An- Najah National University

Faculty of Graduated Studies

DESIGN, FORMULATION AND ANALYTICAL METHOD DEVELOPMENT OF CYCLOBENZAPRINE AND PARACETAMOL TABLET

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Dedication

All praise to Allah, with great respect and prayers through the days to help me to go forward in all difficulty every day a head.

To the woman whom is like no other, she gave me life, held me and loved me unconditionally, to my affectionate Mother “Sanaa”, to the person who is my hero in the life who is giving without stop, be with me in all steps and stand me in the life up, the most important person in my life, my Father “Abd-Alraoof”. To my lovely supporting family and my loyal best friend.

Acknowledgment

At the beginning, all thanks to Allah for guiding me through every stage of this work, without his blessing it couldn't have been accomplished the way it's today.

To my beloved parents, my brothers and sisters, to my family and best friends for supporting me spiritually throughout my life.

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Declaration

I, the undersigned, declare that I submitted the thesis entitled:

DESIGN, FORMULATION AND ANALYTICAL METHOD DEVELOPMENT OF CYCLOBENZAPRINE AND PARACETAMOL TABLET

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: _____

Signature: _____

Date: _____

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ABSTRACT

Background: Cyclobenzaprine HCl is a muscle relaxant, and Paracetamol is a pain relief drug. There are many indications for the co-administration of both medications. The aim of this project was to formulate and evaluate the stability of a novel tablet containing Cyclobenzaprine HCl and Paracetamol together. Moreover, a new fully validated and stability indicating HPLC method was developed to test the stability of the obtained product.

Method: The Cyclobenzaprine HCl and Paracetamol novel tablet formula was optimized and selected according to several critical quality attributes (CQAs), including assay, content uniformity, dissolution, and degradation profiles. Method development it's validation included linearity and range, accuracy and recovery, precision, specificity and stress conditions. Moreover, tablet stability was evaluated after 3 and 6 months under different storage conditions. A pilot study was conducted among doctors and patients to evaluate their opinions and acceptance of this combination.

Results: Successfully formulated tablets, including 5 mg Cyclobenzaprine and 500 mg Paracetamol, were uniform in weight, with an average tablet weight of 650 mg. All product quality parameters were within specifications, including those for critical and non-critical quality attributes. A fully validated and stability-indicating method was established for assay and dissolution testing. The developed method exhibited high linearity with an R2 of more than 0.98 precision with a relative standard deviation of less than 2% and an accuracy result of between 98.0 and 102% for Cyclobenzaprine HCl and Paracetamol. The prepared Cyclobenzaprine HCl and Paracetamol tablets showed excellent stability over 6 months. The findings of the pilot field study provided insight into the acceptance of the combination of both drugs by doctors and patients.

Conclusion: Cyclobenzaprine HCl and Paracetamol tablets were successfully formulated and showed an acceptable stability profile. The developed and validated HPLC method was suitable for the characterization and assessment of the formulated tablets. The novel combination is likely to be accepted by doctors and patients.

Key words: Cyclobenzaprine, Paracetamol, Formulation, Validation, Tablets.

Chapter One

Introduction and Theoretical Background

1. Introduction

1.1 Pharmaceutical dosage forms

Pharmaceutical dosage forms are drug products composed of a single or a combination of Pharmaceutical Active Ingredient/s (APIs) and a group of inactive ingredients (excipients) available in the pharmaceutical market to serve dosing, administration and delivery according to patients' needs (1, 2).

All steps regarding formulation, design, processing, evaluation, and achieving high target finished product quality (chemically, physically, biologically and route of administration) are important (3).

Pharmaceutical dosage forms can be classified according to their route of administration such as: parenteral, mucosal, inhalation, topical/dermal and gastrointestinal or according to their pharmaceutical dosage form such as: aerosols, capsules, creams, foams, gels, ointments, tablets, suppositories, lozenges, suspensions, injections and sprays…etc, or according to their release pattern such as: immediate release and modified release which may include: delayed release or sustained release, ..etc. (4-7)

1.2 Oral tablets

Tablets are the most frequent and favorable route of administration of solid dosage forms; which offer the patients drug stability and dosing reproducibility. Some tablets are swallowed whole as it is; others can be chewed before swallowing, some are dispersed or dissolved in water before administration, while some allows liberation of active substance by retaining it in the mouth (8). Tablets are single dose compose of one or more of active materials, obtained by using a suitable manufacturing technique to compress a uniform volume of particles with excipients; that act as binders, diluents, lubricants, fillers, disintegrating agents, glidants, behavior modifiers, coloring agents… etc. Tablets can be produced in different sizes and shapes. Classified into immediate release and modified release if a change in release rate is made (4).

Several techniques combining art and science can be used in order to produce tablets that have specific odor, taste, shape, release pattern and function (1, 8, 9). Tablets can be categorized into: (coated tablets, uncoated tablets, gastro-resistant tablets, soluble tablets, modified release tablets, effervescent tablets, dispersible tablets, oral dispersed tablets, oral lyophilisates and chewable tablets) (1).

In addition to the APIs, tablets contain excipients. Excipients are needed to bulk the actives, to help in compression or to modify the biopharmaceutical properties of the tablet. Examples to add bulk fillers are used, granule and compact. Formation needs binders to allow tablet to break down in the body fluid, disintegrants are used for dissolution particularly for hydrophobic API, wetting agents are need to reduce the friction between powder and dies, lubricants are used, anti-adherents prevent sticking between powder material and surfaces of the compression tooling, for good powder flowability glidants and fillers are needed which can modify the API release from the tablet. All these excipients can work to affect properties of the final tablet and compression. (10)

1.3 Pre-formulation and formulation

Pre-formulation is considered as the first step to be followed for sensible dosage forms development; by which total investigation of the drug substance properties (Physical, Chemical) and its compatibility with excipients is made (11). Pre-formulation aims mainly to give well prospective of stable dosage forms with good bioavailability that can be also manufactured in large scale. To make a successive pre-formulation program, corporation of experts of different disciplines is needed. The pre-formulation program starts with the assessment of the organoleptic properties of the new drug (odor, color & taste), purity of the drug substance, chemical and physical properties of the drug substance which is affected by the particle size distribution, particles shape, solubility, dissolution and determining the parameters that will affect absorption of the drug substance, polymorphism etc. (11).

Formulation based on Quality by Design (QbD) is a risk assessment-based approach used to develop both brand and generic products. This approach depends mainly on defining the quality target product profile (QTPP) according to drug substance characteristics, reference listed drug (RLD) properties and label, in addition to the

patients targeted by this developed product. QTPP can be achieved by defining the critical quality attributes (CQA) based on the safety and efficacy of the product delivered to the patients (12).

Employing QbD approach parameters in any proposed formulation may help in establishing a quality control strategy of manufacturing parameters and changes, which produce\s a product with high quality monitored during its lifecycle based on risk assessment (12).

1.4 Quality control of tablets

Formulated tablets should be evaluated to guarantee an effective dosage form within the accepted requirements. Evaluation is typically done via several physical and chemical testing (13, 14), which include but not limited to,description, identification, assay of active ingredient, uniformity of dosage units, hardness, friability, dissolution, and disintegration.

1.5 Stability testing

Stability means the extent or the level to which the drug product or drug substance remains within approved specifications throughout its storage period (15). The main aim of stability testing is to give obvious evidence of drug substance or a drug product behavior under the influence of several environmental factors with time and how it may impact its quality of the pharmaceutical formulation.

Stability testing is considered as a mandatory requirement for pharmaceutical dosage forms as it helps in avoiding any ingredient or condition that causes chemical decomposition and/or physical or microbiological deterioration of the drug products or materials. Stability testing includes determination of the content of active ingredient, degradation products, physical properties and appearance, in addition to other properties such as (moisture content, hardness, friability, dissolution, and disintegration). According to these parameters, stability is classified into five types: (chemical, physical, microbiological, therapeutic and toxicological). The main environmental parameters that influence the drug stability are exposure to adverse temperature, excessive humidity, light, oxygen etc. (15).

Stability is considered as an important evidence of the drug product or a certain formula quality variation under different environmental factors (as temperature and humidity) with time and it is an important tool in establishing the shelf life or retesting period of the drug product and its most appropriate storage conditions (14).

Testing conditions are selected according to the climatic zone for each country. But the general case is listed in Table (No.1).

Stability general storage conditions were attached in Appendix A table 1.

1.6 Validation

Analytical method is a description of the detailed steps of how to perform tests for evaluating the drug product quality (13, 16). Validation of analytical method is intended to prove that it is suitable for the intended purpose. It includes full assessment of the sample, reagents, apparatus, standards, analytical conditions, preparation, changing analyst, and even the time of preparation (17).

Validation parameters including: Specificity /Selectivity, Accuracy, Precision, Linearity, Range, Robustness and Stress Conditions (17).

- Accuracy: is the measure of closeness of measured value to the true value at a prescribed condition.

- Precision: is the measure of closeness of a series of measurements at prescribed conditions. It is measured in three levels (repeatability which expresses precision at the same operating conditions during short time, reproducibility which means precision between laboratories, and intermediate precision which means precision within laboratory variations as different analysts and days).

- Linearity: it is the ability of method to give direct proportional response to concentration, which expressed by using linearity regression Coefficient (R^2).

- Range: is the interval between upper and lower limits of concentrations or amounts of the sample analyte which achieves suitable levels of accuracy, precision, and linearity within these limits.

- Robustness: it is the ability of method to be unaffected by small and deliberate changes of conditions and parameters under normal conditions(17).

- Selectivity and Specificity: it is the measure of procedures ability to assess the effect of components on the analyte, these components might be impurities, degrades, or matrix. It is determined by chromatographing the matrix and solvents rather than the analyte.

- Limit of Quantitation (LOQ): It is the lowest amount of analyte in a sample that can be determined with acceptable Precision and Accuracy under the stated experimental conditions.

- Limit of Detection (LOD): It is the lowest amount of analyte in a sample that can be detected with confidence and distinguished from noise/baseline, but not necessarily quantitated, under the stated experimental conditions (16, 17).

- Stress testing of the drug substance helps in potential degradation products identification, that helps in establishing the degradation pathway. It is also used as a tool for indicating power of the used analytical procedures(18). Stress testing includes effect of high temperatures above that of the accelerated conditions, humidity, oxidation, photolysis and evaluation of hydrolysis over a wide pH range (acidic and basic) conditions (19).

Any change in the analytical procedure, drug substance synthesis and composition of finished product; needs revalidation. However it depends on the change degree and its nature (13, 20).

1.7 Muscle relaxants & Analgesic

Low back pain is associated with considerable suffering and disability linked to a range of symptoms, including tingling or burning, dull ache, sharp pain, and weakness in the legs or feet. Back pain is among the most common reasons patients visit their primary care physicians. A plethora of effective treatment options are available. (21)

These range from pharmacologic measures (eg, analgesics, anti-inflammatory medications, muscle relaxants and steroid injections) to non-pharmacologic approaches (eg, bed rest, massage therapy, exercise, application of heat or ice, acupuncture and spinal manipulation). (21, 22)

Analgesics such as Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) have often been used as first-line agents for controlling the symptoms of low back pain which should be taken at the maximum anti-inflammatory dose (ie, ibuprofen 600-800 mg TID, for more than two weeks). Cyclooxygenase (COX)-2 selective inhibitors do not offer analgesic benefit over traditional NSAIDs and are indicated only for patients at risk for gastrointestinal bleeding. (21)

Although analgesic pain management may be the treatment of first choice, relief from low back pain may also require alleviation of muscle spasm with oral muscle relaxants. Muscle relaxants as (Carisoprodol, orphenadrin, cyclobenzaprine hydrochloride, and metaxalone) can be used as monotherapy or in combination with analgesics for patients with low back pain.(21)

Paracetamol and Orphenadrine combination as a muscle relaxant combined with analgesic drug available as oral tablet under the trade name (Relaxone tablet, Beit jala pharmaceutical) is used to relieve pain and stiffness caused by muscle strains and sprains. In fact it is indicated for the relief of severe skeletal muscle spasms associated with painful conditions such as low back pain, sprains and strains.

Skeletal muscle relaxants are a heterogeneous group of medications commonly used to treat two different types of underlying conditions: spasticity from upper motor neuron syndromes and muscular pain or spasms from peripheral musculoskeletal conditions (23).

Common musculoskeletal conditions causing tenderness and muscle spasms include fibromyalgia, tension headaches, myofascial pain syndrome, and mechanical low back or neck pain. If muscle spasm is present in these conditions, it is related to local factors involving affected muscle groups. These conditions are commonly encountered in clinical practice and can cause significant disability and pain in some patients. Skeletal

muscle relaxants are one of several classes of medications frequently used to treat these conditions (23).

Benzodiazepines like tetrazepam are used as anxiolytics, hypnotics, sedatives anticonvulsants or skeletal muscle relaxants. Generally there is no evidence that any one benzodiazepine is more effective than another if enough dosage is taken; as a result, pharmacokinetic differences between the drugs may be important considerations in prescription choice.(24)

Non-benzodiazepines include a variety of drugs like Cyclobenzaprine that can act at the brain stem or spinal cord level.(24)

Cyclobenzaprine hydrochloride has been recommended as an adjunct to rest and physiotherapy for the relief of muscle spasm associated with acute, painful musculoskeletal conditions. At therapeutic doses, the compound does not affect central nervous system (CNS) function. As a result, it depresses motor neuron hyperactivity without significant ataxia and is ineffective in muscle spasm caused by CNS disease (23).

Cyclobenzaprine is in a class of medications called skeletal muscle relaxants. It works by acting in the brain and nervous system to allow the muscles to relax. Cyclobenzaprine is used for short time together with rest and physical therapy to treat skeletal muscle conditions such as pain or injury (25).

Chemically defined as N, N- dimethy l- 3- (2- tricycle [9.4.0.03,8] pentadeca-1(15),3,5,7,9,11,13-heptaenylidene) propan-1-amine (26).

Cyclobenzaprine is a centrally acting skeletal muscle relaxant with antidepressant activity. The exact mechanism of action of cyclobenzaprine has not been fully determined, but this drug seems to primarily act at the brain stem to reduce tonic somatic motor activity, influencing both gamma and alpha motor neurons leading to a reduction in muscle spasms (26).

Cyclobenzaprine blocks tonic α-motoneuronal excitation produced by serotonergic descending neurons. The blockade of 5-HT 2 receptors to be the major action of cyclobenzaprine as muscle relaxant. (27)

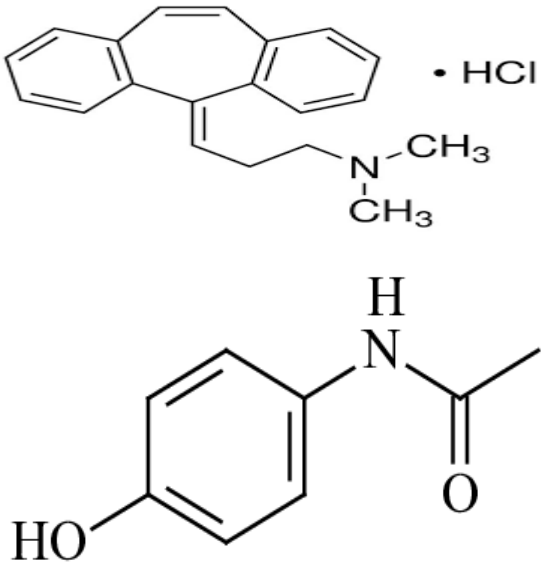
The oral bioavailability of cyclobenzaprine has been estimated to be between 0.33 and 0.55. maximum concentration (C_{max}) is between 5-35 ng/mL and is achieved after 4-hours maximum time (T_{max}). AUC over an 8-hours dosing interval was reported to be approximately 177 mg.hr/mL. Orally administered Cyclobenzaprine HCl is well absorbed. Cyclobenzaprine HCl undergoes enterohepatic circulation, and appears to be metabolized by both oxidative and conjugative pathways during its first pass through the gastro intestinal (GI) tract and/or liver. Mean oral bioavailability of the drug is estimated to range from 33-55% (26).

The common Cyclobenzaprine HCl oral tablet side effects may include: drowsiness, tiredness, headache, dizziness, dry mouth, upset stomach, nausea, constipation (28).

The following figure show the chemical structure of Cyclobenzaprine HCl:

Figure 1

Cyclobenzaprine HCl (A) & Acetomenophine (B) chemical structures



Acetaminophen (Paracetamol) is the most commonly used analgesic worldwide and is recommended as first-line therapy in pain conditions by the World Health Organization (WHO).

It is also used for its antipyretic effects, helping to reduce fever. This drug was initially approved by the United States food and drug administration (U.S. FDA) in 1951 and is available in a variety of forms including syrup form, regular tablets, effervescent tablets,

injection, suppository, and other forms. Acetaminophen is often found combined with other drugs in more than 600 over the counter over the counter (OTC) allergy medications, cold medications, sleep medications, pain relievers, and other products (26).

Chemically defined as N-(4-hydroxyphenyl) acetamide & molecular formula is C8H9NO2 (26).

Acetaminophen is mainly metabolized in the liver by first-order kinetics, about 80-85% of the acetaminophen in the body undergoes conjugation principally with glucuronic acid and to a lesser extent with sulfuric acid. Overdoses of acetaminophen can lead to hepatic necrosis due to the depletion of glutathione and of binding of high levels of reactive metabolite (NAPQI) to important parts of liver cells (25, 26).

Acetaminophen has 88% oral bioavailability and reaches its highest plasma concentration 90 minutes after ingestion. Peak blood levels of free acetaminophen are not reached until 3 hours after rectal administration of the suppository form of acetaminophen and the peak blood concentration is approximately 50% of the observed concentration after the ingestion of an equivalent oral dose (10-20 mcg/mL) and it is rapidly and almost completely absorbed from the GI tract following oral administration (26).

The following figure shows the chemical structure of Paracetamol:

1.8 Significance of the study

The main aim for any formulated drug is patient. The idea was to design a tablet that contains two active ingredients in the same tablet core instead of taking two tablets separately; this may be easier for the patient and improve compliance with treatment. Paracetamol and Orphenadrine Citrate is the only formulation on the market that contains both paracetamol and a muscle relaxant. The combined is used to improve patients compliant especially the elderly patients & pregnant women as a safe drug for them and which is good as to have a rapid result from the drug as analgesic then as muscle relaxant and patient & companies will save money when they found these drug. The suggested formulation in this study includes paracetamol and cyclobenzaprine HCl.

Because this formulation was not available in our marker, we needed to develop and validate an analytical method

1.9 Objectives of the study

The aim of this project is to formulate and evaluate novel combination of Cyclobenzaprine HCl and Paracetamol (oral tablet).

Specific objectives

1. Formulation and examination of the mixed powder compressed tablet drug.
2. Development and validation of analytical method to be used for testing the active ingredient in the product (Assay).
3. Full assessment of the finished product characterization and specifications for all physical and chemical parameters.
4. A pilot study questionnaire to collect doctors' and patients' perspectives regarding combining Paracetamol and Cyclobenzaprine HCl into a single tablet.

Chapter Two

Method

2. Materials & Method

2.1 Materials and reagents

pharma grade Cyclobenzaprine HCl raw material (Vasudha manufacturer, India) was provided by Pharmacare PLC (Ramallah, Palestine) and Paracetamol (merck manufacturer, Germany) from the An-najah University laboratories. Cyclobenzaprine HCl (Xaprine 5 or 10 mg) and Paracetamol (Panadol 500 or 1000 mg) products found in the Palestinian pharmaceutical market were used. Solvents such as Acetonitrile, Water and Methanol (were provided from the university and Dana Pharm, provided from Honeywell (USA, HPLC grade). Other reagents and chemicals used in this study; sodium starch glyconate, magnesium stearate and Avicel 101 were from Pharmacare PLC. Ammonium acetate (sigma Aldrich manufacturer), sodium hydroxide (Gadot manufacturer) and acetic acid (Gadot manufacturer) were provided from the university and Dana Pharmaceutical Company.

