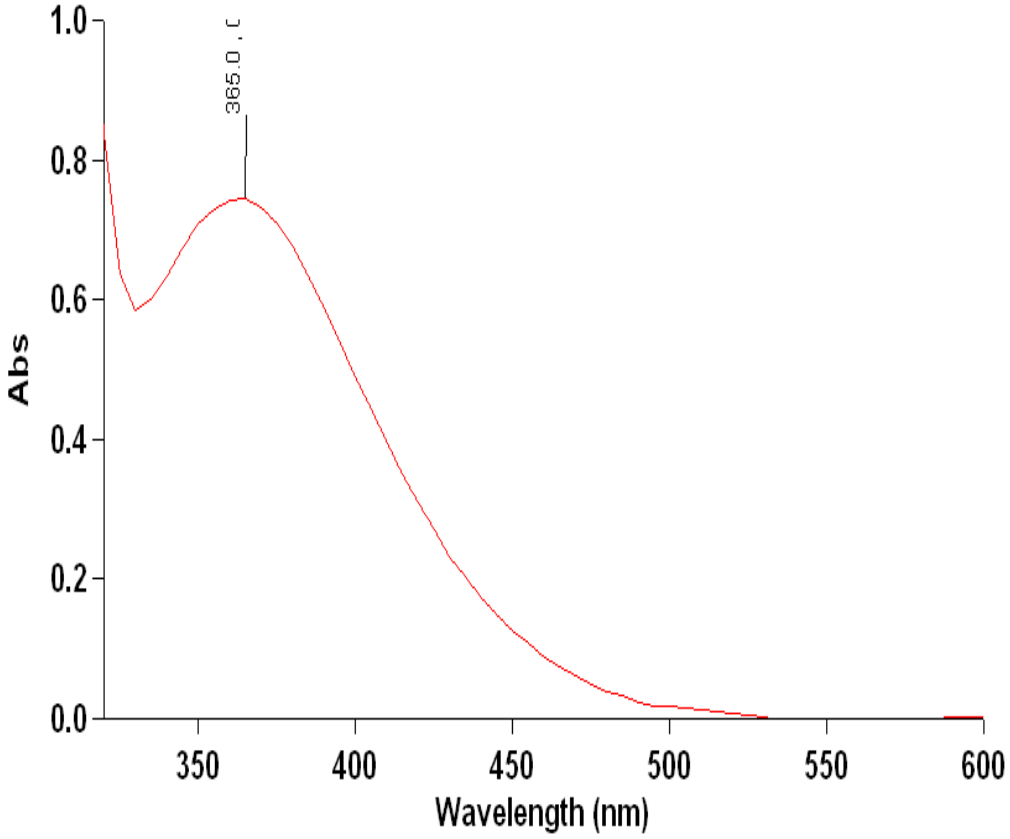


Table 1 Amoxicillin Capsules /precision of Disintegration behavior

TEST NUMBER	T final – T Initial	FASTEST DISINTEGRATION RATE (MICRONS/MIN)	TIME TO ACHIEVE FASTEST DISINTEGRATION RATE(SECONDS)
1	64	4100	150
2	42	4700	180
3	45	5900	150
4	45	5800	175
5	62	3500	160
6	46	5700	140
AVERAGE	51	4950	159
STD. DEVIATION	9	1007	16

Table 2: Comparison of drug disintegration of amoxicillin capsule by Iso tma and photographic methods.

TEST NUMBER	DISINTEGRATION ONSET/SECONDS (VISUAL/T1V)	DISINTEGRATION ONSET/SECONDS (TMA/T1T)	DISINTEGRATION COMPLETE (VISUAL/T2V)	DISINTEGRATION COMPLETE (TMA/T2T)	ΔTIME T2V-T1V	ΔTIME T2T-T1T
1	120	120	180	150	60	30
2	150	135	220	170	70	35
3	150	140	200	180	50	40
4	150	140	230	210	80	70
5	150	140	195	190	45	50
6	130	130	210	180	80	50
AVERAGE	142	134	206	180	64	46
STD. DEVIATION	13	8	18	20	15	14
% ERROR	9	6	9	11	23	30

Table 3: DISINTEGRATION TIMES OF AMOXYCILLIN CAPSULES

TEST NUMBER	SECONDS TO MAX. RATE pH=3	MAX. RATE MICRONS/MM pH=3	SECONDS TO MAX. RATE pH=4	MAX. RATE MICRONS/MM pH=4	SECONDS TO MAX. RATE pH=7	MAX.RATE MICRONS/MM pH=7
1	30	11000	33	9800	46	5700
2	38	10000	45	6000	64	4100
3	36	9100	42	6300	47	4700
4	32	7500	41	6500	45	5900
5	33	7100	38	6600	39	6200
6	30	7900	32	6800	45	5800
AVERAGE	33	8767	38	7000	48	5400
STD. DEVIATION	3	1533	5	1399	8	815
% ERROR	9	17	13	20	17	15

Table 4: initial and final drug disintegration of tablets and capsules and their target organ

