Deanship of Graduate Studies

Al-Quds University

Determination and Evaluation of Stability of Extemporaneous Preparations

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M.Sc. Thesis

Jerusalem – Palestine

1443/2022 هـ

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A Thesis Submitted in partial fulfilment of requirements for the degree of Master of Chemical Industry in Applied and Industrial Technology Program. Al-Quds University

1443/2022هـ

Al-Quds University
Deanship of Graduate Studies
Applied and Industrial Technology
Department of Science and Technology

Thesis Approval

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Master thesis submitted and accepted, Date: 31/5/2022

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Jerusalem/ Palestine

1443/2022

Dedication:

I would like to dedicate this work to my first hero, my father, Arafat, "May God have mercy on him," who was the first one to encourage me to complete my academic degree, from bachelor's to a master's degree, to provide myself with a lot of knowledge.

To my beloved mother, Amira, who supported me during my educational journey and stood by me in all the circumstances that made me stop my education for a while,

To my husband, Ismael, who supported me all the time. I could never have done this without your support and encouragement.

To my dear teacher, Dr. Tariq Jubeh, who always believed in me.

To my precious brothers and sisters, I am grateful to you all for always having my back.

To my husband's family for their warm wishes, smiles, and love.

To all my friends and everyone who supported me and helped me,

Anwar

Declaration:

I certify that this thesis is submitted for the degree of Master graduation in applied industrial technology is my own research, except where otherwise acknowledges, and that this thesis (or any part of the same) has not been submitted for the higher degree to any other university or institute.

Name: Anwar Arafat Musa Abu Sneineh

Signed: 

Date: 4/6/2022

Acknowledgment:

If you are grateful, I will surely give you more and more. Surat Ibrahim, aya7.

All thanks firstly to Allah almighty, Lord of power and givenness.

Dr. Tariq Jubeh, my supervisor, deserves special thanks for his expert advice, direction, and tireless efforts in completing this project.

Special thanks for Dr. Mahmoud Khateeb for his assistance, advice and guidance.

All my heartfelt thanks to my family, my friends, and my colleagues, and An honest thanks to all who supported me without expecting it during my studies.

Abstract:

Introduction and aims: Extemporaneous preparations are those made by the pharmacist, usually by using previously prepared dosage forms such as tablets and creams. These preparations are prepared when there is a need to change the concentration or the dosage form of the drug. The most frequent types in Palestine are the liquid dosage forms prepared for children using tablets as the starting materials. However, there are several problems with these preparations, most importantly their stability and homogeneity. The uniformity of the dose applied may be the most critical issue. A survey we conducted in local pharmacies showed that no single standard is followed in these preparations, and no quality control study has been conducted so far to check the validity of these products. This study was conducted to make a comparison and suggest formulative solutions by analyzing formulations made by methods followed in local pharmacies and by methods that are pharmaceutically more accurate. Two drugs were chosen that are widely used for extemporaneous preparations; furosemide and pantoprazole. The experiments on these two drugs were aimed at testing the uniformity of the dose of the oral liquids prepared. A third drug, aspirin, was chosen to test the stability of the oral liquid prepared since many pharmacies make a suspension of aspirin in water without taking into consideration the effect of hydrolysis of aspirin on the stability and uniformity of the product.

Methodology: In the first part of the study, tablets of furosemide and pantoprazole were used to make oral liquids of three different formulations. The first method was by dissolving the tablets in water. The second method was by using syrup as the vehicle. The third method was by using syrup with a suspending agent, either carboxymethyl cellulose or xanthan gum, at different concentrations. The suspensions were stored at room temperature or at 4C and samples were taken periodically for analysis of the concentration of active material. The effect of the type of suspending agent and its concentration on the uniformity of the preparation was examined. In the second part of the study, aspirin degradation in the aqueous environment was examined by conductivity measurement. The conductivity measures the increase in ion concentrations as the aspirin degrades into two acids, acetic acid and salicylic acid. In this part, a calibration curve was constructed to simulate the percentage of aspirin degradation with the relevant conductivity values. Aspirin was dissolved in water and a stability study was done by periodically reading conductivity values. In

another study, propylene glycol was used as a co-solvent in order to examine the ability of propylene glycol to decrease the rate of aspirin degradation.