2.2 Instruments

High-performance liquid chromatography

High-performance liquid chromatography (HPLC) is an instrument used to analyze material using analytical method to distinguish, separate and quantify each ingredient in a mixture. The system of HPLC used in this study is Hitachi Lachrom Elite HPLC, with (2 - 4.6) mm internal diameter, columns for liquid chromatography (LC) and flow-rate range of (0.00 -10.00) mL/min in 0.01 mL increments, column temperature in the range of (20 – 60) °C was controlled using attached column heater.

Dissolution apparatus

Dissolution tests were performed to determine the rate and extent of drug release from prepared drug formulations. Dissolution tester (Hsiang Tai machinery industry, Taiwan, China) was used in all dissolution testing. Dissolution Apparatus 2 Paddle with six vessels each of them filled with 900 ml of dissolution media was used. Paddle speed was fixed to 50 rpm. The quantity of dissolved API(s) was determined using UV visible

spectroscopy (Shimadzu, Japan, UV 1280 spectrophotometer) which offers 190-1100 nm wavelength scanning.

2.3 Formulation development and optimization

The work plan includes the determining all physicochemical properties of Cyclobenzaprine HCl and Paracetamol mixed powder tablets and performing all required pre-formulation studies. Cyclobenzaprine HCl and Paracetamol mixed powder tablets were formulated by using fixed dose of Cyclobenzaprine HCl 5 mg/tablet and 500 mg/tablet of Paracetamol. Pharmaceutical excipients were selected based critical quality parameters and required final specifications of the oral tablets. Types and quantities of excipients were determined based on their compatibility and typical used levels for each with optimization. Tablets were produced using direct compression technique. Physical properties, hardness, dimensions of tablets, appearance and friability were tested for the obtained oral tablets.

2.4 Establishing stability indicating method

Stability indicating method relied on assay test of Cyclobenzaprine HCl and Paracetamol drug substance using stress conditions for drug degradation as listed in ICH and USP.

The degradation of tablet was demonstrated using: Acid Degradation (1M HCl), Base Degradation (1M NaOH) & Oxidation (3% H_2O_2) (16)

2.5 Method

2.5.1 Preformulation

Prior to processing, powder properties were determined by measuring the powder inter-particulate interactions (14).

Bulk Density

Mass of powder taken (m) and volume of untapped powder (Vi) were measured to calculate: Bulk density = m/Vi

Tapped Density

Mass of powder (m) Tapped volume (Vt) were measured to calculate:

Tap density = m/Vt

Compressibility Index

$$Compressibility\ Index = \left(100 \times \left(\frac{\rho\ tapped - \rho\ bulk}{\rho\ tapped}\right)\right)$$

Hausner Ratio

$$Hausner\ Ratio = \frac{(\rho\ tapped)}{\rho\ bulk} = \left(\frac{0.504}{0.346}\right) = 1.457$$

The flow ability scale of the powder with Hausner ratio were attached in appendix A table 2.

Water Content/LOD Determination

Water content/LOD of the API and each excipient used in the formulation was tested according to its testing procedure in the pharmacopeias (11); as illustrated in Table (3) in appendix A.

Excipients and APIs Compatibility

A high-quality, safe, and effective drug product is the main target of any formulation. Not only during manufacturing, but also after long-term use; to ensure this before beginning the formulation, a compatibility study between API and excipients is recommended, which is considered a limiting step in any successful formulation and ensures that no impact of any used excipient on the API characteristics and properties, because any change in appearance, quantitative parameters, physical and chemical properties gives evidence of a lack of opacity. This, in turn, leads to risk and a direct impact on the product's quality and safety.

Intended used excipients were mixed with API in optimized quantities (as listed in Table 4 Appendix A) and stored at 40°C and 75% RH for 30 days, and then every portion was analyzed for appearance, flowability and assay (using Assay Method).

2.5.2 Preparation of the formulation (Optimized Formula)

After thoroughly testing the compatibility, physical and chemical properties, function, and test/odor characteristics of each component of the formulation, we evaluated mixtures. Many formulation trials were initiated to reach the best one.

2.6 Pharmaceutical Quality Control

The prepared tablets were visually inspected for general appearance such as shape, color, or any other physical defect. In addition, to assure pharmaceutical quality of the tablets other pharmacopeial quality control tests were performed including friability of tablets, hardness of the tablet, weight uniformity, assay, disintegration time and dissolution.

I. Assay

Assay of tablet product was assessed according to USP monographs. In-house method trial done at the university and Dana Pharm Company for drug analysis was employed in this research under their permission.

T Mobile phase composition, mobile phase gradient, wavelength, column and flow rate were the parameters that were optimized to reach the following final method of analysis.

The final used test method

Mobile phase: a mixture of 650 ml of buffer (11.4 g/L ammonium acetate in water with pH adjustment to 7.2 using ammonium hydroxide) and 350 ml methanol then it was filtered through 0.45 micro membrane filtered.

Diluent: same as mobile phase.

Standard preparation:

Standard solution 1: an accurate weight quantity in 100 ml volumetric flask (VF) of 500 mg Cyclobenzaprine HCl WS was dissolved with diluent to 100 ml.

Standard solution 2: an accurate weight quantity in 100 ml VF of 50 mg Cyclobenzaprine HCl WS was dissolved with diluent to 100 ml.

Standard solution: dilute 1 ml of standard solution 1 and 10 ml of standard solution 2 in 100 ml with diluent to obtain a concentration of 0.005 mg/ml of Cyclobenzaprine HCl and 0.5 mg/ml of paracetamol, stir and filtrate with 0.45 µm syringe filter.

Sample preparation: transfer not less than 10 tablet to a suitable mortar to crush into a powder, transfer accurately amount of powder equivalent to weight of one tablet to 100 ml VF and dilute to 100 ml with diluent, stir for 10 min to dissolve to prepare sample stock solution. Dilute 10 ml of sample stock solution to 100 ml with diluent to obtain a concentration of 0.005 mg/ml of Cyclobenzaprine HCl and 0.5 mg/ml of paracetamol, stir and filtrate with 0.45 µm syringe filter.

Chromatographic system:

Column: C8 (Octyl) HPLC Column 25cm x 4.6mm 5µm, L7, Column temperature: 30ºC, Detector wavelength: 226 nm, Flow rate: 1 ml/min, Injection volume: 15 µL.

The percentage of the Cyclobenzaprine HCl & Paracetamol content in the tablet compared to the standard was measured using the following equation:

$$\%Asssy = (''r_t'' / ''r_s'')*(''C_t'' / ''C_s'')* \text{STD Potency} *100$$

Where:

r_t: sample solution Peak area response.

r_s: standard solution peak area response.

C_s: standard solution concentration (mg/ml).

C_t: sample solution concentration (mg/ml)

II. Weight uniformity test

To evaluate the weight uniformity of tablets, 20 tablets were randomly picked out and weighed individually using an analytical weighing balance. The average weights for each product and the percentage relative standard deviation were calculated according to USP test of weight uniformity.

III. Hardness and friability

To assess the crushing strength of tablet products the hardness test performed, 10 formulated tablets were randomly selected to measure the hardness using the hardness tester.

IV. Disintegration

To assess the disintegration time of tablet, 6 tablets were placed in a disintegrator which consists of a basket with 6 tubes. The basket loaded with the tablets was immersed in a bath of water and the temperature was 37°C. The disintegration time of the tablets was noted when it completely disappeared (disintegrated) and no stacked particles were left on the mesh of the basket of the disintegrator.

V. Dissolution

The dissolution of tablet products calculated by preparing a standard solution which was used to establish the different products dissolution profile, 0.0055 mg/ml of cyclobenzaprine and 0.55 mg/ml of paracetamol were prepared in dissolution medium acetate medium (acetate buffer, pH 4.5 per one litter dissolve 5.9 g of sodium acetate and 7.4 ml of Acetic acid and pH adjust with sodium hydroxide). To prepare the sample solution, six tablets were tested using USP Dissolution Apparatus 2 Paddle, 900 ml of dissolution medium was added to each vessel and the temperature was maintained at 37 ± 0.5 °C. One tablet was placed in each of the dissolution vessels with a paddle stirrer at 50 rpm. At the end of 30 minutes, sample aliquots (5 ml) were withdrawn from a zone, filtered using a 0.45 µm filter syringe. The filtered sample was tested in comparison with standard by ultra violet (UV) spectroscopy at wavelengths of 290 nm and 250 nm for Cyclobenzaprine HCl and Paracetamol, respectively.

The percentage of the content in the pharmaceutical products compared to the standard was calculated using the following equation:

$$\% \text{ Recovery} = (A_T/A_S)*(C_T/C_S)* \text{ STD Potency } (\%)$$

A_T: Sample solution absorption.

A_S: Standard solution absorption

Cs: Standard solution concentration (mg/ml).

C_T: Sample solution concentration (mg/ml).

2.7 Validation of Assay

The following validation tests were performed (16), the results were compared with the requirements of the Palestinian Ministry of Health according to Word Health Organization.

I. Linearity and Range

Mobile phase: a mixture of 700 ml of buffer (11.4 g/L ammonium acetate in water with pH adjustment to 7.2 with ammonium hydroxide) and 350 ml methanol then it was filtered through 0.45 micro membrane filter.

Diluent**:** Same as Mobile phase.

Paracetamol standard stock solution of 5 mg/ml and Cyclobenzaprine HCl standard stock solution of 0.05 mg/ml were used for preparation of subsequent aliquots; aliquots of 0.2, 0.225, 0.25, 0.275, 0.3, 0.4, 0.45, 0.5, 0.55 and 0.6 mg/mL concentrations were prepared by serial dilution for Paracetamol and aliquots of 0.002, 0.00225, 0.0025, 0.00275, 0.003, 0.004, 0.0045, 0.005, 0.0055 and 0.006 mg/mL concentrations were prepared by serial dilution for Cyclobenzaprine HCl. The solution of 2 mL was loaded in autosampler tray and 15 µL was being injected into column. All measurements were repeated three times for each concentration. The calibration curves of the area under curve versus concentration were recorded.

Acceptance criteria: R^2 is NLT 0.98.

II. Precision

Standard solution (conc. 0.5 mg/ml Paracetamol & 0.005 mg/ml Cyclobenzaprine HCl) was injected into the chromatogram six times; RSD was calculated.

Acceptance criteria: (RSD should be NMT 2.0 %).

III. Accuracy and Recovery

Sample Solution: 3 aliquots were prepared from each concentration as following:

116 mg placebo were mixed with 400 mg paracetamol & 4 mg Cyclobenzaprine HCl dissolved in 100 ml diluents; sonicated for 5 min; cooled to room temp. Then volume completed to 100 ml with diluents, 10 ml of obtained solution was diluted to 100 ml with diluents (conc. 0.4 mg/ml paracetamol & 0.004 mg/ml Cyclobenzaprine HCl).

145 mg placebo were mixed with 500 mg paracetamol & 5 mg Cyclobenzaprine HCl dissolved in 100 ml diluents; sonicated for 5 min; cooled to room temp. Then volume completed to 100 ml with diluents, 10 ml of obtained solution was diluted to 100 ml with diluents (conc. 0.5 mg/ml paracetamol & 0.005 mg/ml Cyclobenzaprine HCl).

174 mg placebo were mixed with 600 mg paracetamol & 6 mg Cyclobenzaprine HCl dissolved in 100 ml diluents; sonicated for 5 min; cooled to room temp. Then volume completed to 100 ml with diluents, 10 ml of obtained solution was diluted to 100 ml with diluents (conc. 0.6 mg/ml paracetamol & 0.006 mg/ml Cyclobenzaprine HCl).

Procedure: 15 µl of each prepared sample and standard solution were injected into the chromatogram, % Recovery was calculated for each injected sample.

Acceptance criteria: ± 2.0 %.

IV. Specificity

40 ml of diluent added to 145 mg placebo; sonicated for 5 min and cooled to room temperature, then volume completed to 100ml with diluent; 10 ml of obtained solution was diluted to 100 ml with diluent. 15 µl were injected, in the chromatogram obtained it should show no signals at the retention time of paracetamol and Cyclobenzaprine HCl peaks.

V. Stability Indicating Method (Stress Conditions)

Base Degradation (NaOH): 5.0 ml of SSS1, 5.0 ml of SSS2 & 5.0 ml of 1M NaOH solution were diluted to 50 ml with diluents. (Conc. 0.55 mg/ml paracetamol & 0.0055 mg/ ml Cyclobenzaprine HCl).

Acid Degradation (HCl): 5.0 ml of SSS1, 5.0 ml of SSS2 & 5.0 ml of 1M NaCl solution were diluted to 50 ml with diluents. (Conc. 0.55 mg/ml paracetamol & 0.0055 mg/ ml Cyclobenzaprine HCl).

Oxidation (H_2O_2) Degradation: 5.0 ml of SSS1, 5.0 ml of SSS2 & 5.0 ml of 3% H_2O_2 solution were diluted to 50 ml with diluents. (Conc. 0.55 mg/ml paracetamol & 0.0055 mg/ ml Cyclobenzaprine HCl).

2.8 Stability of tabletx

In this study, samples of mixed powder Cyclobenzaprine HCl & Paracetamol Tablets were paced in a high density polyethylene HDPE bottles covered with child proof caps, and stored at two different conditions at 25°C/60% RH & 40°C/75% RH. Testing Frequency: samples analyzed at different time intervals (Zero-time, 3rd Month & 6th month) in order to evaluate the changeover the time of the formula and its proper storage conditions.

2.9 A pilot field study

2.9.1 Study design and setting

This study was a cross-sectional questionnaire-based to evaluate doctors' and patients' perspectives regarding the use of Paracetamol and Cyclobenzaprine HCl. It was conducted between March 2021 and December 2021.

The population was doctors who may prescribe Cyclobenzaprine for patients in Nablus city. Convenience sampling was used to recruit participants.

2.9.2 Inclusion and exclusion criteria

The inclusion criteria were as follows for doctors: males and females, with specialties that may prescribe Paracetamol and Cyclobenzaprine as orthopedic doctors neurosurgeons and neurologists. The inclusion criteria for patients were male or female patients who were prescribed Cyclobenzaprine for any type of pain.

2.9.3 Data collection and management

Data Collection Forms (Appendix B) were used to gather information. The form for doctors was in English and it included some sociodemographic data as gender, age, specialty, years of experience and working place, then they were asked about the frequency of prescribing these two medications and if they support combining them in a same tablet. For patients, the form was in Arabic and it included some sociodemographic data also as gender, age, education, living place, chronic disease, in addition to questions regarding the use of Paracetamol and Cyclobenzaprine.

Initially the doctor prescribed Cyclobenzaprine HCl tablet as a muscle relaxant for the patient and asked him/her to use it for the first 3 days and record efficacy and any side effects then the doctor added Paracetamol tablet and tried to notice the differences before and after taking Paracetamol tablet. The doctor then completed the questionnaire for the patient.

2.9.4 Ethical approval

All aspects of the study protocol, including access to patients' clinical information, were authorized by the Institutional Review Boards (IRBs) (Appendix C) before the initiation of this study. In addition, a verbal consent form was obtained from each patient (Appendix C).

2.9.5 Statistical analysis

The Statistical Package for Social Sciences program version 21 (SPSS) and Excel sheets were used to enter and analyze data. Data was expressed as mean ± SD for continuous variables and as frequencies (percentages) for categorical variables.

Chapter Three

Results

3. Results

Solid dosage forms are the preferable ones among other pharmaceutical forms due to its stability, reproducibility, handling, and dosing. Successful formulation and evaluation of Cyclobenzaprine/paracetamol tablet will provide a new pharmaceutical combination with lower cost, which may improve the patient compliance by reducing the tablets needed to be taken and thus improve patient's compliance to prescribed therapeutics.

3.1 Preformulation Testing

3.1.1 Compatibility & flow properties

For cyclobenzaprine bulk density was 0.48 g/ml, tapped density was 0.57 g/ml with compressibility index of 15.8 and Hausner Ratioof 1.17 and for Paracetamol bulk density was 0.43 g/ml, tapped density was 0.51 g/ml with compressibility index of 15.7 and Hausner Ratio of 1.18 as index for flowability and compressibility of the formulated tablet.

The powders results show good flowability properties with good compressibility index (11).

3.1.2 Water Content/LOD Determination

Table 1

API& Excipients Water content (WC)/loss on drying (LOD) Results

Material	Test	Limit	Result
Cyclobenzaprine HCl	LOD	*NMT 5.0 %	0.9 %
Paracetamol	LOD	NMT 5.0 %	2.1 %
Avicel 101	LOD	NMT 7.0 %	4.8 %
Magnesium stearate	LOD	NMT 6.0 %	2.7 %
Sodium starch glucolate	LOD	NMT 10%	6.7 %

*NMT: not more than

LOD/W.C for each excipient should be within specifications, because out of range LOD/W.C results in stability problems and thus degradation of product. As illustrated in the table above all results are within specifications.

3.1.3 Excipients and APIs Compatibility

Table 2

Compatibility Testing Results.

No	(API: Excipient)	Appearance	Assay (API) after month
1	Paracetamol: Avicel 101	White powder	99.5%
2	Paracetamol: magnesium stearate	White powder	99.7 %
3	Paracetamol: sodium starch glycolate	White powder	99.2 %
4	Paracetamol: Cyclobenzaprine HCl	White powder	100.5%, 99.4%
5	Cyclobenzaprine HCl: Avicel 101	White powder	100.0 %
6	Cyclobenzaprine HCl: magnesium stearate	White powder	99.5%
7	Cyclobenzaprine HCl: sodium starch glycolate	White powder	100.7%

As obtained in the results above; no change in appearance of each mixture was observed after a month. In addition; no significant change in API Assay observed, which means that no impact of any used excipient on the quantitative and qualitative results of the API and more importantly the combing the two APIs is not expected to induce significant degradation of each.

3.2 Preparation of the formulation (Optimized Formula)

the optimized formula of the tablets was obtained as illustrated in Table 7. The powders were mixed using direct mixing and compressing method.

All excipient was weighted and mixed well together, Paracetamol was added and mixed for 15 min then cyclobenzaprine was added and all powders mixed together for other 15 min to ensure that the powders distributed well. Small amount of powder was taken for analysis and the other added to the hopper (inlet) of the compression machine and compressed to obtain a tablet with required specifications.

Table 3

Tablets Optimized Formula.

No.	Material	Function	Quantity (mg/tablet)	(% w/w)
I.	Paracetamol	Active	500	76.9
II.	Cyclobenzaprine HCl	Active	5	0.769
II.	Avicel 101	Binder	110	16.9
V.	sodium starch glycolate	Disintegrant	10	1.54
V.	magnesium stearate	Lubricant	5	0.769
Total Wt. of Tablet= 650 mg				

3.3 Evaluation of Compressed Tablets

Description of Tablets

The obtained tablets were oval convex tablet, white coloured free from spots, cleavage, cracking, and sticking.

Accordingly the dimensions of Tablet, uniform dimensions (length and thickness) of tablets obtained after compression (Table 7), are evidence of good processing and good blend properties prior to compression including the optimized quantities of excipients used. (RSD between readings < 2.0 %).

Table 4

Tablets parameters (length, thickness & hardness).