DRUG	INTITIAL	FINAL	TARGET ORGAN	MAX DIS RATE mm/min
ABILIFY	1.49	17	STOMACH	2.0
AMANTADINE	8.63	26.75	STOMACH	-0.3
AMBIBN	3.7	8.8	STOMACH	2.4
AMOXICILLIN	3.2	8	STOMACH	0.18
COLDACT	2.9	44.14	INTESTINE	3.9
HALOPERIDOL	4.89	19.0	STOMACH	36.24
PAROXTINE	0.6	21.0	STOMACH	0.63
RISPERDAL	2.5	13.0	STOMACH	1.4
ROZEREM	.5	0.9	MOUTH	0.87
SERTRALINE	29.15	41.0	INTESTINE	191.04
ZYPREXA	.03	0.23	MOUTH	41.6
LEXAPRO	0.6	3.0	STOMACH	29.64

CHAPTER IV

RESULTS AND DISCUSSIONS

The IsoTMA results for capsules and tablets are shown in figures .

Abilify® (Aripiprazole) capsule at pH 7 and 24ºC immediately swells and then disintegrates over a period of 45-50 minutes (Figure 4). For this type Abilify 10 mg tablet the disintegration time is 3.5 min and rate of disintegration 1100 um/min is another form of Abilify described above the difference in disintegration is due to capsule vs tablet the tablet disintegrates quickly.

AMANTADINE Capsule (100mg) at pH 7 and 24^0C disintegrates and swells over a period of 25-30 minutes (fig). The disintegration peaks are noted at 6.6 min, 10.3 min, 18.1min these times reflect the dimensional change showing three distinct different times which have been corrected to starting time .

AMBIEN tablet 10 mg at pH 7 and temperature 24^0C disintegrates and swells over a period of 7-10 minutes (fig). The disintegration of the ambien tablet occurs 1.2 min followed by three distinct swelling curves at 2.7 min, 4.2min, 5.5min. their rate of initial

disintegration was 1200um/min. the average swelling time 2.7 in, 4.2 min, 5.5 min. the average swelling rate is 1300 um/min (932, 1470, 2400)

Amoxicillin: Amoxicillin capsule

COLDACT: Coldact capsule at pH 7 and temperature 34^0C swells and disintegrates slowly and again swells and disintegrates over a period of 40 -45 minutes (fig). Coldact capsule initially swells 3 min and 5min at a rate of 1300 and 3900um/min respectively. Further swelling characteristics are observed at 22min, 31min, 42min. there are no apparent disintegration no structural change of capsule the only observed change of capsule is swelling upto 42 min.

FEMHRT: Femhrt tablet 1 mg at pH5.5 and 7 and temperature 24^0C slight swelling at 0.2 min and 0.3 min in pH7 and mechanically collapsed at 0.3 min and was dispersed in acidified water in 0.5 min at ph 5.5 again the material swelled initially and disintegrated in 0.5 min. the acidified water accelerated the disintegration time frim 0.5 to 0.3 and the rate in ph 7 was 2500 and acidified water was 2400. The disintegration time is about 1 minute.

HALOPERIDOL: Haloperidol 5mg tablet at pH7 and temperature 24^0C initially it swells at 5min, with rate of 36mm/min. and after it disintegrates step wise at 9min, 10 min, and 16min over a period of 18-20 min and the average initial rate of disintegration was 10mm/min, 17mm/min 42um/min. we can see in figure

PAROXETINE.HCL: Paroxetine tablet 1000mg at pH 7 and temperature 24^0C swells slowly and then rapidly at 8-9 min the swelling rate is 64um/min. and swelled upto 23 min this swelling profile implies that the drug is being released not by structural collapse but by structural opening. The disintegration time of the Paroxetine is 20-23 minutes

RITALIN® (Methylphenidate.HCl) 10 mg tablet at pH 7 and 24^{o}C, on the other hand, did not swell but rather disintegrated stepwise over 32 to 96 minutes (Figure). The dimensional change and derivative (i.e. rate) curves show multiple stages of disintegration with three major derivative peaks at (1) 38 ±3 (2) 58 ±2 and (3) 82±2 minutes. The disintegration rates at 620 and 610um/min corresponding to these three major peaks and their standard deviations are (1) 2.1±0.6; (2) 2.8 ±0.8 and (3) 2.0±0.3 (microns/min).