Results and discussion: a lack of uniformity of furosemide suspensions was observed for liquids made by tablets dispersed in water or syrup as compared to those preparations made using a suspending agent. Using a suspending agent greatly increased the stability and uniformity of the products, as indicated by measurements of yield values and the range. These results were attributed to the low solubility of furosemide, which calls for the preparation of a well-established extemporaneous pharmaceutical suspension. Different results were obtained in the case of pantoprazole, where dispersing tablets in water offered a homogeneous preparation. This could be explained by the good solubility of pantoprazole. However, using a suspending agent did decrease the range calculated, which is a measure of the fluctuation in the concentration of the drug in daily samples. In the second part of the study, the hydrolytic degradation of aspirin was clearly demonstrated, as indicated by the increase in conductivity in the aspirin solution per time. The addition of propylene glycol decreases the rate of aspirin degradation, probably by decreasing the polarity of the solvent.

Conclusions: It is concluded that pre-formulation studies are vital prior to the compounding of extemporaneous preparations. These studies should include testing of the physico-chemical properties of the active ingredient, such as solubility, pka, and stability in aqueous solutions. Formulative considerations taken into account should include using suspending agents, viscosity modifying agents, and materials that prevent the hydrolysis or increase the stability of the active ingredient when applicable.

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Abbreviations

CMC	**Carboxymethyl cellulose**
PG	**Propylene Glycol**
FDA	**Food and Drug Administration**
USP	**United States Pharmacopeia**
GERD	**Gastroesophageal Reflux disease**
PPI	**Proton pump inhibitor**
NSAIDs	**Non-steroidal anti-inflammatory drugs**
ZE	**Zollinger-Ellison**
UPLC	**The ultra-performance liquid chromatography**
HPLC	**high-performance liquid chromatography**
R.T	**Room Temperature**
SA	**salicylic acid**
AA	**acetic acid**
ASA	**Acetyl salicylic acid**

Chapter One:

Introduction

1.1 Introduction:

The world's population is increasing rapidly, and the number of patients is increasing, some of them with difficulty swallowing, including older and pediatric patients.

A lack of commercially available oral liquids creates a problem for health care professionals, especially pharmacists with practice who receive formal training in compounding medications and are licensed to dispense them. They are now required to provide a solution for them.

It is essential for every medication to have access to a special dosage form when administered to infants, children, and other required populations. Sometimes the drugs for pediatric patients are not available in suitable dosage forms for them to use.

Most commercial medicines are available in dosage forms suitable for specific groups of patients. As such, drugs may be prepared extemporaneously, taking into consideration the chemical and physical properties of drugs and their excipients. These kinds of preparations lack studies to document stability, efficacy, tolerability, pharmacodynamics, pharmacokinetics, and bioavailability.

The lack of pharmacopoeial stability formulae and the fact that their stability is not easily determined by both the active pharmaceutical ingredient and the ability of excipients from a product to interact with each other and with the pharmaceutical ingredient makes the preparation challenging.

The complexity of the stability considerations is increased within these oral liquids, increasing the number of parameters to be considered in every extemporaneous preparation of oral liquids.

Pharmacists and pediatricians are often faced with modifying oral dose forms intended for adult use into suitable forms for pediatric administration.

The lack of quality control measures increases the risks associated with compounding by putting patients at risk of contamination in medicine. In addition, there are no quality control tests done to assure the safety and quality of these medicines. As a result, extemporaneous compounding is necessary to provide health care to populations of patients such as geriatrics, pediatric patients, and other adults who are not able to swallow solid dosage forms due to swallowing difficulties.

1.2 Extemporaneous preparations:

The process by which a pharmacist, using traditional compounding techniques, produces a medicinal product that is suitable for fulfilling some special needs of a particular patient or a particular category of patients is called "extemporaneous preparation." [1]

1.2.1 Importance of extemporaneous preparations:

1. For drug products that are not commercially available in liquid form.
2. For patients with allergies to some of the additives present in commercial formulations.
3. For patients who cannot swallow solid dosage forms, such as infants, pediatrics, geriatrics and some psychiatric patients.
4. For products that are therapeutically better in liquid dosage form.
5. For geriatric patients who are often administered oral liquids to prevent them from placing solid dosage forms under the tongue and not swallowing those at the time of administration, i.e., nursing homes, incarcerated patients.
6. For patients on the enteral feeding method who require a liquid dosage form.
7. They offer a wide diversity of dosage forms and dosage strengths.
8. More bioavailability in oral liquids than in oral solids