Tablet No.	Parameter Length (mm)	Thickness (mm)	Hardness (Newton N)
1	1.58	0.75	82
2	1.58	0.75	76
3	1.60	0.74	88
4	1.59	0.75	79
5	1.58	0.76	75
6	1.57	0.76	79
7	1.59	0.75	85
8	1.58	0.75	81
9	1.58	0.74	77
10	1.59	0.74	86
Average	1.58 cm	0.75 cm	82 N
Specification	1.58 cm ±0.3 mm	0.75 cm ±0.3 mm	Not less than (NLT) 60 N
SD	0.016364	0.021499	-
RSD	0.15 %	0.5 %	-

Friability and Disintegration Time

Balance achieved between the three parameters (Disintegration Time & Friability) was acceptable for such dosage form leading to uncoated tablets that should be hard enough to be handled, disintegrate easily and meet friability criteria as shown in tables 8, 9 and 10.

Friability of tablets:

The weight of tablets before test = 10 gm

The weight after test = 9.982 gm

The friability % = 0.18% which is in an acceptable limit (NMT 1.0%)

Disintegration of the tablet:

The disintegration results for 6 tablets were between 40 & 78 seconds with an average of 57 seconds which is in acceptable limit (NMT 15 min)

Weight and Uniformity of Weight

All tablets were uniform in weight with no deviation from the target weight by more than 5.0 %. This uniformity of weight also achieved by right selection of excipients quantities and processing method (Table 11).

Table 5
Weight Variation Results.

Tablet No.	Weight (mg)	Tablet No.	Weight (mg)
1	658	11	659
2	637	12	647
3	662	13	662
4	652	14	654
5	645	15	637
6	669	16	645
7	637	17	660
8	651	18	650
9	659	19	658
10	670	20	642
Average weight = 652.7 mg			
SD= 1.5			
Minimum Wt.		617.5 mg	
Maximum Wt.		682.5 mg	
Acceptance Limit		650.0 mg ± 5.0 %	

Dissolution/in vitro test

Dissolution results were within acceptance limits, with low CV. This also a good indicator of uniform distribution of APIs within the blend before and during compression as well as good formulation that passed one of the critical quality attributes tests.

Absorbance of Standard:

Paracetamol Solution at 250 nm = 2.96

Cyclobenzaprine HCl at 290 nm = 3.1

Panadol tablet dissolution results:

The mean of dissolution = 98.9%, the lower value was 97.5% and higher value was 101.0%, which are within acceptable limit (NLT 70% Q)

Xaprine tablet dissolution results:

The mean of dissolution = 94.5%, the lower value was 92.5% and higher value was 96.0%, which are within acceptable limit (NLT 70% Q)**.**

Formulated combined Paracetamol & Cyclobenzaprine HCl tablet dissolution results:

For Paracetamol: The mean of dissolution = 101.5%, the lower value was 100.3% and higher value was 103.0%, which are within acceptable limit (NLT 70% Q)**.**

For Cyclobenzaprine: The mean of dissolution = 88.2%, the lower value was 97.1% and higher value was 89.7%, which are within acceptable limit (NLT 70% Q)**.**

Assay

Percent (%) content of the API in the portion of powdered tablets taken for analyzing assay was high and within acceptance limit, with RSD less than 2.0 % between tested samples. The chromatographic trials and results were attached in appendix D.

Table 6
Assay Results.

Average paracetamol standard solution	59922718
Sample (1)	%Assay= (61190065/59922718)×100= 102.1%
Sample (2)	%Assay= (60291303/59922718)×100= 100.6%
Sample (3)	%Assay= (60621468/59922718)×100= 101.2%
Average Assay	101.3 %
Acceptance Limit	90.0 %-110.0 %
Average Cyclobenzaprine HCl standard solution	1919711
Sample (1)	%Assay= (1885712/1919711)×100= 98.2%
Sample (2)	%Assay= (1918083/1919711)×100= 99.9%
Sample (3)	%Assay= (1976150/1919711)×100= 101.9%
Average Assay	100.0%
Acceptance Limit	90.0%-110.0 %

3.4 Validation/Verification Results

Any used analytical procedure for any test; should be validated /verified in order to assure that used procedure can achieve the desired purpose. This assessment can be judged according to several parameters to assure that the method is linear in the range used with high recovery and precision, good robustness and selectivity.

Assay Validation

Tables 14-17 and Figures 1 and 2 show validation results, which were all within the accepted range and the chromatographic results, were attached in appendix D.

I. Linearity and Range

Table 7

Assay Linearity Results for Paracetamol & Cyclobenzaprine HCl

Pracetamol Conc. (mg/ml)	Avg. Area of Paracetamol	Cyclobenzaprine Conc. (mg/ml)	Avg. Area of Cyclobenzaprine
0.2	25307491	0.002	784484
0.225	29478402	0.00225	893564
0.25	32663902	0.0025	1005309
0.275	34320554	0.00275	1050000
0.3	38623912	0.003	1170930
0.4	50934697	0.004	1539160
0.45	56421714	0.0045	1724130
0.5	62659004	0.005	1983586
0.55	69021202	0.0055	2157754
0.6	74102473	0.006	2316641
R^2	0.999	R^2	0.9983
Y-intercept	$2*10^6$	Y-intercept	12985
Slope	$1*10^8$	Slope	$4*10^8$
Acceptance Limit	R^2 NLT 0.98	Acceptance Limit	R^2 NLT 0.98

Figure 2

Linearity of Assay for paracetamol.

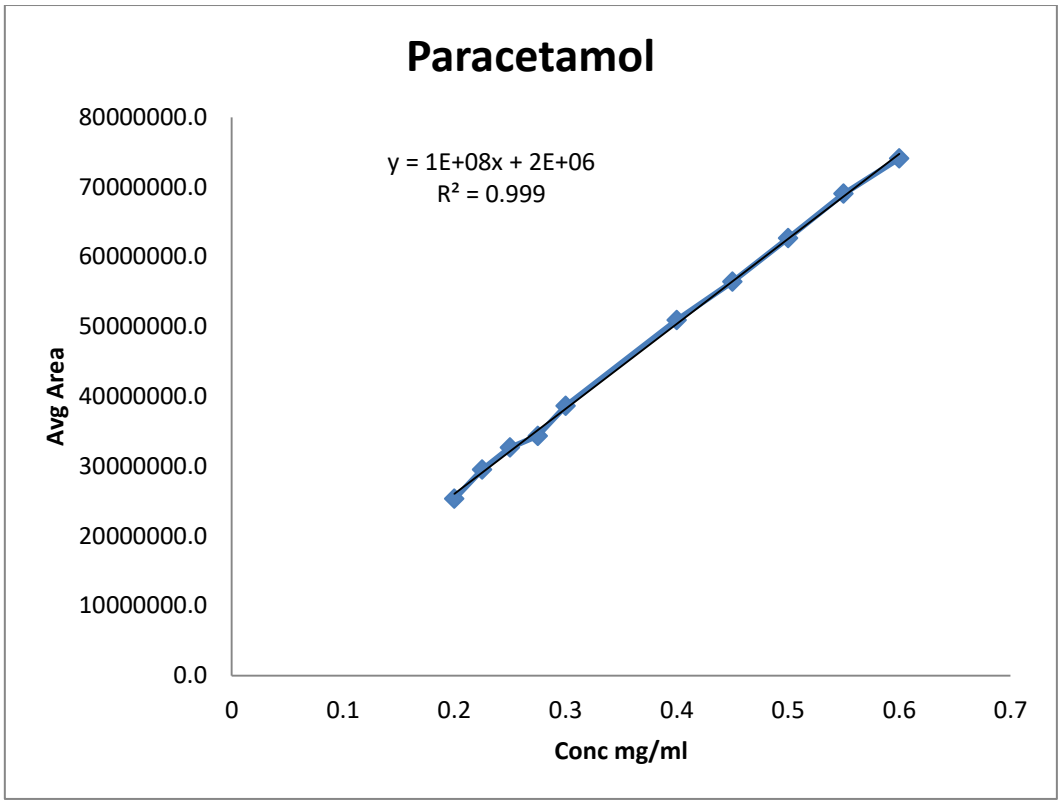
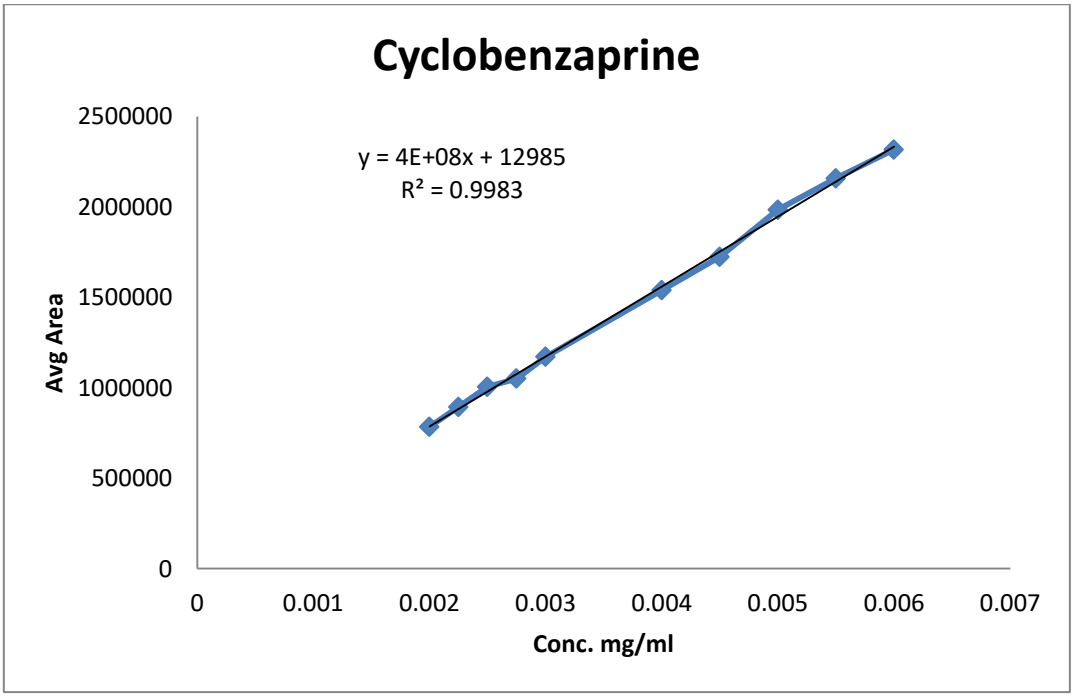


Figure 3

*Linearity of Assay for Cyclobenzaprine HCl***.**



As the above results illustrate; method of analyzing Assay is linear in the range of 0.2 mg/ml to 0.6 mg/ml conc. for paracetamol and 0.002 mg/ml to 0.006 mg/ml for Cyclobenzaprine HCl.

II. Precision

Table 8

Assay Precision Results.

Sample No.	Area of paracetamol (A.U)	Area of Cyclobenzaprine HCl (A.U)
1	62385309	1959491
2	62621729	1943405
3	62687558	1944042
4	62481827	1952605
5	62668664	1948029
6	62739815	1943715
Mean	62597484	1948548
SD	135956.3	6427.912
RSD	0.21%	0.33%
Acceptance Limit	RSD should not exceed 2.0 %	

As illustrated above; RSD between readings was 0.5 % < 2.0 %; which means that assay method is precise.

III. Accuracy and Recovery

Table 9

Assay Accuracy/Recovery Results for paracetamol.

Conc. (mg/ml)	Sample No.	Area of Paracetamol (A.U)	Area of Cyclobenzaprine HCl (A.U)	% Recovery Paracetamol	% Recovery Cyclobenzaprine HCl
0.4	1	51094168	1503625	100.4	100.7
0.4	2	50853868	1493975	100.0	100.0
0.4	3	508976360	1494641	1000.5	100.1
0.5	1	62866862	1962391	100.3	100.9
0.5	2	62866862	1949041	100.3	100.3
0.5	3	62725970	1946778	100.1	100.1
0.6	1	73921612	2306714	99.7	100.8
0.6	2	73902022	2292841	99.6	100.2
0.6	3	73981606	2306714	99.8	100.8
Acceptance Limit: Recovery should not exceed ± 2.0 %					

Recovery was within acceptance limit (±2 %) for every 3 samples analyzed at different concentrations from (80% to 120 % of target concentration).

IV. Selectivity: no absorbance found for the placebo sample.

V. Stability under stress conditions

Stress conditions are necessary to develop a stability indicating method that illustrates all potential degradation products at different stressed conditions; without interfering with the API. This also helps in determining the suitable conditions for storage. The method shows a degradation result in the APIs when expressed under acidic, basic and oxidation condition.

3.5 Stability Study Results

Stability of formulated mixed powder tablets was studied after 3 and 6 months at different storage conditions (25 °C, 60 % RH) and at (40°C, 75% RH). Stability results are listed in Table 18. As obtained from the results, the product was stable at the two different conditions; with slight changes at 40° Cover the time period; however, all results were within acceptable limits.

Table 10

The result of stability listed in the following table

Test for tablet	Specification	3rd Month result		6th Month result	
		25C/60%RH	40C/75%RH	25C/60%RH	40C/75%RH
Length	1.58 cm ± 0.3 mm	1.57 mm	1.58 mm	1.59 mm	1.57 mm
Thickness	0.75 cm ± 0.3 mm	0.76 mm	0.78	0.75 mm	0.74 mm
Hardness	NLT 60 N	81	78	84	80
Friability	NMT 1.0%	0.13%	0.16%	0.15%	0.18%
Disintegration	NMT 15 min	1 min	52 sec	55 sec	57 sec
Average weight	650.0 mg ± 5.0%	658.1 mg	656.1 mg	654.7 mg	654.0 mg
Dissolution					
Paracetamol	NLT 70%Q	99.1%	98.5%	N.A	N.A
Cyclobenzaprine HCl	NLT 70%Q	90.7%	88.7%	N.A	N.A
Assay					
Paracetamol	90.0%-110.0%	99.5%	99.3%	99.8%	98.5%
Cyclobenzaprine HCl	90.0%-110.0%	98.8%	98.1%	97.7%	98.0%

3.6 The pilot observation clinical study

This part included two questionnaires:

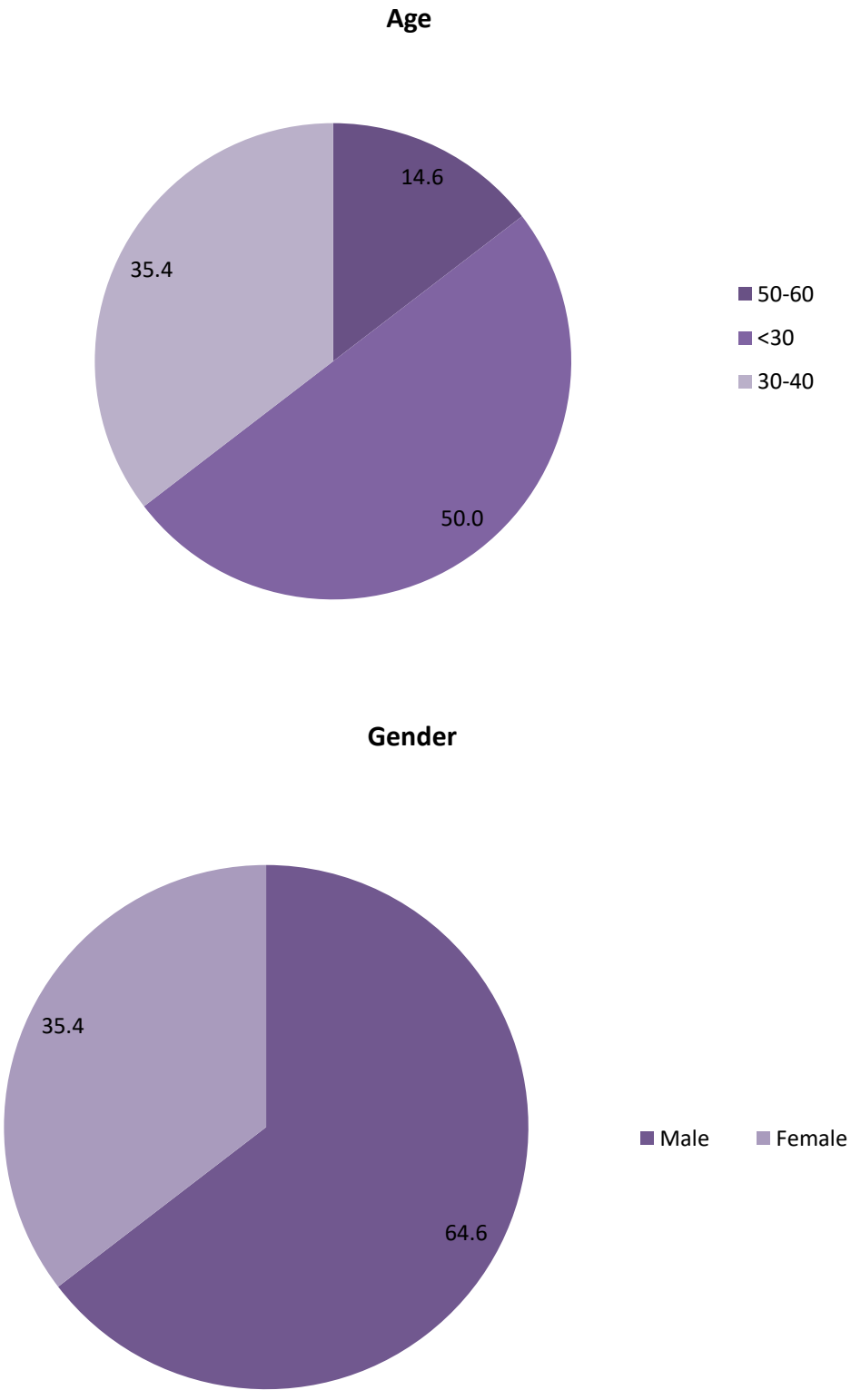
The doctor's questionnaires were answered by fifty doctors through a face-to-face interview (Figure 5). Around 50% of them were between 50 and 60 years old, 14.6% less than 30 years and 35.4% between 30 and 40 years, 64.6% were males. 18.8% had more than 20 years of experience, 12.5% had 10 to 20 years of experience, 18.8% had 5-10 years of experience and 50% had less than 5 years of experience. Regarding their working places, 52.1% of doctors worked in governmental hospitals, 29.2% worked in private hospitals, 10.4% worked in private clinics, and 8.3% worked in other places. Their prescribing of Paracetamol was very common as 79.2% of them said that they prescribe it daily, while for cyclobenzaprine, the frequency of prescribing was divided as yearly, monthly, weekly, and daily (14.6%, 25.0%, 41.7%, and 18.8% respectively). Almost all doctors (93.8%) supported the idea of combining the two medications in one tablet and said it could be a tablet in tablet, mixed powder tablet, or two-layer tablet (29.2%, 39.6%, and 31.3%, respectively).

The patient questionnaires were answered by thirty patients (Figure 6). The percentage of male patients was 57.1%, 92.9% were married, 50% were between 40 and 60 years old, 35.7% were less than 40 years old, and 14.3% were more than 60 years old, 32.1% had a university degree and 35.7% had only a high school, 39.3% had a monthly income of between 3000 and 5000 NIS, while for 36.7% it was between 1000 and 3000 NIS, 10.7% of the patients had no health insurance, 46.4 had private health insurance and 42.9% had government health insurance, 64.3% had no chronic diseases while 14.3% had diabetes and 10.7% had hypertension. Most of them evaluated their health status as excellent (71.4%). The reasons for visiting the doctor were back pain, neck pain, or others, with a percentage of 67.9%, 25.0%, and 7.1%, respectively. All were prescribed the trade name of Cyclobenzaprine HCl drug (Xaprine)® with a 5mg concentration. Only 10.7% of patients used Xaprine before this time. 14.3% of patients suffered from Xaprine side effects, which were tiredness, headache, dizziness, drowsiness, constipation, and dry mouth. All patients said that their symptoms improved when Paracetamol was added to Cyclobenzaprine.