RISPERDAL: Risperdal 0.5 mg and 2mg and 3mg tablets are used for disintegration at pH7 and temperature 24^{0}C

Risperdal 0.5mg tablet swells slowly at 2.5min with a disintegration rate of 173um/min and after it disintegrates step wise 5.7 min, 6.2min, 7.0min, 8.1min and the disintegration rates are 13mm/min, 17mm/min, 10mm/min, 7200um/min. and the average disintegration rate was 9900um/min. we can see in the fig

Risperdal 2mg tablet swells slowly at 2.5min, 3.15min. with a disintegration rate of 3088um/min 2439um/min and after it disintegrates step wise 4..7 min, 5.2min, 7. 5.9min and the disintegration rates are 4143um/min, 3652um/min, 2126um/min, 7200um/min. and the average disintegration rate was 4500um/min. we can see in the fig

Risperdal 3mg tablet swells slowly at 2.1min. With a disintegration rate of 1579um/min and after it disintegrates step wise 10.97 min, 12.42min, 15.27min, 16.24min and the disintegration rates are 1547um/min, 2642um/min, 15.1mm/min, 49.5mm/min and the average disintegration rate was 170mm/min. we can see in the fig

LEXAPRO: Lexapro 20mg tablet at pH7 and temperature 24^0C the tablet disintegrates at 0.63min with a disintegration rate of 35mm/min and swells at 0.83min with a disintegration rate of 26mm/min. we can see in figure (

SERTRALINE: Sertraline 25mg tablet at pH7 and temperature 24^0C the tablet swells at 29.6min,33min, 34.7min, 35.7min and disintegration rates are 191mm/min, 173mm/min, 87mm/min, 160mm/min and disintegration time are32.1min, 35.51min, 35.9minand the disintegration rates are 241mm/min, 89mm/min, 155mm/min.we can see in the fig

ROZEREM: Rozerem 8mg tablet at pH7 and temperature 24^0C disintegrates in step wise time interval of 0.12min, 0.15min, 0.18min, 0.22min and the disintegration rates are 1348um/min, 1500um/min, 1200um/min, 1100um/min. we can see in fig

ZYPREXA: Zyprexa tablet at pH7 and temperature 24^0C when we immerse the tablet in the medium it disintegrates so fastly less than 25 sec. we can see in figure

A comparison of capsule disintegration rates (microns/min) and peak disintegration times (min) at different pH (=3, 4, and 7) is shown in figure10. The derivative rate curves indicate multiple disintegration processes. The fastest disintegration time was associated with pH 3 and the slowest time with pH 7. At pH=7, with the longest disintegration time, the fastest dimensional rate of change was 9.8 mm/min after 3.1 minutes. At pH=4, the fastest rate was 9.1 mm/min after 2.7 minutes. At pH = 3, there are two derivative peaks at 6.6 mm/min after 2.6 min and 4.3 mm/min after 3.3 min. This double peak may be related to two different processes of disintegration at lower pH including the dissolution of the gel capsule and the delivery of the drug into the surrounding fluid. The pH dependence is related to the structure of the gel capsule and the disintegration of the API and any excipients.

Figure 9 is a comparison of Amoxicillin gelatin capsule dimensional change rates and fastest disintegration times as a function of temperature; 25, 32 and 37°C at pH=7. The room temperature maximum disintegration rate is 7.0 mm/min at 55 minutes. The maximum rate at 32°C is 8.1 mm/min after 6.3 minutes. At 37°C, the maximum rate is 9.9 mm/min after 2.8 minutes. Clearly temperature has a significant effect on the disintegration of the capsule.

Some other factors to be considered in a future study are residual stresses in the gel capsule ends, the uniformity of the gel capsule as a whole, and the particle size of the API.

Statistical analysis of the IsoTMA disintegration of Amoxicillin in a solution of pH 7 at 37°C is summarized in Table 1. Statistical analysis of the values determined by a photographic and the TMA methods are summarized in Table 2.

Comparisons of the IsoTMA and the optical photography behaviors of the capsule at pH 4 and 37°C are show in Figure 25. The initial, midrange and final disintegration times can be visualized from 1.7 min (100 sec) to 8.0 min (480 sec).

CHAPTER V

CONCLUSIONS

The IsoTMA protocol yields direct information on formulated drug delivery. Some tablets disintegrate rapidly in less than two minutes, corresponding to oral dissolution. Others disintegrate over a period of forty to ninety minutes, corresponding to gastric or intestinal dissolution. The disintegration times as determined by using the IsoTMA method can aid in designing a drug delivery target. The disintegration rate for capsules significantly depends on the temperature and pH of the dissolving fluid. The percent relative error for IsoTMA disintegration rates for both capsules and tablets is about 20%. One possible reason for the TMA error might be the difficulty in consistent probe placement due to the convex surface of many tablets. Another reason might be the embossed logo on the pill causing variations in IsoTMA behavior. We are currently assessing these problems with a variety of tablets. We are also evaluating the behavior of formulated tablets with longer disintegration times, tablets with minimum curvature and imprinted logos and possibly applying higher stress to fix the tablet in place while being submersed in the in vitro fluid. Another possible improvement in IsoTMA precision

could result from increasing the contact surface area of the quartz probe by using a wider diameter rod.

CHAPTER VI

FUTURE STUDIES

- Instrumentally improve the probe contact area for the fully formulated drugs
- Evaluate class 1 drugs(anti arithmetic drugs or cardio vascular drugs)
- Determine disintegration properties by micro Calorimetry and compare with IsoTMA test
- Implement Iso TMA test for drugs synthesized in medicinal chemistry.
- Study the effects of a number of known disintegrant on formulated drugs prepared in our laboratory**.**

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