1.2.2 Problems and objectives of concern in extemporaneously prepared drug products:

1. Lack of published standards
2. Lack of access to various publications containing stability data on diverse medication formulations
3. Lack of information about chemical, physical, and microbiological stability data, as well as a short shelf-life
4. Lack of knowledge concerning about validation and reproducibility
5. Inadequate confirmation of dose uniformity
6. Lack of an appropriate dosage form

7. Lack of pure drug compound, the need to manipulate the adult dosage form of the available tablet, capsule, or injection.
8. Cutting, crushing, or dissolving of controlled-release tablets releases the entire drug content at once, that may lead to significant overdose.
9. Difficulty of swallowing solid dosage forms.
10. Several various strengths are prepared extemporaneously or as "special" products, with a 10-fold difference in available strengths.
11. Alternative routes of administration for commercial products, such as oral liquids rectally, eye drops in the ear or injectable solutions orally, cause irritation and altered kinetics of absorption and bioavailability.
12. Dilution of commercial formulations leads to dilution of cosolvents, thus precipitating the drug.
13. Microbiological contamination in several doses extemporaneous preparations with insufficient preservation leads to potential risks, especially in the premature and newborn.
14. Variability in general compounding practices and training
15. Suspicions about ingredient compatibility.
16. There is concern about compatibility between manipulated solid dosage forms with food and beverages.
17. The flavor of the drug or the preparation itself.
18. Inaccuracy of dosing (dose uniformity and reproducibility)
19. Concern about bioavailability and efficacy [2]

1.2.3 Oral liquids categories:

Oral liquids are separated into two main categories: solutions and suspensions.

1. **Solutions** are one of the oldest pharmaceutical dosage forms. Solutions refer to liquids where all solid ingredients, including the active, are fully solubilized in a solvent(s). The solvent may be aqueous, organic, or a combination of both. Examples of oral solutions include syrups, elixirs, linctuses, and aromatic waters. [3]

(Table 1.1): type of solutions

Types of Solutions	
Type of Solutions	**Definition**
Syrup	Aqueous preparation containing a high proportion of sucrose or another sweetener
Elixir	Elixir A hydroalcoholic liquid containing syrup
Linctus	A viscous liquid containing sucrose with a small intended volume of administration
Aromatic Waters	Saturated solutions of volatile liquids

Table (1.2) advantages and disadvantages of solutions:

Advantages	**Disadvantages**
Drug may be immediately absorbed	Drug stability may be reduced, due to events such as hydrolysis
Homogeneous, no need to shake the container	Unpalatable tastes are difficult to mask
	Some drugs are poorly soluble

2. **Suspensions** are one of the most significant pharmaceutical dosage forms that are widely acceptable of poorly soluble drugs with different therapeutic purpose .[4]

They are indicated for use in the preparation of tropical, parental, otic, ophthalmic, and oral dosage forms. They are a dispersed system with two phases: particulate materials (dispersed phase) and continuous medium (dispersion medium). [4]

Qualities of an ideal suspension:

a. The particles in disperse phase should not be readily settled down and redisperse on shaking.
b. There should be no cake formation on settled particles.
c. The suspension should be free from grittiness (for tropical use).
d. It should be chemically and physically stable.[4]

1.3 Suspending agents:

Suspending agents are used to aid in the uniform dispersion of powders evenly throughout the preparation to prevent particle flocculation in the preparations. When flocculated particles clump together, gravitational forces pull the particles down, resulting in sedimentation. Alternatively, if the clumped particles are small enough, they can float to the top of the suspension and cause creaming. Suspensions, if improperly prepared, can result in incorrect patient dose.