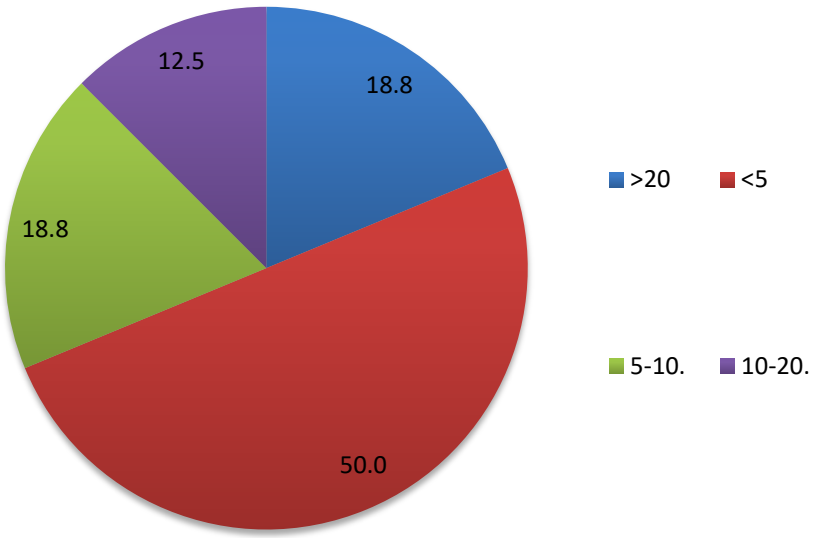
The following figure (5,6) show the result:

Figure 4

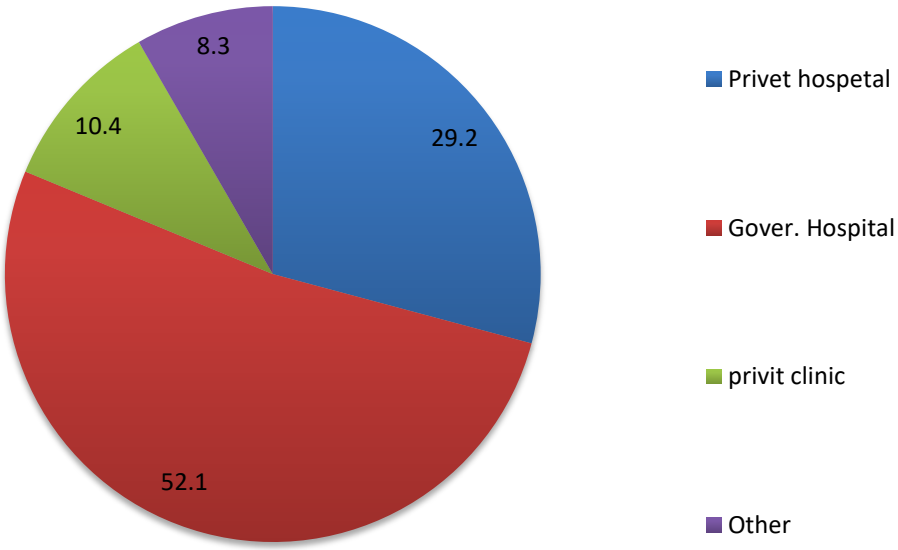
Doctors' questionnaire results (N =50)



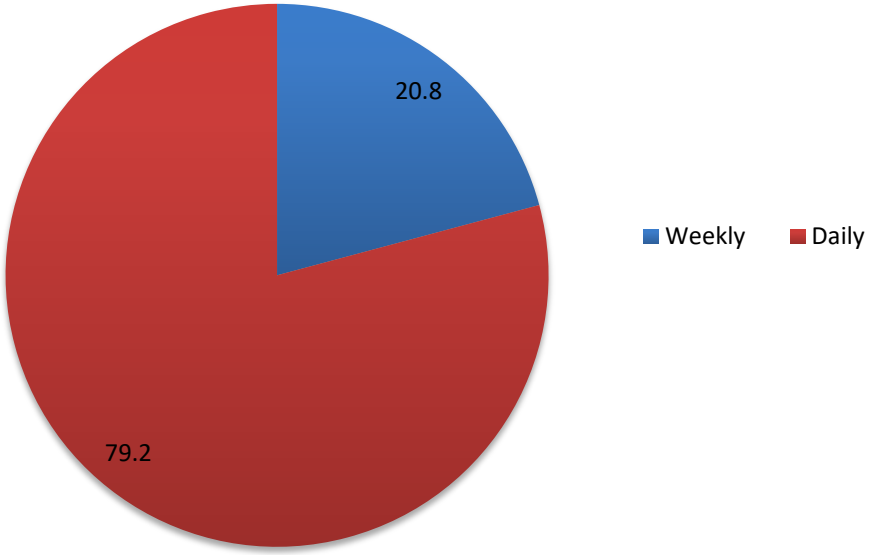
Years of experience



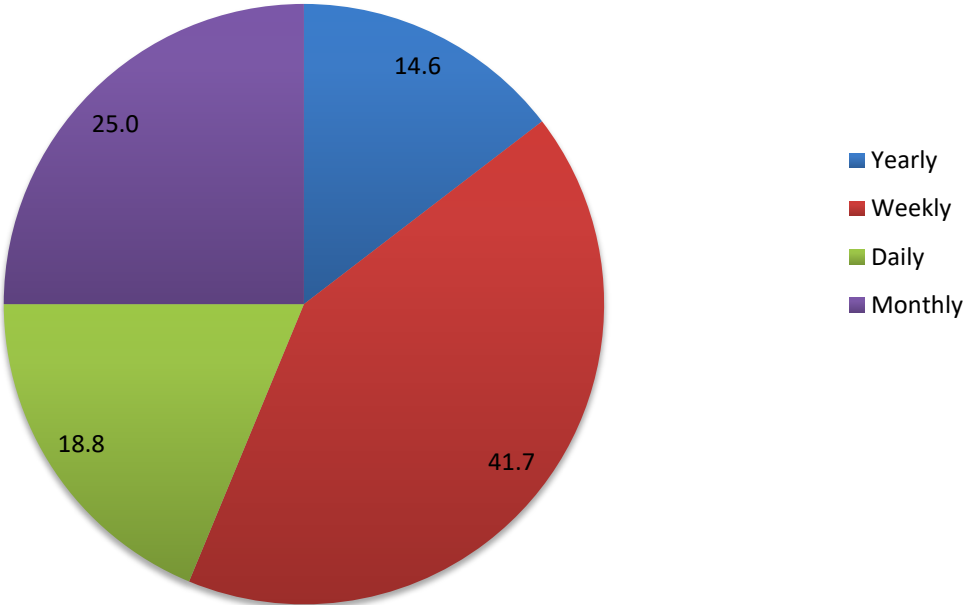
Working place



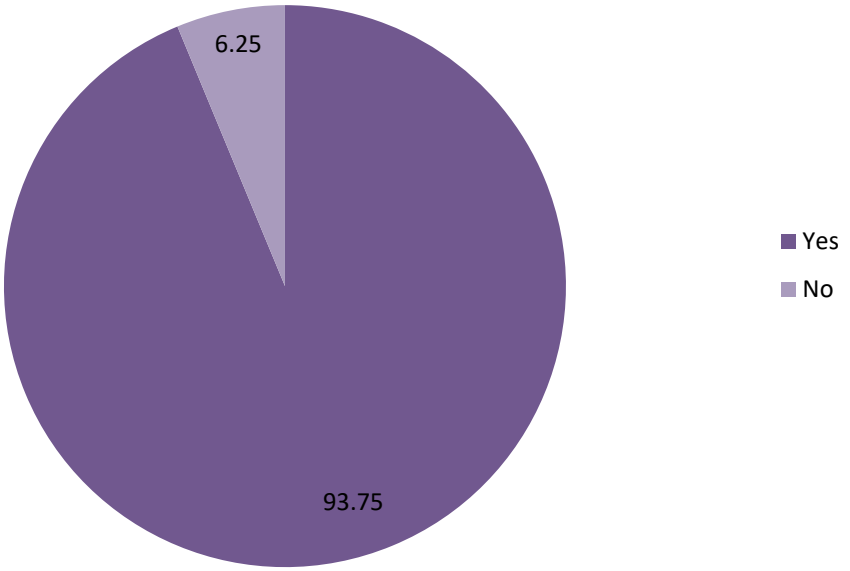
Paraetamol prescibtion frequincy



Cyclobenzoprine prescrition frequancy



The ideae is useful



Best formulation idea

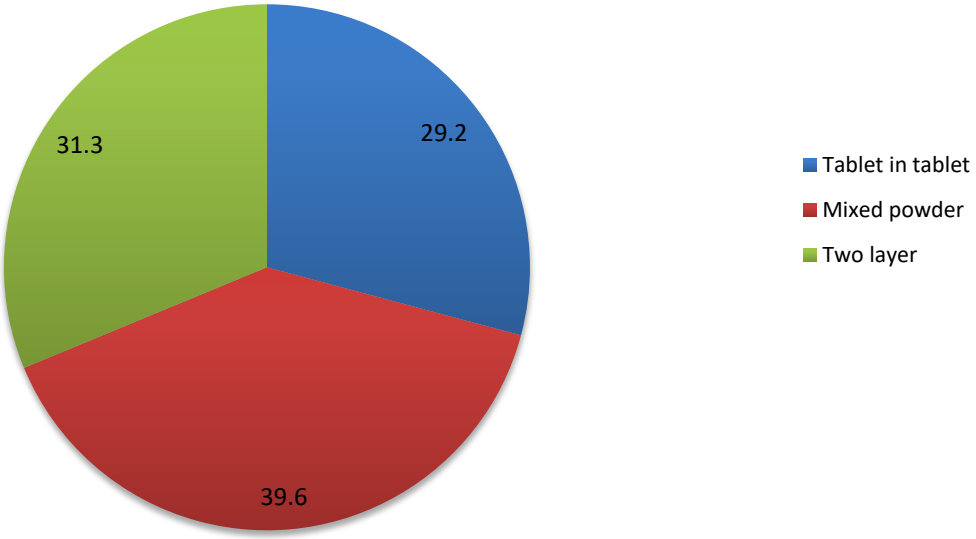
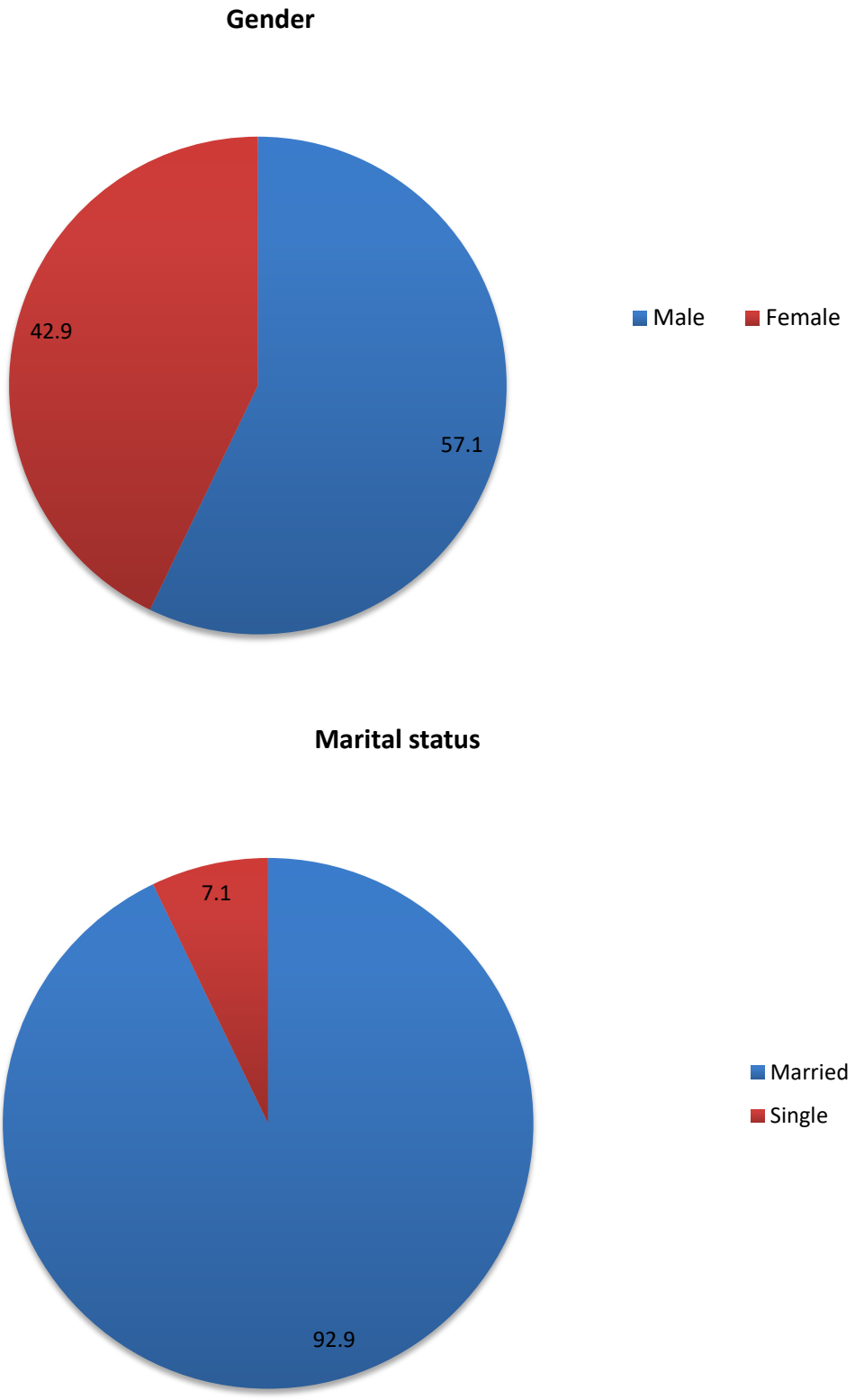
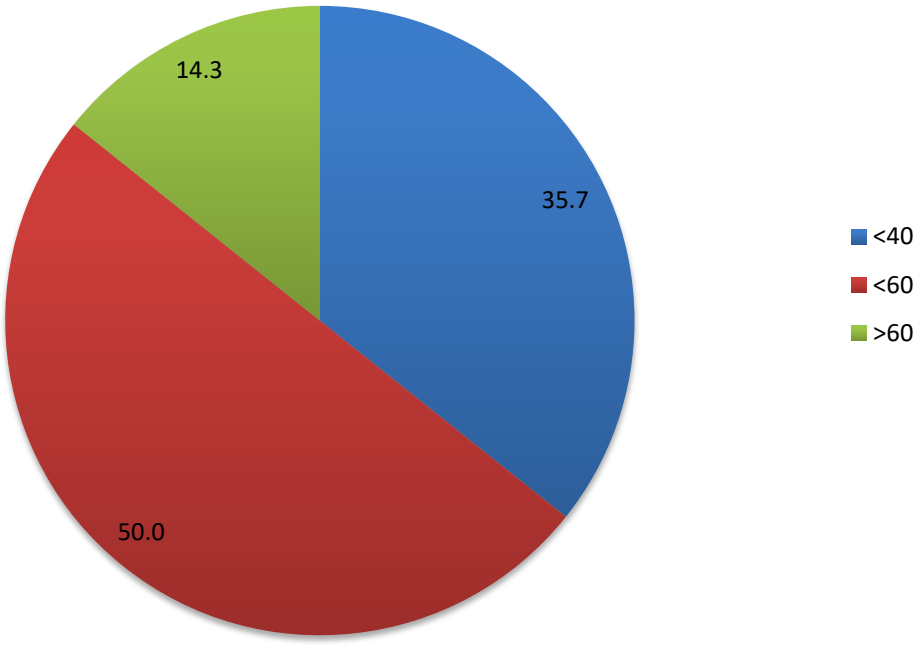


Figure 5

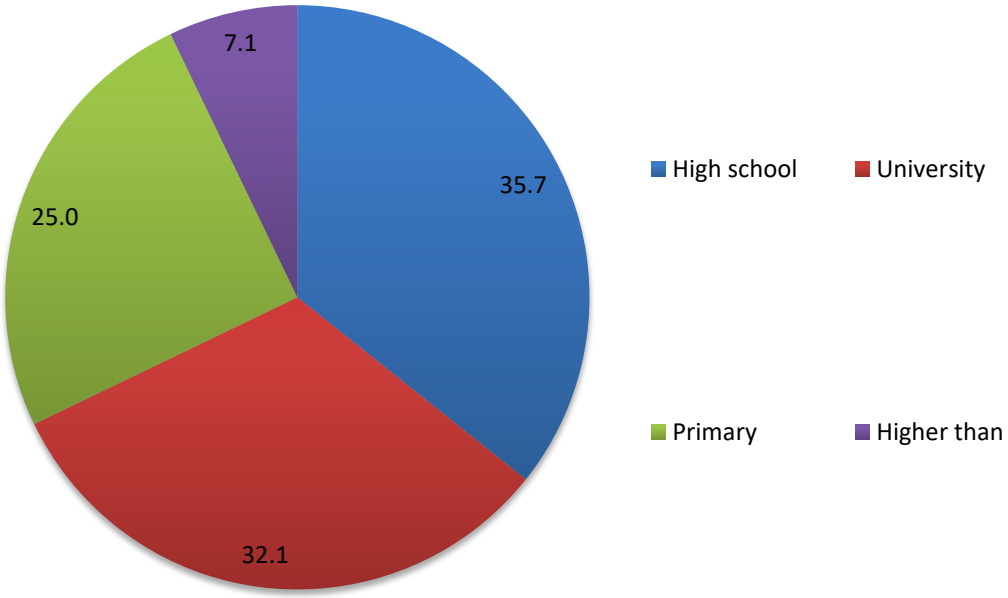
Patients' questionnaire results (N=30)



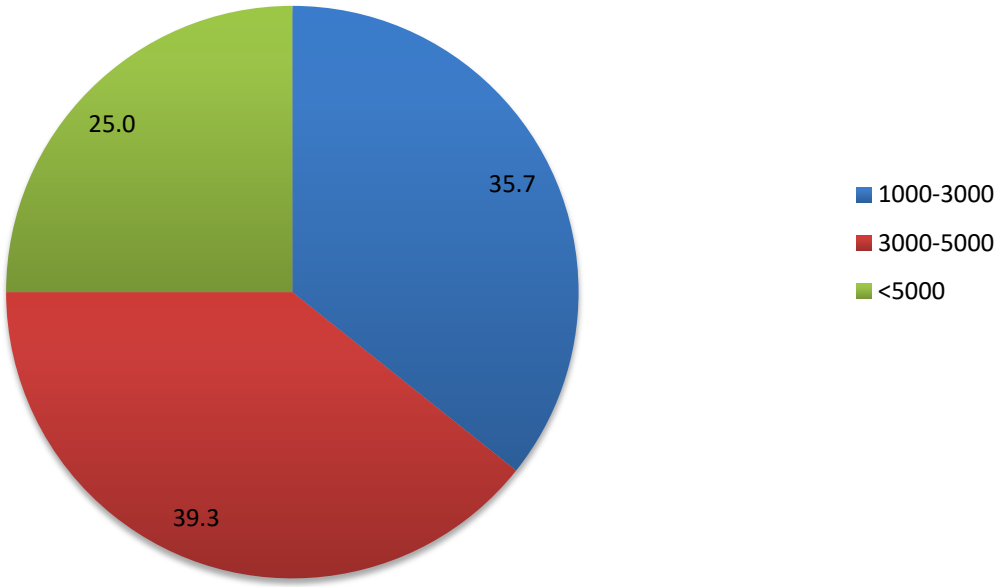
Age



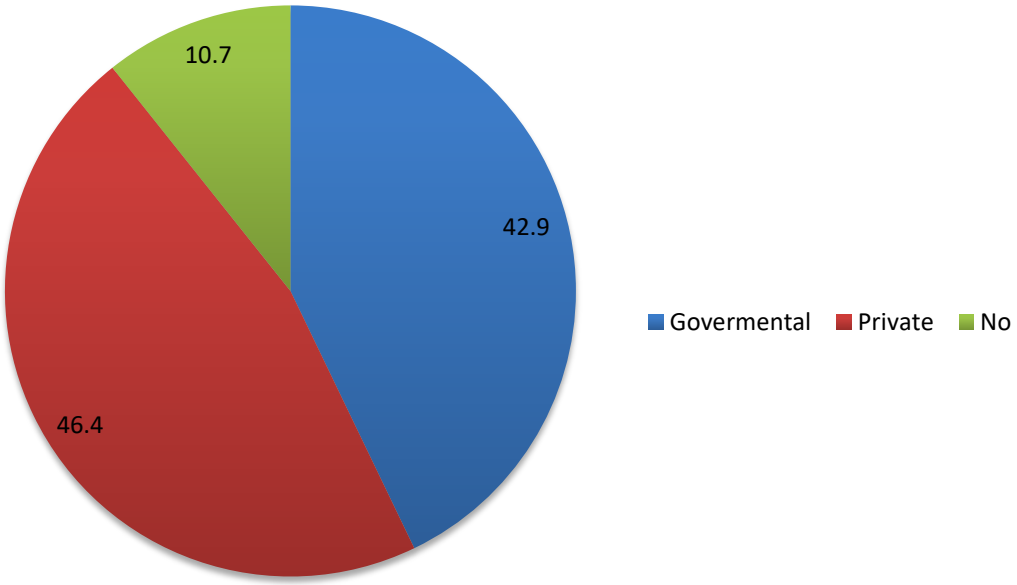
Education level



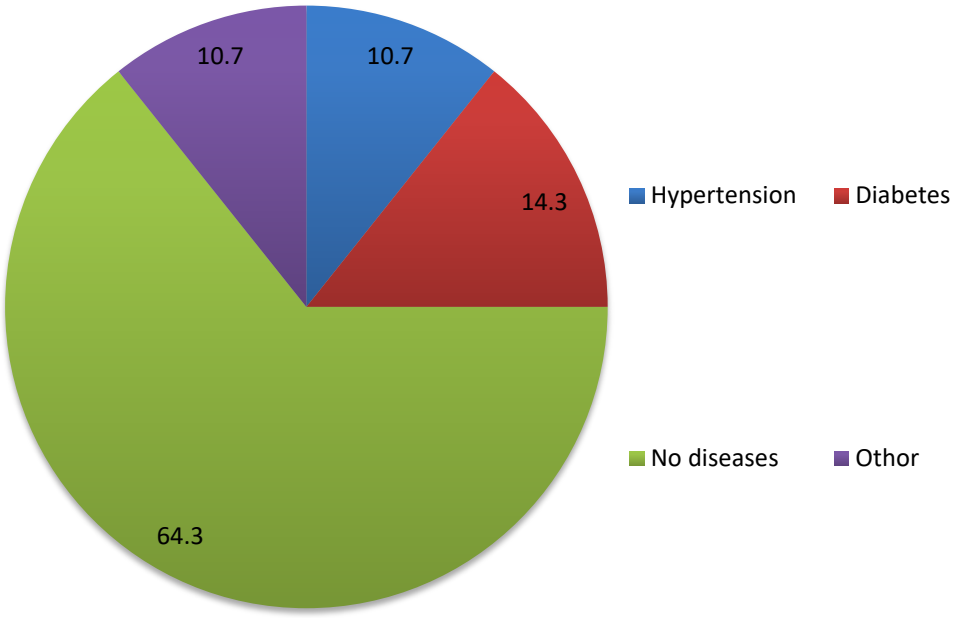
Income level



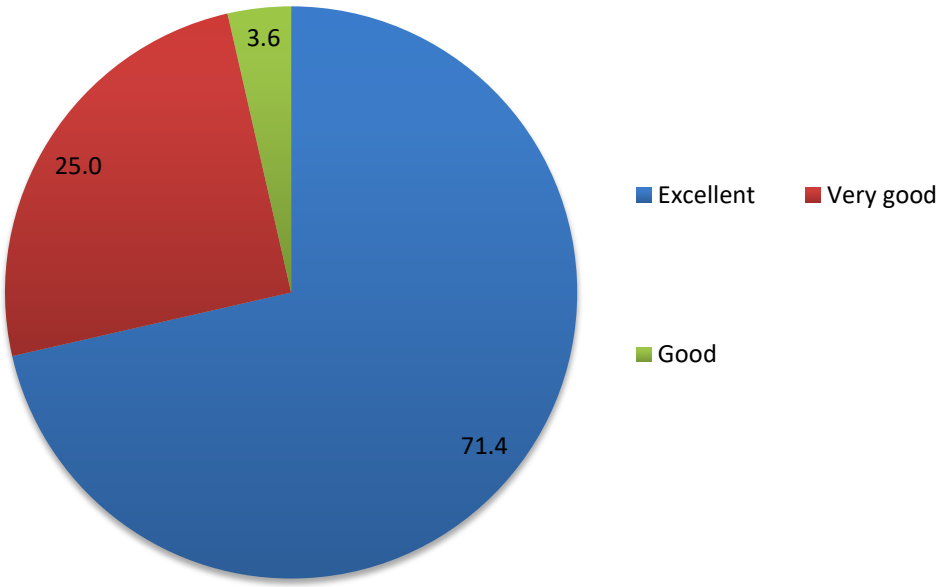
Health insurance



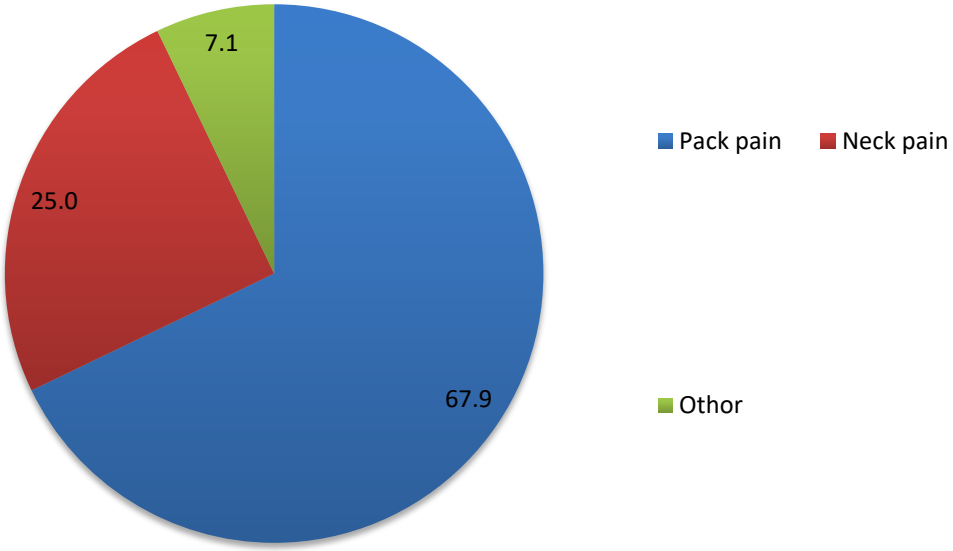
Suffers from diseases



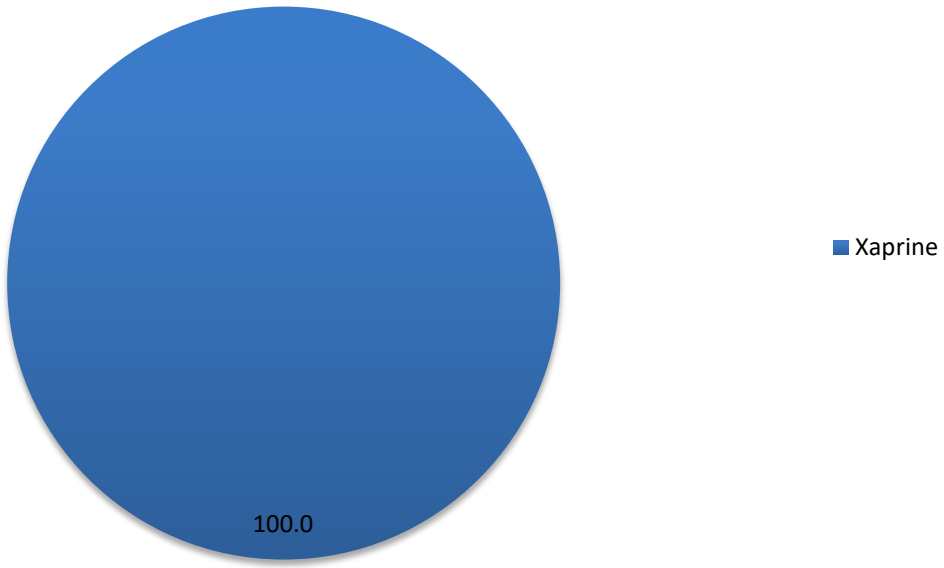
Health status



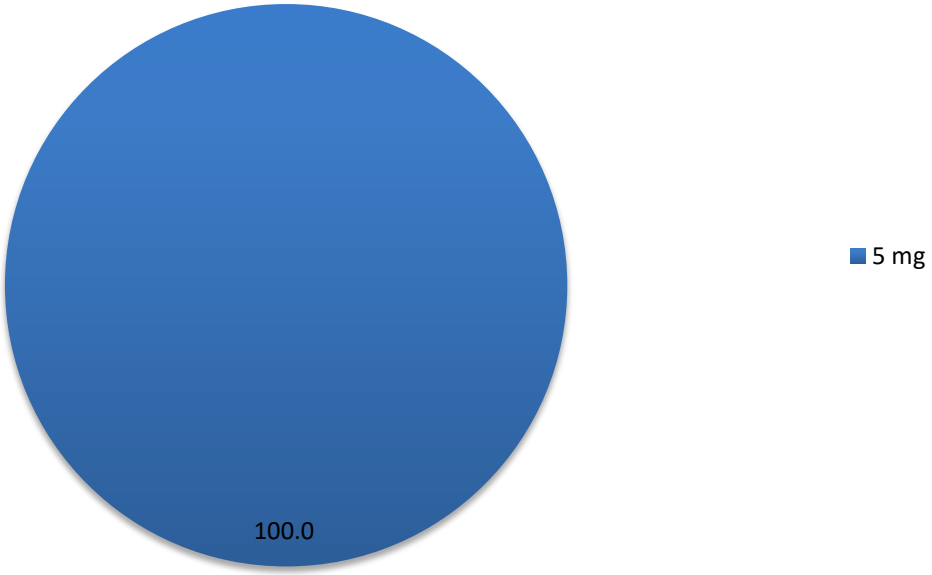
Reason for visiting Dr.



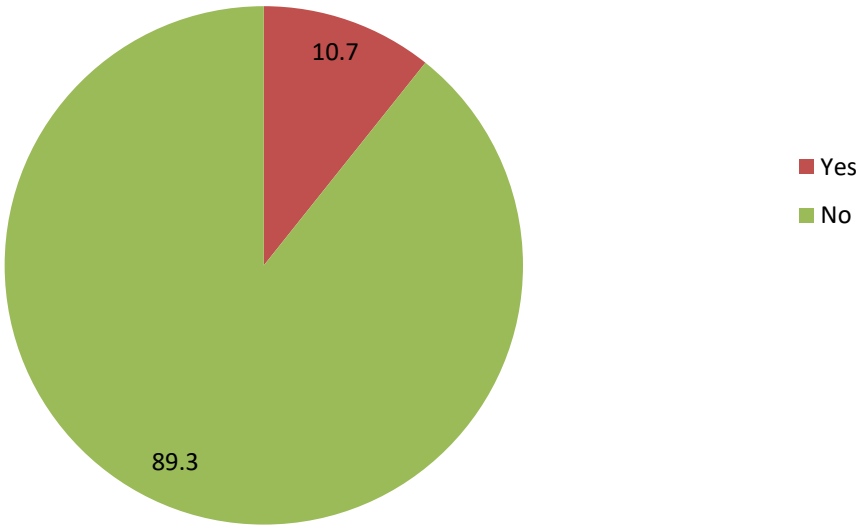
Drug trade name



Cyclobenzaprine Conc.



Have you used Xaprine before this time?



Chapter Four

Discussion and Conclusion

4. Discussion and conclusion

The effectiveness of Cyclobenzaprine is improved with paracetamol when they are taken together. Using a muscle relaxant and an analgesic is common for some types of muscle pain (28) . So a formulation of Cyclobenzaprine HCl and Paracetamol combined powder tablet was done to achieve an effective drug and reach consumer's requirements. Using both active ingredients in one tablet instead of using two separated tablets is easier for patients and may improve patient compliance.

According to the results of the active pharmaceutical drug powder properties, bulk density, tapped density, compressibility index and Hausner ratio calculation were evaluated and the powder has good flowability properties with good compressibility (11).

Active ingredients and excipients were within water content and loss of drying specification which have a good compatibility (14). The formulated tablet has disintegration time lower than 2 min.

The direct compressed formulated tablet contained magnesium stearate as lubricant, sodium starch glycoside as disintegrant, avicel 101 as binder and Paracetamol 500mg and Cyclobenzaprine HCl 5mg as active ingredients.

The formulated tablet is physically tested for colour, shape, length, thickness, hardness, weight, friability and disintegration. It was white in colour oval convex shaped compressed tablet that has a length of 1.58 cm ± 0.3 mm and 0.75 cm ± 0.3 mm in thickness, with an average of 82 N hardness and 652.7 mg weight, and acceptance result for friability and disintegration time test.

The formulated tablet has a dissolution of NLT 70% Q and assay within the limit of 90%-110%. And all these tests' results were within the accepted and recommended ranges (14).

All tests under assay validation were within accepted limit also (16).This means that the method is linear with R^2 more than 0.98, accurate with less than 2% recovery precise with %RSD less than 2%, and selective with no peak interference which means that it will give a good result on any HPLC by any expert analyst at a different concentration and time (16).

The formulated tablet was chemically and physically stable for 6 months at different storage zones (25 °C, 60 % RH) and at (40°C, 75% RH) (14).

Regarding the questionnaires, they showed an acceptance for the combination of both drugs by the doctors and patients, the doctors told that they prescribe both medications together for muscle pain and almost all of them supported having the two active ingredients in one tablet. The patients were using the 5 mg dose of the cyclobenzaprine and all of them told that the efficacy of treatment improved when paracetamol was added which means that they also support having both medications together.

4.1 Conclusion

Cyclobenzaprine HCl and Paracetamol mixed powder tablets were successfully formulated and showed an acceptable stability profile. The developed and validated HPLC method was suitable for the characterization and assessment of the formulated tablets and can be used for convenient forms analysis especially for those tests not listed in the pharmacopeias.

The formulated mixed powder compressed tablet can be manufactured in pharmaceutical companies with a stable formula physically and chemically and validated test method.

The future work may concentrate on changing the type of formulated tablet as many layer tablet, tablet in tablet or other types, or may try to work on adding other active ingredients to have more effective tablets, in addition to having different strength of both medications, such as adding caffeine which may potentiate the analgesic effect of paracetamol and at the same time lessen the sedative side effect of cyclobenzaprine.

List of Abbreviations

Abbreviation	Meaning
APIs	Active ingredients
ºC	Celsius grade
CNS	Central nervous system
CV	Corrective value
CQA	Critical quality attributes
GI	Gastro intestinal
g	Gram
HDPE	High density poly ethylene
HPLC	High performance liquid chromatography
hr	Hour
LC	Liquid chromatography
C_{max}	Maximum concentration
T_{max}	Maximum time
µL	Micro liter
µm	Micro meter
µg	Microgram
mg	Milligram
ml	Milliliter
mm	Millimeter
min	Minutes
ng	Nano gram
nm	Nanometer
N	Newton
NLT	Not less than
NMT	Not more than
OTC	Over the counter
QbD	Quality by design
QTPP	Quality target product profile
RLD	Reference listed drug
RH	Relative humidity

RSD	Relative standard deviation
rpm	Revolution per minutes
Sec	Second
UV	Ultra violet
U.S. FDA	United states food and drug administration
VF	Volumetric flask
WHO	World health organization

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Appendices

Appendix A

Tables of Study

Table A.1
General stability storage conditions

Study Term	Storage Condition	Minimum Period of Study at Submission
Long term	25°C± 2°C/60% RH± 5% RH or: 30°C± 2°C/65% RH± 5% RH	12 Months
Intermediate	30°C± 2°C/65% RH± 5% RH	6 Months
Accelerated	45°C± 2°C/75% RH± 5% RH	6 Months

Table A.2
Scale of Flowability

Compressibility Index	Powder Flow Properties	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

Table A.3
API& Excipients Water content (WC)/loss on drying (LOD)

Material	Test	Limit
Cyclobenzaprine HCl	LOD	*NMT 5.0 %
Paracetamol	LOD	NMT 5.0 %
Avicel 101	LOD	NMT 7.0 %
Magnesium stearate	LOD	NMT 6.0 %
Sodium starch glucolate	LOD	NMT 10%

*NMT: Not more than.

Table A.4

(API: Excipients) Ratios for Compatibility Test.

No.	(API: Excipient)	Ratio
1	Paracetamol: Avicel 101	(1:1)
2	Paracetamol: magnesium stearate	(1:1)
3	Paracetamol: sodium starch glycolate	(1:1)
4	Paracetamol: Cyclobenzaprine HCl	(1:1)
5	Cyclobenzaprine HCl: Avicel 101	(1:1)
6	Cyclobenzaprine HCl: magnesium stearate	(1:1)
7	Cyclobenzaprine HCl: sodium starch glycolate	(1:1)

Appendix B

Data collection form

استمارة بحث علمي

جامعة النجاح الوطنية

كلية الدراسات العليا

ماجستير علوم صيدلانية

استمارة رقم ( )

2022/2021

هذا الاستبيان تقوم به طالبة ماجستير علوم صيدلانية في جامعة النجاح الوطنية لغرض الدراسة العلمية لتقييم الفعالية والأعراض الجانبية الناتجة عن دواء مرخى العضلات مع المسكن وهما سيكلوبينزوبرابن مع الباراسيتامول لدى المرضى في فلسطين.

نرجو الاجابة على جميع الأسئلة بدقة علما بأنها ستستخدم لأغراض البحث العلمي.