The suspending agent must be able to slow the sedimentation rate of the drug, help avoid caking, provide a pseudoplastic flow and also be compatible with the active drug and also with the excipients. . [3]

1.4 Challenges and Limitations:

1.4.1 Chemical Instability: Drugs in extemporaneously prepared liquids may be susceptible to chemical reactions leading to degradation. Hydrolysis, oxidation, isomerization, polymerization, and photochemical decomposition are the different types of chemical degradation reactions. [2]

This includes considering the potential degradation of the API by pathways such as oxidation, hydrolysis, photolysis, or thermolysis, as well as any potential interactions between the API, the excipients in the vehicle, the excipients in the original dosage form (e.g., tablet or capsule), and the packaging. [5]

1.4.2 Physical Instability: Extemporaneously prepared oral suspensions may have altered physical qualities such as appearance, palatability, uniformity, dissolution, and suspendability. This includes considering suspension and the ability to administer an accurate dose. Antifoaming chemicals to prevent excessive foaming caused by strong shaking prior to providing a dose, and caking or crystal development that may occur during storage. [5]

1.4.3 Microbiological Instability: Microbial growth in an oral liquid may cause foul odor and turbidity and adversely affect palatability and appearance. High microbe content may be critical to health particularly in very young or immunocompromised patients. By-products of microbial

metabolism may affect the pH of the preparation and reduce the drug's chemical stability or solubility. Microbial contamination must be avoided during preparation by using clean equipment, sterile water (Water for Irrigation BP) and avoiding contaminated raw materials and containers. Preservatives at a suitable strength are used to prevent microbial development in a largely water-based preparation. [5]

1.4.4 Lack of bioavailability and pharmacokinetic/pharmacodynamics studies:

Most extemporaneously prepared drugs have infrequently undergone bioavailability and pharmacokinetic/pharmacodynamics studies. When a regular-release tablet or capsule is used to prepare a suspension, it is anticipated that the bioavailability, pharmacokinetics, and pharmacodynamics will not be impaired in patients. However, when a tablet is crushed and changed to a liquid dosage form before administration, the sustained-release qualities are lost. [5]

1.4.5 Lack of Funding for Research: Because most diseases are more prevalent in adults, the medications are only advised for this population when they are approved by the US Food and Drug Administration (FDA). Due to the low return on investment, manufacturers may be less interested in completing costly Phase I to III trials for labeling in pediatric patients (particularly in neonates, babies, and young children). They may also be hesitant to sponsor studies for the development of pediatric drug formulations since the FDA may see such funding as advocating the use of a drug without undertaking efficacy and safety trials in young patients. The manufacturers of generic medications would be even less interested in funding such independent research projects. [5]

1.4.6 Dose calculation: Errors in converting units from one to another are examples of common calculation errors linked with extemporaneous preparation (e.g., milligrams to micrograms, conversions from weight in volume to millimoles). Problems can also develop when doses are prescribed as free base or salt, potentially leading to calculation errors while preparing and administering formulations (e.g., two-fold errors if caffeine citrate is confused with caffeine base). [5]

1.4.7 Variations in Practice: Although the necessity for extemporaneous formulations may be identical across health care institutions for certain pharmaceuticals, variable drug concentrations, excipients, and procedures may be used to prepare particular formulations. This is due to a lack of

established or "standard" formulations, as well as a lack of information in the literature about stable formulations. [5]

1.5 The disadvantage to using commercially manufactured drug products as the drug source is:

1. The manufactured drug product contains excipients that may alter the stability of the drug.
2. The actual drug content is unknown since variation is permitted, e.g., 90–110% of the active drug in the product.
3. It may make the analytical methods more involved**.**

2. Drugs profile:

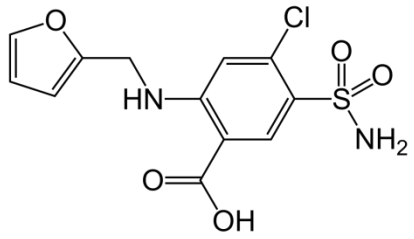
2.1 Furosemide

Is a sulfamoylanthranilic acid derivative, also known as furosemide, it is a potent loop diuretic. Furosemide is widely used to treat hypertension and edema. This agent is highly bound to albumin and is largely excreted unchanged in the urine.

Furosemide is an odorless, white to slightly yellow crystalline powder. A diuretic drug almost tasteless.