القسم الأول : معلومات عامة

- العمر:_____
- الجنس: ذكر أنثى
- المستوى التعليمي: أمي المرحلة الابتدائية/الإعدادية المرحلة الثانوي التعليم الجامع أعلى من ذلك
- أين تعيش في فلسطين؟ مدينة قرية مخيم
- الحالة الاجتماعية: أعزب متزوج مطلق **أرمل**
- الدخل الشهري للعائلة بالشيكل: اقل من1000 1000-3000 3000-5000 أكثر من 5000
- هل لديك تأمين صحي؟ نعم, تأمين حكومي نعم, تأمين خاص لا
- الحالية الصحية بشكل عام: ممتازة جيدة جدا جيدة مقبولة سيئة

القسم الثاني : التاريخ المرضي

سبب الحضور للطبيب :

الامراض التي تعاني منها :

هل تستعمل ادوية اخرى مرخية للعضلات او دواء اخر مع السيكلوبينزوبرين : ☐ لا ☐ نعم

(في حال الجواب ب نعم) ما هي الادوية الاخرى :

No.	Medication

جرعة الدواء : ☐ 5 mg 10 ☐ mg

الاسم التجاري:

هل استعملت سايكلوبنزوبراين من قبل: ☐ نعم ☐ لا

هل فعالية الدواء كانت افضل خلال استخدامه مع الباراسيتامول: : ☐ نعم ☐ لا

القسم الثالث : الأعراض الجانبية من الدواء

هل عانيت من اي من الاعراض التالية بعد استعمال دواء سايكلوبنزوبراين:

الاعراض الجانبية	نعم	لا
النعاس		
التعب		
وجع في الراس		
دوخة		
جفاف بالفم		
الام في المعدة		
غثيان		
امساك		

عند تناول السيكلوبنزوبراين مع البراسيتامول هل الاعراض /بعضها التي عانيت منها من السيكلوبنزوبران وحده قلت او اختفت: نعم ☐ لا ☐

اذا كان الجواب نعم , ما هي:

شكرا لتعاونكم

Data Collection Form

Dear doctor, could you please give us a few minutes to fill this questionnaire.

We are carrying out this questionnaire as a part of master thesis to study a muscle relaxant drug (Cyclobenzaprine HCl) in term of uses and whether it is used with Paracetamol, how often they are both prescribed together and to collect opinions about development of a new formulation that contains both drugs in one tablet to meet patient compliance.

Sociodemographic data

Gender

- Male
- Female

Age

- < 30 years
- 30-40 years
- 50-60 years
- >60 years

Place of work

- Governmental hospital
- Private hospital
- Governmental healthcare center
- Private clinic
- Others: _____

Specialty:

- Orthopedics doctor, if you have subspecialty, please identify _____
- Surgical, if you have subspecialty, please identify _____
- Nerve doctor, if you have subspecialty, please identify _____
- Others: _____

Years of experience”

- < 5 years
- 5-10 years
- 10-20 years
- >20 years

Paracetamol is a commonly used analgesic. How often do you prescribe paracetamol (acetaminophen)?

- Daily
- Weekly
- Monthly
- Yearly

Cyclobenzoprine is a muscle relaxant. How often do you prescribe Cyclobenzoprine?

- Daily
- Weekly
- Monthly
- Yearly

Do you need sometimes to prescribe Paracetamol with Cyclobenzoprine?

- Yes
- No

If yes, In what cases both drugs may be prescribed togather for the same patient?
……
……
……
……

In your opinion Is it a useful idea to develop Cyclobenzaprine HCl and paracetamol in a combination as a one tablet drug?

- Yes
- No

If yes, what do you think the best formulation type is:

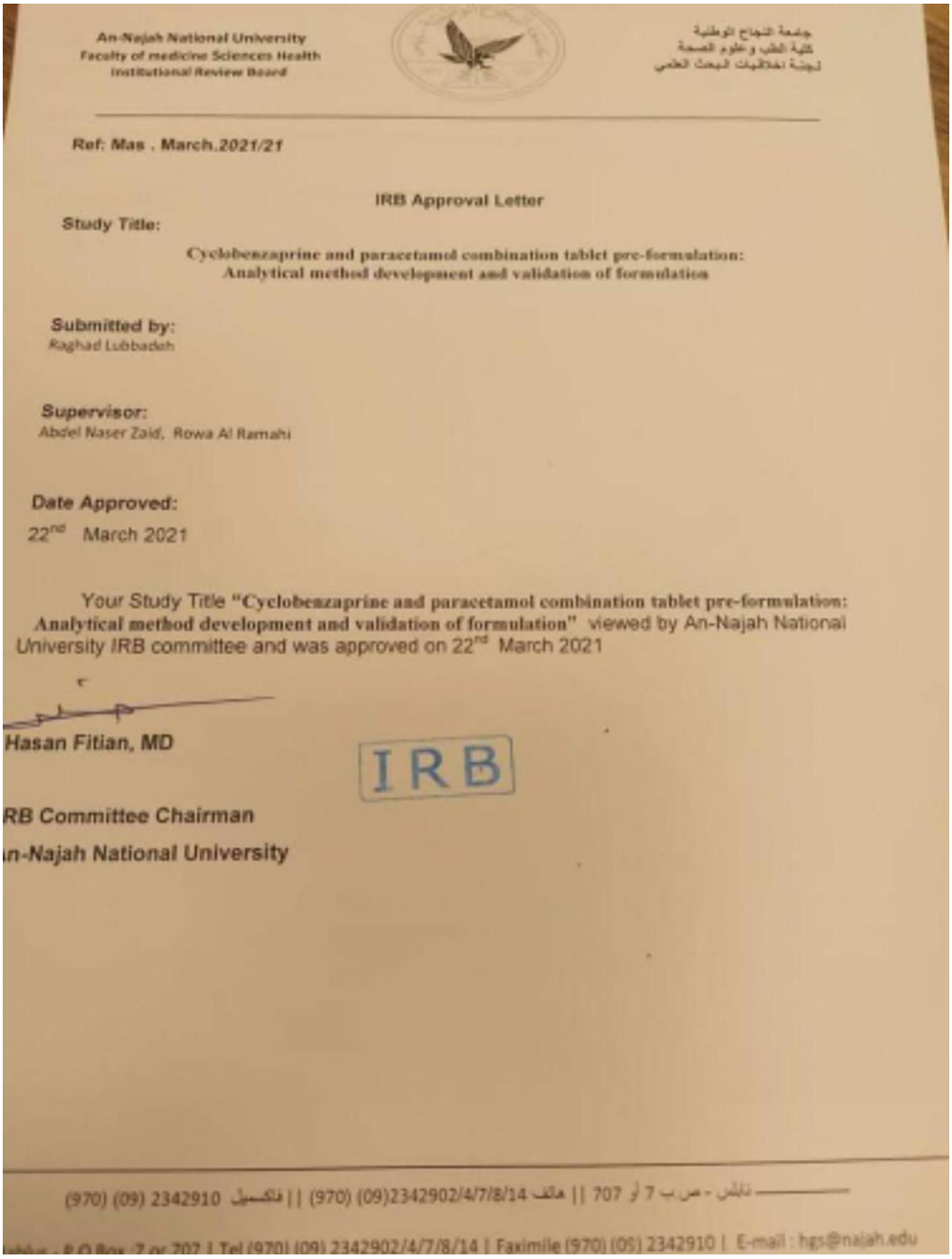
- Mixed powder tablet.
- Two layer tablet.
- Tablet within tablet.

Other notes:
……
……
……
……

We thank you for your cooperation

Appendix C

IRB approval



An-Najah National University
Faculty of medicine Sciences Health
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب و علوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas . March.2021/21

IRB Approval Letter

Study Title:

Cyclobenzaprine and paracetamol combination tablet pre-formulation: Analytical method development and validation of formulation

Submitted by:
Raghad Lubbadeh

Supervisor:
Abdel Naser Zaid, Rowa Al Ramahi

Date Approved:
22nd March 2021

Your Study Title "Cyclobenzaprine and paracetamol combination tablet pre-formulation: Analytical method development and validation of formulation" viewed by An-Najah National University IRB committee and was approved on 22nd March 2021

Hasan Fitian, MD

IRB

RB Committee Chairman
n-Najah National University

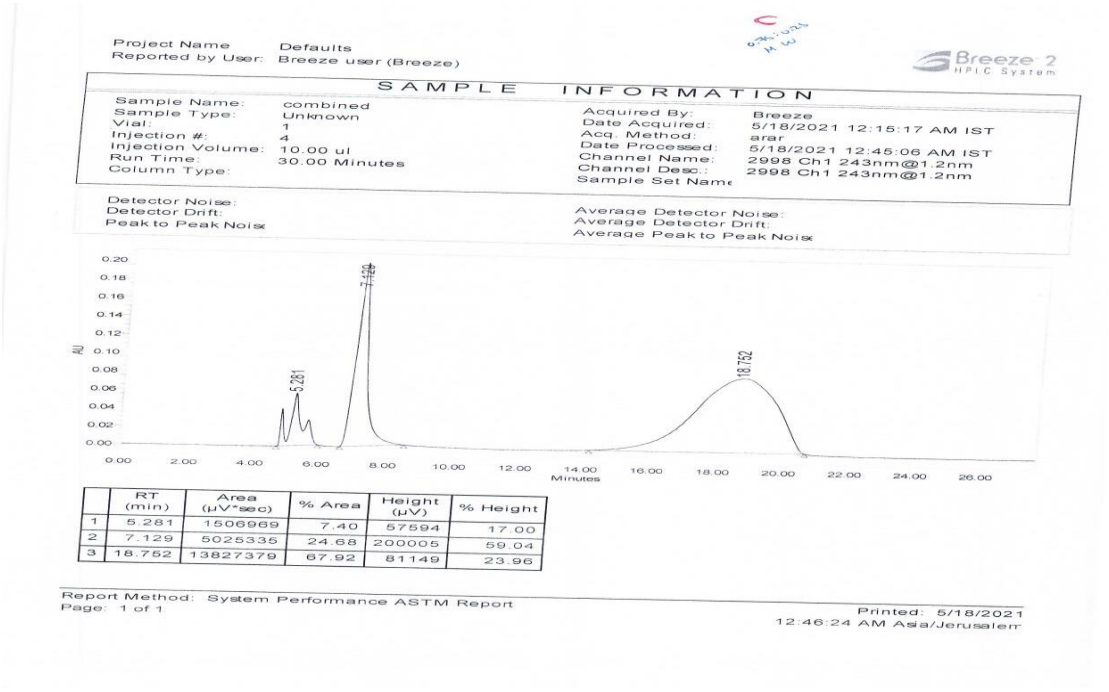
(970) (09) 2342910 فاكسميل || (970) (09)2342902/4/7/8/14 هاتف || 707 أو 7 ص.ب - نابلس

Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (05) 2342910 | E-mail : hgs@najah.edu

Appendix D

Chromatogram results

Trials



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Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	5/18/2021 12:15:17 AM IST
Vial:	1	Acq. Method:	arar
Injection #:	4	Date Processed:	5/18/2021 12:45:06 AM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 243nm@1.2nm
Run Time:	30.00 Minutes	Channel Desc.:	2998 Ch1 243nm@1.2nm
Column Type:		Sample Set Name:	

Detector Noise:
Detector Drift:
Peak to Peak Noise:
Average Detector Noise:
Average Detector Drift:
Average Peak to Peak Noise:

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	5.281	1506969	7.40	57594	17.00
2	7.129	5025335	24.68	200005	59.04
3	18.752	13827379	67.92	81149	23.96

Report Method: System Performance ASTM Report
Page: 1 of 1
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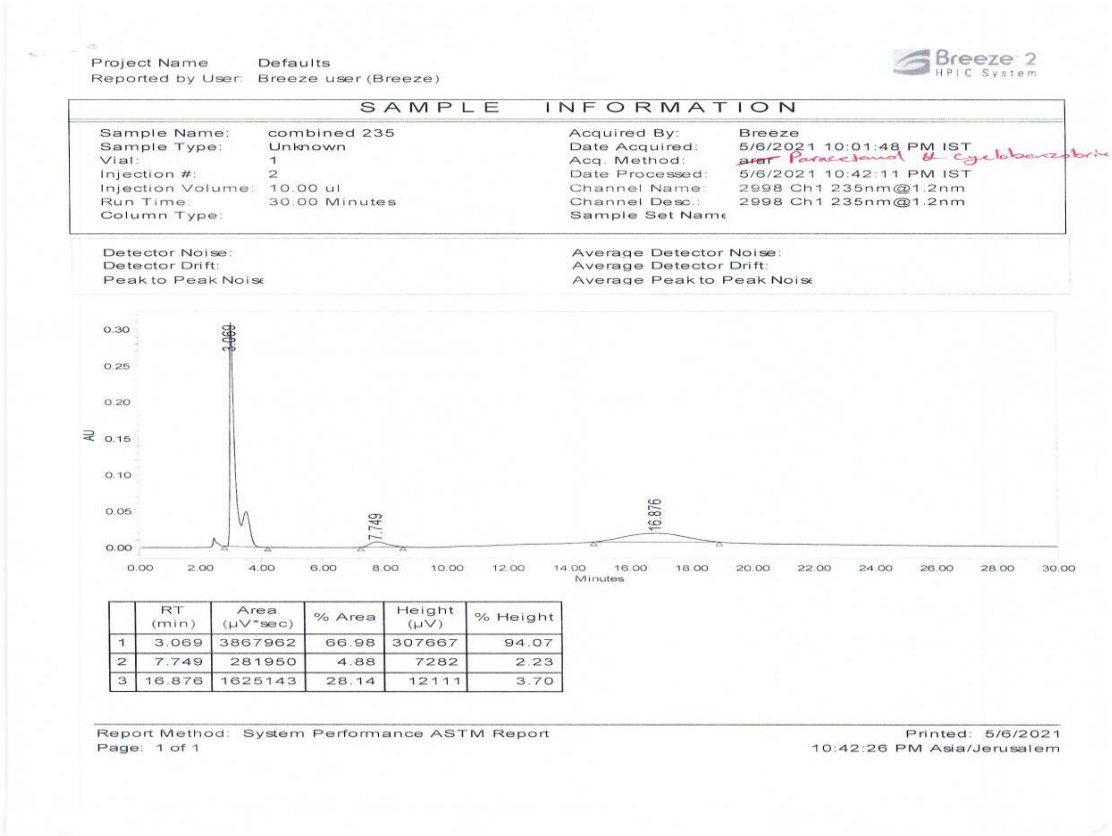

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Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	combined 235	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	5/6/2021 10:01:48 PM IST
Vial:	1	Acq. Method:	arar Paracetamol & Cyclobenzaprine
Injection #:	2	Date Processed:	5/6/2021 10:42:11 PM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 235nm@1.2nm
Run Time:	30.00 Minutes	Channel Desc.:	2998 Ch1 235nm@1.2nm
Column Type:		Sample Set Name:	

Detector Noise:
Detector Drift:
Peak to Peak Noise:
Average Detector Noise:
Average Detector Drift:
Average Peak to Peak Noise:

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	3.069	3867962	66.98	307667	94.07
2	7.749	281950	4.88	7282	2.23
3	16.876	1625143	28.14	12111	3.70

Report Method: System Performance ASTM Report
Page: 1 of 1
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Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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Injection #:	9	Date Processed:	6/16/2021 12:46:03 AM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 235nm@1.2nm
Run Time:	40.00 Minutes	Channel Desc.:	2998 Ch1 235nm@1.2nm
Column Type:		Sample Set Name	

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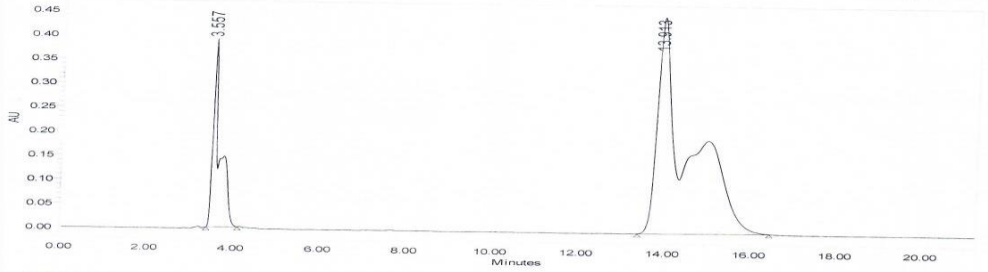
Detector Drift:	Average Detector Drift:
Peak to Peak Noise	Average Peak to Peak Noise



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	3.557	4549253	17.04	391272	46.59
2	13.913	22150937	82.96	448634	53.41

Report Method: System Performance ASTM Report
Page: 1 of 1

Printed: 6/16/2021
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Project Name: Defaults
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Breeze 2 HPLC System

SAMPLE INFORMATION

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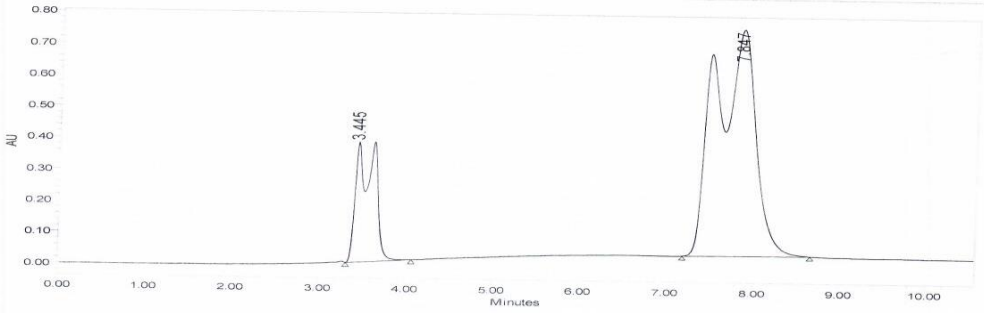
Sample Type:	Unknown	Date Acquired:	6/16/2021 11:17:01 PM IST
Vial:	1	Acq. Method:	C8
Injection #:	2	Date Processed:	6/16/2021 11:57:42 PM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 235nm@1.2nm
Run Time:	40.00 Minutes	Channel Desc.:	2998 Ch1 235nm@1.2nm
Column Type:		Sample Set Name	

Detector Noise:
Detector Drift:
Peak to Peak Noise:

Average Detector Noise:
Average Detector Drift:
Average Peak to Peak Noise:



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	3.445	5513891	19.36	380281	34.63
2	7.847	22959874	80.64	717781	65.37

Report Method: System Performance ASTM Report
Page: 1 of 1

Printed: 6/16/2021
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Project Name: Defaults
Reported by User: Breeze user (Breeze)

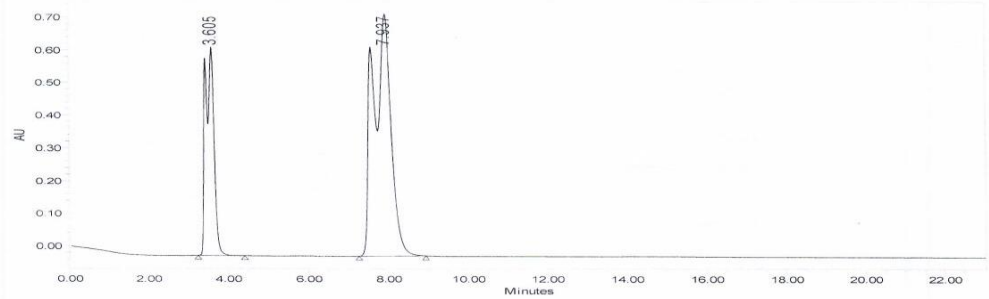
Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	comb 20:10 (0.7)2	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	6/16/2021 11:28:36 PM IST
Vial:	1	Acq. Method:	C8
Injection #:	3	Date Processed:	6/16/2021 11:58:11 PM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 235nm@1.2nm
Run Time:	40.00 Minutes	Channel Desc.:	2998 Ch1 235nm@1.2nm
Column Type:		Sample Set Name	

Detector Noise:
Detector Drift:
Peak to Peak Noise:

Average Detector Noise:
Average Detector Drift:
Average Peak to Peak Noise:



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	3.605	9599450	29.32	638403	46.26
2	7.937	23135960	70.68	741636	53.74

Report Method: System Performance ASTM Report
Page: 1 of 1

Printed: 6/16/2021
11:58:23 PM Asia/Jerusalem

Project Name Defaults
Reported by User: Breeze user (Breeze)

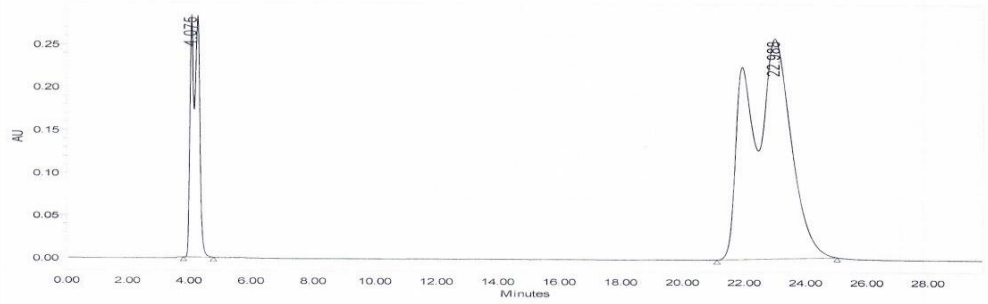
Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	comb 20:5	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	6/16/2021 9:55:34 PM IST
Vial:	1	Acq. Method:	C8
Injection #:	2	Date Processed:	6/16/2021 11:55:59 PM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 235nm@1.2nm
Run Time:	40.00 Minutes	Channel Desc.:	2998 Ch1 235nm@1.2nm
Column Type:		Sample Set Name	

Detector Noise:
Detector Drift:
Peak to Peak Noise

Average Detector Noise:
Average Detector Drift:
Average Peak to Peak Noise



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	4.075	5229734	17.40	283615	52.38
2	22.988	24821404	82.60	257885	47.62

Report Method: System Performance ASTM Report
Page: 1 of 1

Printed: 6/16/2021
11:56:16 PM Asia/Jerusalem

Project Name Defaults
Reported by User: Breeze user (Breeze)

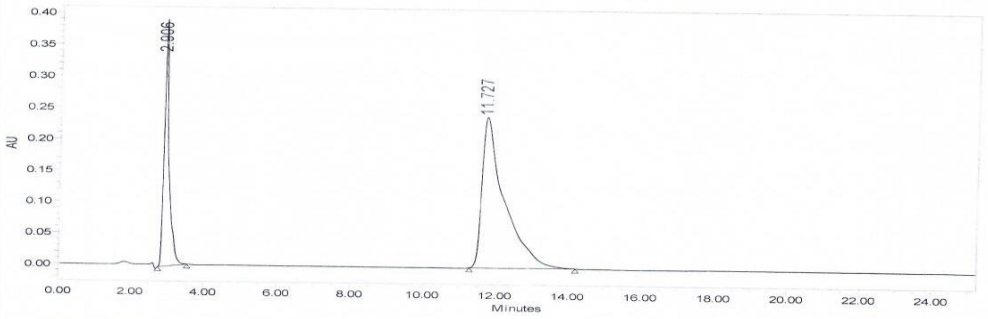
Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	com.31-5	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	6/1/2021 1:07:15 AM IST
Vial:	1	Acq. Method:	C8
Injection #:	10	Date Processed:	6/1/2021 1:37:38 AM IST
Injection Volume:	10.00 ul	Channel Name:	2998 Ch1 235nm@1.2nm
Run Time:	40.00 Minutes	Channel Desc.:	2998 Ch1 235nm@1.2nm
Column Type:		Sample Set Name	

Detector Noise:
Detector Drift:
Peak to Peak Noise

Average Detector Noise:
Average Detector Drift:
Average Peak to Peak Noise



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	2.906	3683521	26.41	392975	62.07
2	11.727	10264203	73.59	240104	37.93

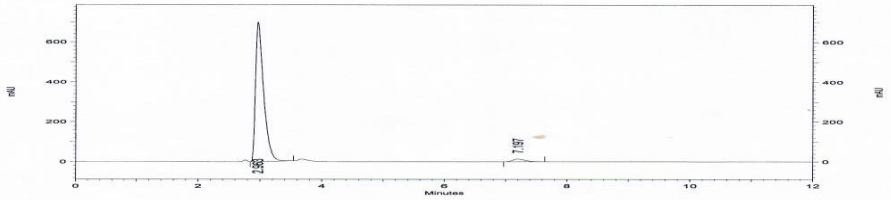
Report Method: System Performance ASTM Report
Page: 1 of 1

Printed: 6/1/2021
1:37:57 AM Asia/Jerusalem

Validation chromatograms:

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.2 & 0.002 mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\054Paracetamol & Cyclobenzoprine linearity 0.2 & 0.002 mg per ml
Analysis Date: 1/19/2022 1:50:04 AM



UV Results

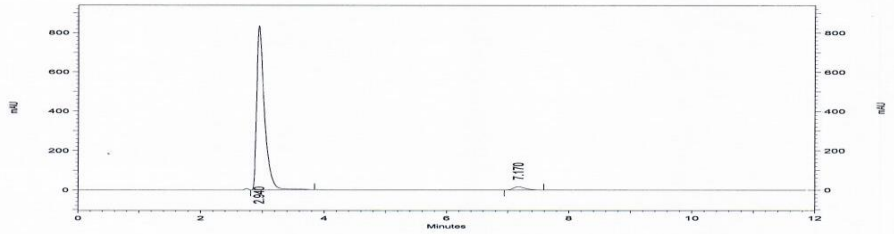
Pk #	Name	Retention Time	Area	Height
1		2.963	25324393	2802441
2		7.197	788000	56488
Totals			26112393	2858929

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.225 & 0.00225mg per ml

Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\004Paracetamol & Cyclobenzoprine linearity 0.225 & 0.00225mg per ml
Analysis Date: 1/18/2022 2:45:42 PM



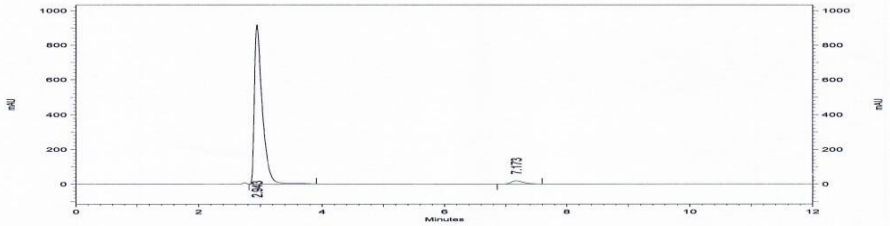
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.940	29529447	3338425
2		7.170	902820	66361
Totals			30432267	3404786

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.25 & 0.0025mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\007Paracetamol & Cyclobenzoprine linearity 0.25 & 0.0025mg per ml
Analysis Date: 1/18/2022 3:25:27 PM



UV Results

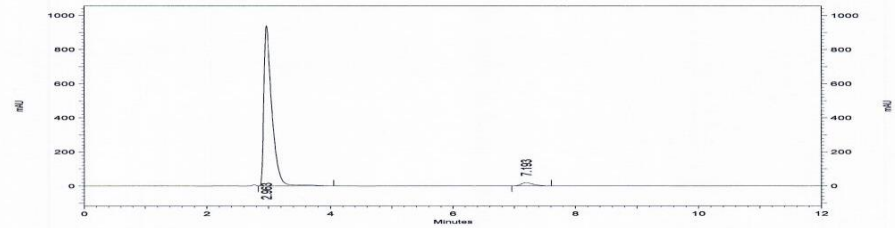
Pk #	Name	Retention Time	Area	Height
1		2.943	32706502	3674518
2		7.173	1006440	73882
Totals			33712942	3748400

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.275 & 0.00275mg per ml

Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\011Paracetamol & Cyclobenzoprine linearity 0.275 & 0.00275mg per ml
Analysis Date: 1/18/2022 4:18:35 PM



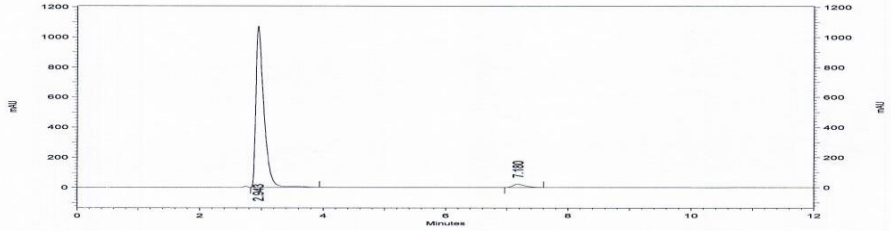
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.963	34375485	3754997
2		7.193	1037110	75526
Totals			35412595	3830523

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.3 & 0.003 mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\015Paracetamol & Cyclobenzoprine linearity 0.3 & 0.003 mg per ml
Analysis Date: 1/18/2022 5:11:31 PM



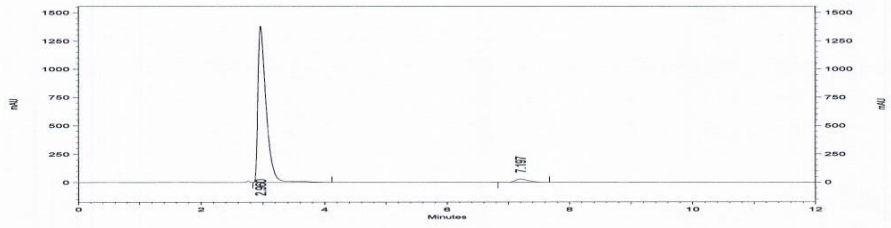
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.943	38588784	4292248
2		7.180	1166900	85353
Totals			39755684	4377601

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.4 & 0.004mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\016Paracetamol & Cyclobenzoprine linearity 0.4 & 0.004mg per ml
Analysis Date: 1/18/2022 5:24:53 PM



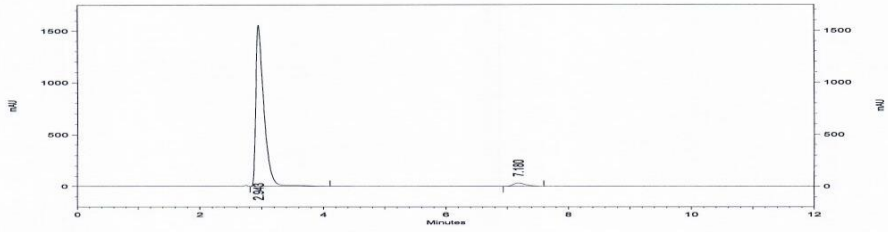
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.960	50952170	5529452
2		7.197	1570122	112439
Totals			52522292	5641891

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.45 & 0.0045 mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\019Paracetamol & Cyclobenzoprine linearity 0.45 & 0.0045 mg per ml
Analysis Date: 1/18/2022 6:04:53 PM



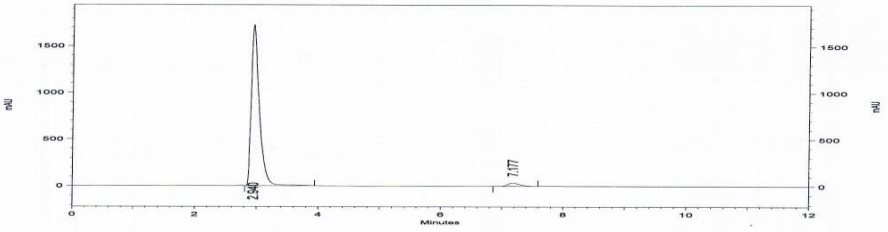
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.943	56554141	6225831
2		7.180	1724920	125727
Totals			58279061	6351558

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.5 & 0.005mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\024Paracetamol & Cyclobenzoprine linearity 0.5 & 0.005mg per ml
Analysis Date: 1/18/2022 7:11:21 PM



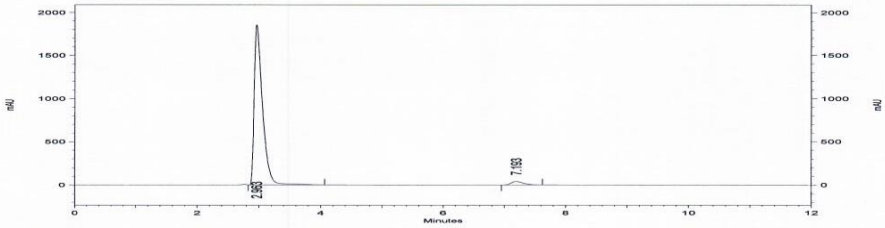
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.940	62727920	6913946
2		7.177	1988457	142305
Totals			64716377	7056251

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.55 & 0.0055mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\026Paracetamol & Cyclobenzoprine linearity 0.55 & 0.0055mg per ml
Analysis Date: 1/18/2022 7:37:53 PM



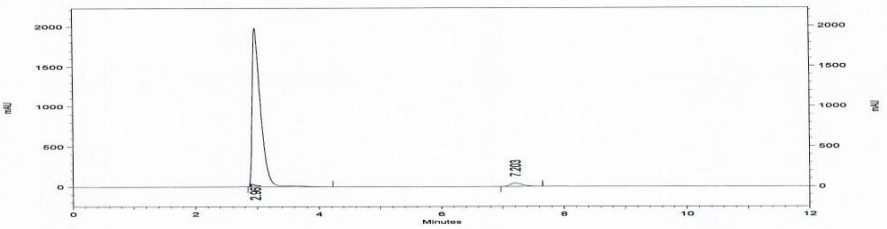
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.963	69014188	7430914
2		7.193	2160502	155550
Totals			71174690	7586464

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine linearity 0.6 & 0.006mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\028Paracetamol & Cyclobenzoprine linearity 0.6 & 0.006mg per ml
Analysis Date: 1/18/2022 8:04:17 PM



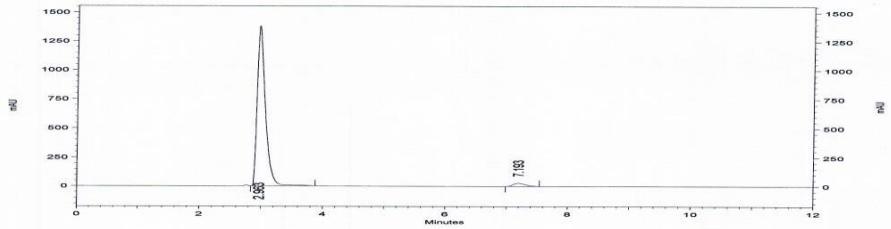
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.967	74352001	7919849
2		7.203	2322893	166941
Totals			76674894	8086790

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine accuracy samp 0.4 & 0.004mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\037Paracetamol & Cyclobenzoprine accuracy samp 0.4 & 0.004mg per ml
Analysis Date: 1/18/2022 10:04:01 PM



UV Results

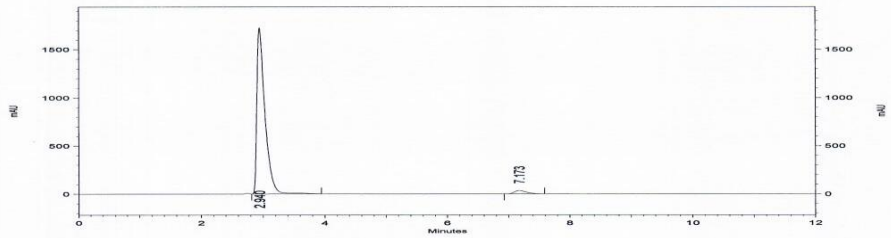
Pk #	Name	Retention Time	Area	Height
1		2.963	50897636	5529669
2		7.193	1494641	110629
Totals			52392277	5640298

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

100.1
100.1

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine accuracy samp 0.5 & 0.005mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\045Paracetamol & Cyclobenzoprine accuracy samp 0.5 & 0.005mg per ml
Analysis Date: 1/18/2022 11:50:20 PM



UV Results

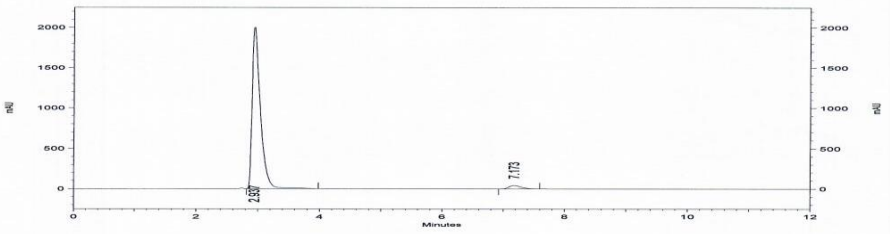
Pk #	Name	Retention Time	Area	Height
1		2.940	62866862	6915720
2		7.173	1949041	141125
Totals			64815903	7056845

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

100.5
100.0

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine accuracy samp 0.6 & 0.006mg per ml
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\050Paracetamol & Cyclobenzoprine accuracy samp 0.6 & 0.006mg per ml
Analysis Date: 1/19/2022 12:56:50 AM



UV Results

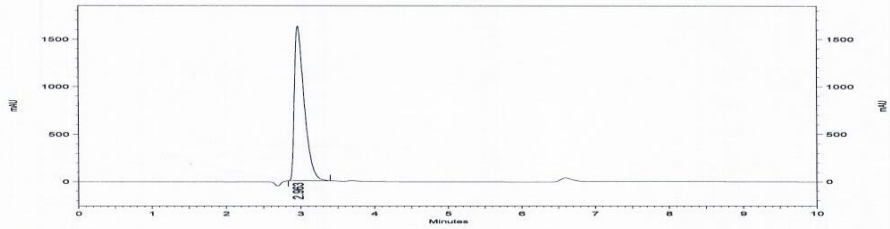
Pk #	Name	Retention Time	Area	Height
1		2.937	73921612	7998726
2		7.173	2306714	167330
Totals			76228326	8166056

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1

99.7
100.8

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine acid stress condition zero time
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\058Paracetamol & Cyclobenzoprine acid stress condition zero time
Analysis Date: 1/19/2022 9:41:18 AM



UV Results

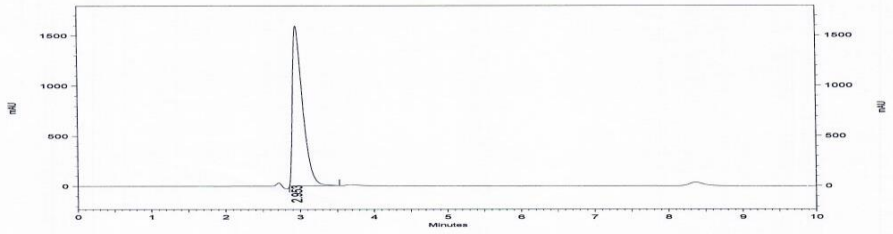
Pk #	Name	Retention Time	Area	Height
1		2.963	59522330	6516829
Totals			59522330	6516829

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (2)

Dana Pharmaceuticals

R&D Department

Sample Name: Paracetamol & Cyclobenzoprine base stress condition zero time
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\059Paracetamol & Cyclobenzoprine base stress condition zero time
Analysis Date: 1/19/2022 9:52:34 AM