Furosemide is a chlorobenzoic acid that is 4-chlorobenzoic acid substituted by a (furan-2-ylmethyl) amino and a sulfonyl group at positions 2 and 5, respectively. It is a diuretic used in the treatment of congestive heart failure. It has a role as a xenobiotic, an environmental contaminant, and a loop diuretic. It is a sulfonamide, a chlorobenzoic acid, and a member of the furans. [6]

2.1.1 Furosemide structure:



2.1.2 Molecular Formula: C12H11ClN2O5S.

2.1.3 Solubility:

It is partially insoluble in water at 73.1 mg/L at 30 °C, Slightly soluble in chloroform, ether, Soluble in acetone, methanol, DMF, and aqueous solutions above pH 8.0. Less soluble in ethanol and freely soluble in alkali hydroxide, at 0.0731 mg/mL at 30 °C. [6]

2.2 Pantoprazole sodium:

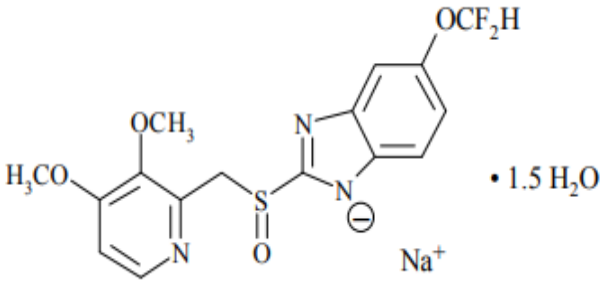
Is a substituted pyridyl methylsulfinyl benzimidazole, is a proton-pump inhibitor (PPI) that is similar in structure and mechanism of action to other acid-activated antiulcer drugs, such as omeprazole, lansoprazole, and rabeprazole. PPIs are weak bases, with a pKa of about 4. [7]

.Pantoprazole sodium is a first-generation proton pump inhibitor (PPI) used for the management of gastroesophageal reflux disease (GERD), for gastric protection to prevent recurrence of stomach ulcers or gastric damage from chronic use of NSAIDs, and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome. It can also be found in quadruple regimens for the treatment of H. pylori infections along with other antibiotics including amoxicillin, clarithromycin, and metronidazole. [8]

Pantoprazole sodium sesquihydrate is a racemic white to off-white crystalline powder. Pantoprazole is both slightly basic and acidic. Pantoprazole sodium sesquihydrate is freely soluble in water , mildly soluble in phosphate buffer at pH 7.4, and essentially insoluble in n-hexane.

The compound's stability in aqueous solution is pH-dependent. The rate of deterioration increases as the pH decreases. The degradation half-life at room temperature is approximately 2.8 hours at pH 5.0 and nearly 220 hours at pH 7.8.[9]

2.2.1 Pantoprazole structure:



2.2.2 Molecular Formula: C16H14F2N3NaO4S · 1.5H2O

2.2.3 Solubility:

Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane [10]

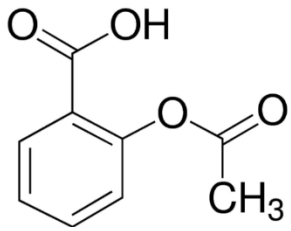
2.3 Aspirin:

Aspirin, also called acetylsalicylic acid, derivative of salicylic acid that is a mild nonnarcotic analgesic (pain reliever) useful in the relief of headache and muscle and joint aches.

Aspirin is effective in reducing fever, inflammation, and swelling and thus has been used for treatment of rheumatoid arthritis, rheumatic fever, and mild infection. In these instances, aspirin

generally acts on the symptoms of disease and does not modify or shorten the duration of a disease.[11]

2.3.1 Aspirin structure:



2.3.2 Molecular Formula: C9H8O4 or CH3COOC6H4COOH.

2.3.3 Solubility

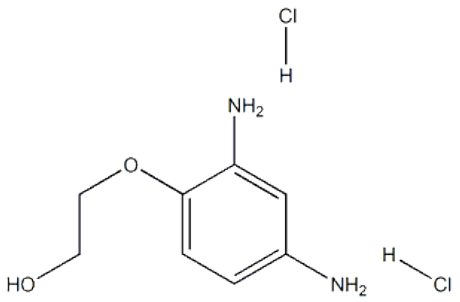
Acetylsalicylic acid is mildly soluble in water, with a reported limit of solubility of around 3 mg/ml at 25 degrees Celsius. It is also 50 mg/ml soluble in ethanol and will dissolve in alkali hydroxide and carbonate solutions with decomposition. [12]

2.4 Xanthan gum

Xanthan Gum is a long chain polysaccharide, which is made by mixing fermented sugars (glucose, mannose, and glucuronic acid) with a certain kind of bacteria. It is mainly used to thicken and stabilize emulsions, foams, and suspensions.