UV Results

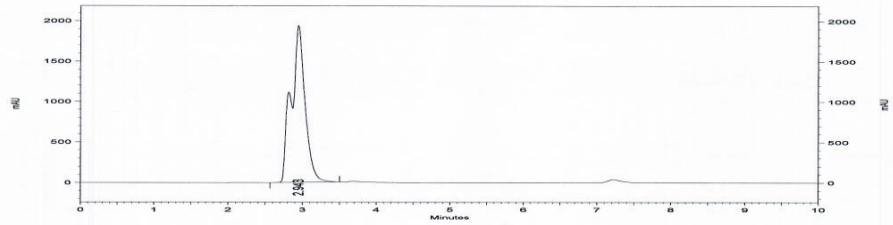
Pk #	Name	Retention Time	Area	Height
1		2.953	60286427	6377155
Totals			60286427	6377155

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (3)

Dana Pharmaceuticals

R&D Department

Sample Name: Paracetamol & Cyclobenzoprine Oxid stress condition zero time
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\060Paracetamol & Cyclobenzoprine Oxid stress condition zero time
Analysis Date: 1/19/2022 10:03:51 AM



UV Results

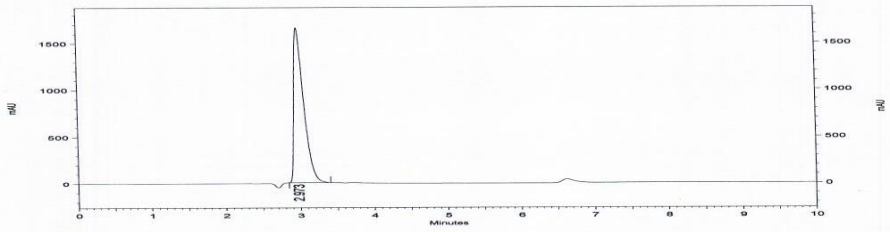
Pk #	Name	Retention Time	Area	Height
1		2.943	100759469	7758640
Totals			100759469	7758640

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (4)

Dana Pharmaceuticals

R&D Department

Sample Name: Paracetamol & Cyclobenzoprine acid stress condition 1 h
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\061Paracetamol & Cyclobenzoprine acid stress condition 1 h
Analysis Date: 1/19/2022 10:15:07 AM



UV Results

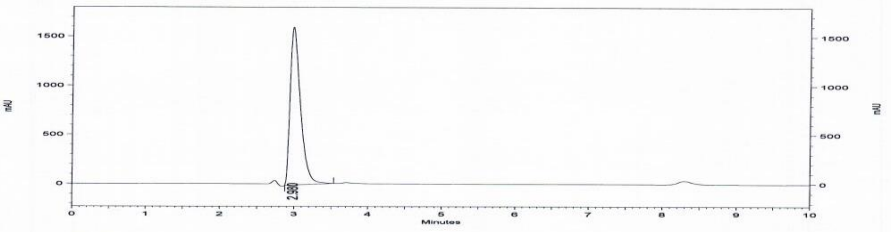
Pk #	Name	Retention Time	Area	Height
1		2.973	60850181	6612556
Totals			60850181	6612556

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (5)

Dana Pharmaceuticals

R&D Department

Sample Name: Paracetamol & Cyclobenzoprine base stress condition 1 h
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\062Paracetamol & Cyclobenzoprine base stress condition 1 h
Analysis Date: 1/19/2022 10:26:29 AM



UV Results

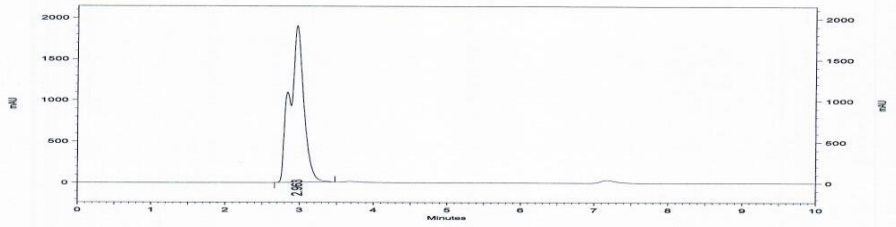
Pk #	Name	Retention Time	Area	Height
1		2.980	62190179	6438438
Totals			62190179	6438438

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (6)

Dana Pharmaceuticals

R&D Department

Sample Name: Paracetamol & Cyclobenzoprine Oxid stress condition 1 h
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\063Paracetamol & Cyclobenzoprine Oxid stress condition 1 h
Analysis Date: 1/19/2022 10:37:48 AM



UV Results

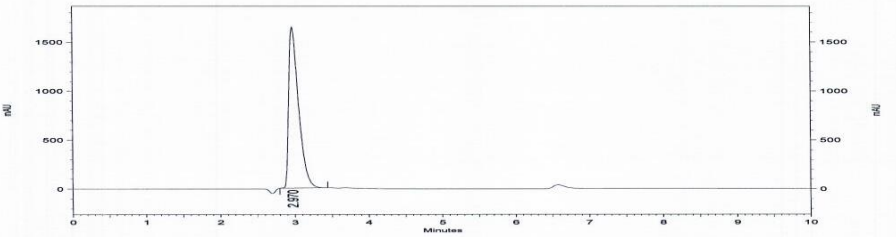
Pk #	Name	Retention Time	Area	Height
1		2.963	99709181	7612682
Totals			99709181	7612682

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (7)

Dana Pharmaceuticals

R&D Department

Sample Name: Paracetamol & Cyclobenzoprine acid stress condition 2 h
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\064Paracetamol & Cyclobenzoprine acid stress condition 2 h
Analysis Date: 1/19/2022 10:49:03 AM



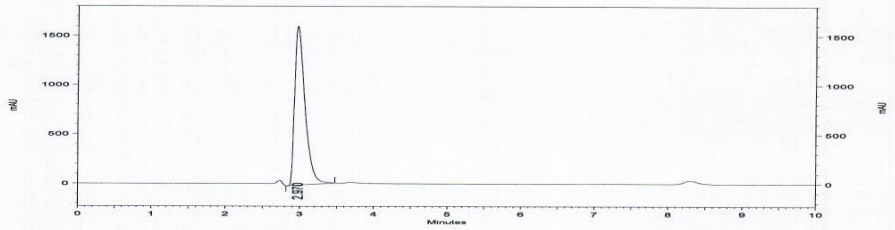
UV Results

Pk #	Name	Retention Time	Area	Height
1		2.970	60605836	6581421
Totals			60605836	6581421

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
Page 1 of 1 (8)

Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine base stress condition 2 h
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\065Paracetamol & Cyclobenzoprine base stress condition 2 h
Analysis Date: 1/19/2022 11:00:25 AM



UV Results

Pk #	Name	Retention Time	Area	Height
1		2.970	62004130	6460231
Totals			62004130	6460231

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
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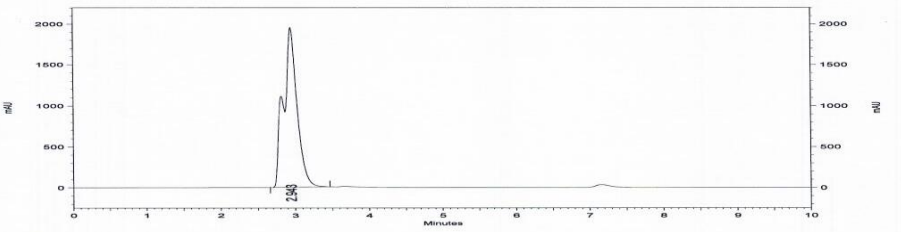
Dana Pharmaceuticals
R&D Department

Sample Name: Paracetamol & Cyclobenzoprine Oxid stress condition 2 h
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\066Paracetamol & Cyclobenzoprine Oxid stress condition 2 h
Analysis Date: 1/19/2022 11:11:49 AM



UV Results

Pk #	Name	Retention Time	Area	Height
1		2.943	100296541	7809014
Totals			100296541	7809014

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
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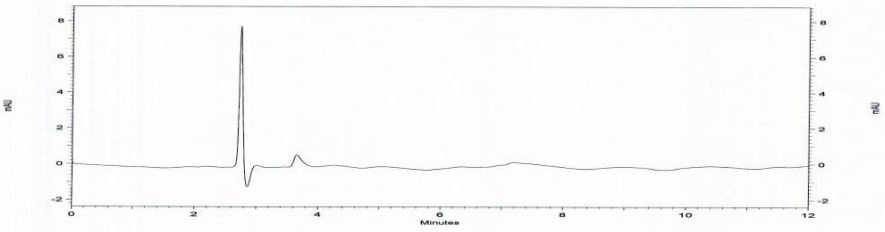
Dana Pharmaceuticals

R&D Department

Sample Name: blank
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\031blank
Analysis Date: 1/18/2022 8:44:12 PM



UV Results

Pk #	Name	Retention Time	Area	Height

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
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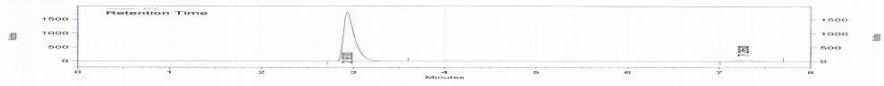
Area % Report Page 1 of 1

Data File: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\010Pracetaml & Cyclbenzoprine std 0.25 & 0.0025
Method: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Method\Raghad Lubbadeh.met
Acquired: 11/1/2021 11:09:07 AM
Printed: 11/1/2021 1:45:24 PM

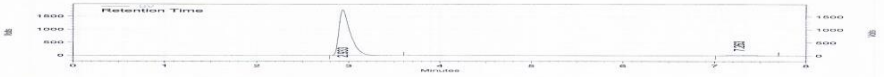


UV Results

Retention Time	Area	Area %	Height	Height %
2.930	60207389	96.82	7013848	98.02
7.360	1974597	3.18	141320	1.98
Totals	62181886	100.00	7154168	100.00

Area % Report Page 1 of 1

Data File: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\019Paracycle sample tab
Method: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Method\Raghad Lubbadeh.met
Acquired: 11/1/2021 12:32:46 PM
Printed: 11/1/2021 1:47:42 PM

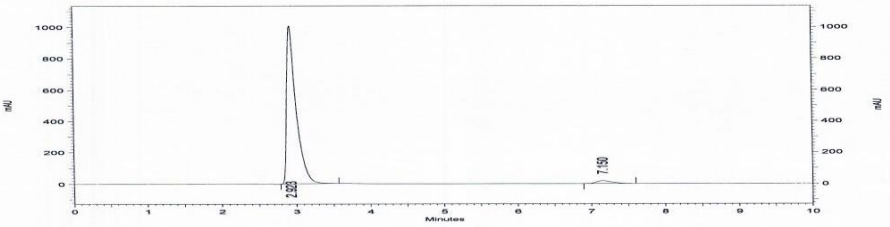


UV Results

Retention Time	Area	Area %	Height	Height %
2.933	60621468	96.84	7002302	98.03
7.263	1976150	3.16	140765	1.97
Totals	62597618	100.00	7143067	100.00

Dana Pharmaceuticals
R&D Department

Sample Name: Cyclobenzaprine and Paracetamol std
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\006Cyclobenzaprine and Paracetamol std
Analysis Date: 1/30/2022 11:05:13 AM



UV Results

Pk #	Name	Retention Time	Area	Height
1		2.923	35163945	4031514
2		7.150	1007303	71957
Totals			36171248	4103471

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
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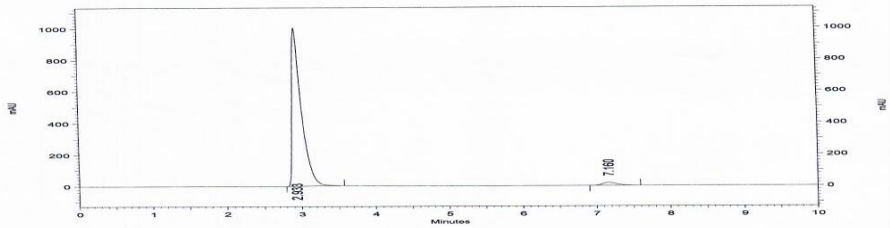
Dana Pharmaceuticals
R&D Department

Sample Name: Paracyclo sample 25 C
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\010Paracyclo sample 25 C
Analysis Date: 1/30/2022 11:50:12 AM



UV Results

Pk #	Name	Retention Time	Area	Height
1		2.933	35216156	4015840
2		7.160	996236	71439
Totals			36212392	4087279

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
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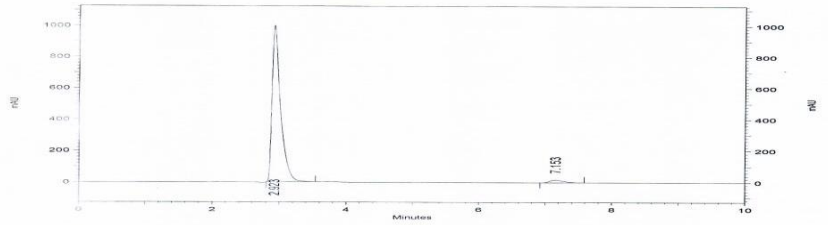
Dana Pharmaceuticals

R&D Department

Vit K3

Sample Name: Cyclobenzaprine and Paracetamol std
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\017Cyclobenzaprine and Paracetamol std
Analysis Date: 02/05/2022



UV Results

Pk #	Name	Retention Time	Area	Height
1		2.923	34956215	3997649
2		7.153	993861	71223
Totals			35950076	4068872

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 **Version 3.1.4**
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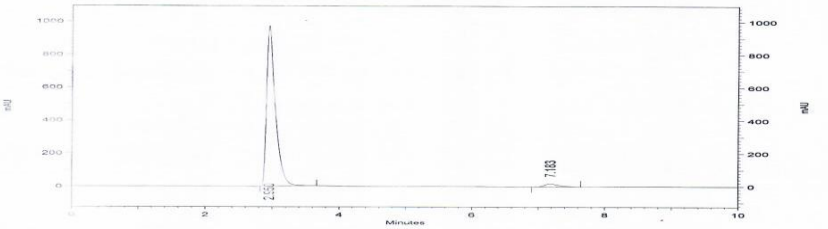
Dana Pharmaceuticals

R&D Department

Vit K3

Sample Name: Paracyclo sample 40 C
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\015Paracyclo sample 40 C
Analysis Date: 02/05/2022



UV Results

Pk #	Name	Retention Time	Area	Height
1		2.950	34945834	3892825
2		7.183	1003243	70669
Totals			35949077	3963494

Computer name: ADMIN-XRK203YVY
Build 3.1.4.2412 Version 3.1.4
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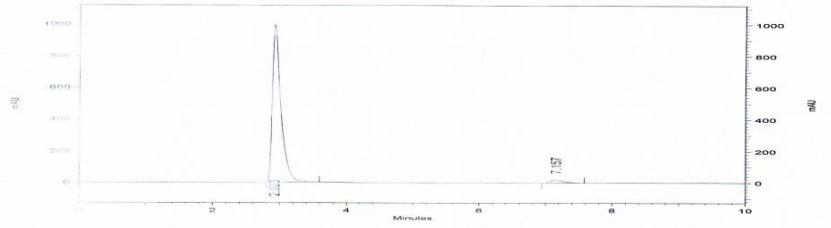
Dana Pharmaceuticals

R&D Department

Vit K3

Sample Name: Paracyclo sample 25 C
Injection Volume: 15 u
File Name: C:\EZChrom Elite\Enterprise\Projects\Raghad Lubbadeh\Data\011Paracyclo sample 25 C
Analysis Date: 02/05/2022



UV Results

Pk #	Name	Retention Time	Area	Height
1		5.923	34931243	3983835
2		7.157	987399	70897
Total			35918642	4054732

Computer name: ADMIN-NRR203YVY
Build 3.1.3.2412 Version 3.1.4
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جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

تصميم وتركيب وتطوير طريقة التحليل لمنتج حبوب السايكلوبينزابراين والباراسيتامول

إعداد

رغد عبد الرؤوف صبحي لبادة

إشراف

أ. د. عبد الناصر زيد

أ. د. رواء الرمحي

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجه الماجستير في العلوم الصيدلانية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

تصميم وتركيب وتطوير طريقة التحليل لمنتج حبوب السايكلوبينزابراين والباراسيتامول

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الملخص

الخلفية: السيكلوبنزابرين والباراسيتامول من الأدوية التي قد تحتاج إلى تناولها معًا، يستخدم السيكلوبينزابرين هيدروكلورايد كمرخي للعضلات والباراسيتامول كدواء لتسكين الآلام.

الهدف: كان الهدف من هذه الدراسة هو تصنيع وتقييم ثبات حبوب السيكلوبنزابرين والباراسيتامول عند تصنيعها في حبوب تحتوي عليهما معًا. بالإضافة إلى ذلك ، تم تطوير طريقة فحص جديدة تم التحقق من صحتها بالكامل واستقرارها وهي طريقة تحليل HPLC لاختبار جودة وثبات الحبوب التي تم تصنيعها.

الطريقة: تم تحسين صيغة حبوب تحتوي على السيكلوبنزابرين والباراسيتامول كلاهما معا واختياره وفقًا لعدة معايير؛ تم استخدام بعض عناصر الجودة حسب التصميم (QbD) لتطوير الأقراص المرغوبة التي يجب أن تكون فعالة علاجياً. وبناءً على ذلك، تم إجراء بحث مركَّز حول عوامل الجودة النوعية التي قد تتأثر بتغيير واقعي في صياغة المنتج الدوائي أو عملية التصنيع أثناء التطوير الصيدلاني. وتضمنت قياس نسبة المادة الفعالة في المستحضر والذوبان وفحص التحلل. علاوة على ذلك؛ تم تقييم ثبات الأقراص بعد 3 و 6 أشهر في ظل ظروف تخزين مختلفة. تم تطوير طريقة التحليل HPLC والتحقق من صحتها وفقًا للمتطلبات الخاصة.

النتائج: كانت حبوب خليط البودرة المكونة من 5 ملغ من سيكلوبنزابرين و500 ملغ باراسيتامول موحدة الوزن بمتوسط 650 ملغ، هي أقراص محدبة بيضاوية الشكل مع عدم وجود عيوب في الشكل بعد المعالجة أو تغيرات في قطرها أو سمكها. كانت جميع معايير جودة المنتج ضمن المواصفات بما في ذلك تلك الخاصة بسمات الجودة الحرجة وغير الحرجة.

تم إجراء طرق التحقق الكاملة من الصحة والثبات للإجراءات التحليلية المستخدمة في اختبار نسبة المادة الفعالة ونسبة التحلل، حيث أظهرت الطرق المستخدمة في التحليل ذوبانًا خطيًا عاليًا مع دقة R^2 أكثر من 0.99 مع انحراف معياري نسبي أقل من 2٪ ونتائج الدقة بين 98.0–102٪ جميعها للسيكلوبنزابرين والباراسيتامول.

لم يظهر ثبات أقراص البودرة المحضرة أي تغيرات في جميع المتغيرات المختبرة؛ التي كانت ضمن الحدود المقبولة خلال فترة الثبات المختبرة (6 أشهر). لذلك يمكن تصنيع حبوب السيكلوبنزابرين والباراسيتامول كخليط مع بعضها في حبة واحدة والتي ستكون على شكل جرعات ذات معايير جودة جيدة؛ وهذا مناسب لإرخاء العضلات وتسكين الآلام معا.

الخلاصة: تمت تصنيع حبوب السيكلوبنزابرين والباراسيتامول كحبة واحدة معا بنجاح وأظهرت نتائج ثباتية مقبولة. كانت طريقة HPLC التي تم تطويرها والتحقق من صحتها مناسبة لتوصيف وتقييم الحبوب المصممة ويمكن استخدامها لتحليل تلك الحبوب حيث ان الاختبارات غير مدرجة في المراجع الخاصة للادوية.

الكلمات المفتاحية: سيكلوبنزابرين، باراسيتامول، تصنيع، تثبت، حبوب.