Xanthan gum is widely used as a food additive to control the rheological properties of a wide range of food products. In manufacturing, xanthan gum is used as a thickening and stabilizing agent in toothpastes and medicines. It is used to make medicine for lowering blood sugar and total cholesterol in people with diabetes. It is used as a laxative. Xanthan gum is sometimes used as a saliva substitute in people with dry mouth. [13]

2.4.1 Xanthan gum structure:



2.4.2 Molecular formula: C8H14Cl2N2O2

2.4.3 Solubility:

Xanthan gum soluble in both cold and hot water and is generally not affected by changes in pH value. Xanthan gum will dissolve in most acids or bases. Xanthan gum as is with all hydrocolloids bind water. [14]

2.4.4 How much xanthan gum should be used?

The higher the weight ratio of xanthan gum added to a liquid, the thicker the liquid will become. In general, 0.2 % xanthan gum by weight results in minor thickening. Using 0.7–1.5 % xanthan gum results in a thicker liquid. Too much xanthan gum can provide an unpleasant and undesirable slimy texture.

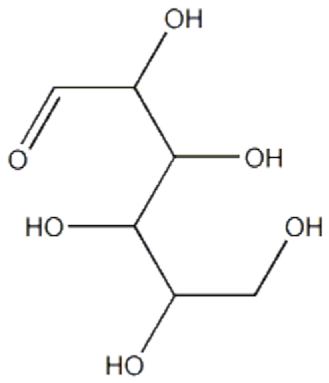
With as little as 0.1% xanthan gum, an emulsion can be created. When the amount of gum is increased, the emulsion becomes thicker and more stable. With around 0.8 % xanthan gum, a thick, stable emulsion is created. [14]

2.5 Carboxy Methyl Cellulose (CMC):

Carboxymethyl cellulose is a cellulose derivative that consists of the cellulose backbone made up of glucopyranose monomers and their hydroxyl groups bound to carboxymethyl groups. It is added in food products as a viscosity modifier or thickener and emulsifier.

It has the properties of a thickening, stabilizer, binder, film forming, and suspending agent. Dressings, ice cream, baked goods, puddings, and sauces are just a few of the items that contain it. The percentage range is 0.05 to 0.5 percent. Also known as cellulose gum. [17]

2.5.1 Carboxy Methyl Cellulose structure:



2.5.2 Molecular formula: C6H12O6

2.5.3 Solubility: Carboxymethyl cellulose CMC is a water-soluble substance that may be dissolved in either hot or cold water. It is insoluble in organic solvents but soluble in miscible solvents such as ethanol or acetone. Its viscosity does not change with temperature. [18]

3 .Problem statement

The stability and homogeneity of extemporaneous preparations in the local Palestinian pharmacy sector are questionable. Many question marks are raised about the way these preparations are made and the pre-formulation steps taken prior to their compounding. A quick survey shows that it is common practice in pharmacies to make oral liquids by grinding tablets and adding either water or syrup to them. These actions do not comply with appropriate compounding requirements for the preparation of oral liquids, such as oral solutions and suspensions. The final product will be missing fundamental elements such as uniformity of dose, stability, and organoleptic properties. Community pharmacies do not perform tests on the prepared extemporaneous products to test their quality, and so this issue raises a lot of concern.

Moreover, it is well known that active pharmaceutical materials differ in their solubilities, molecular weight, pKa, physical form, taste, being acids or bases. Therefore, it is important to know that each drug will have its own requirements when it is to be prepared as an oral liquid product. It is impossible to think that all products can be prepared in the same way, and it must be implied that the physicochemical properties of drugs should be taken into consideration when preparing extemporaneous formulations.

Objectives of the study:

The main objective of this research is to study the dose uniformity and stability of extemporaneous preparations (of furosemide, Pantoprazole and aspirin). This research aims at exploring problems facing these types of preparations and proposing formulative solutions to enhance their quality.

Specific Objectives:

1- To prepare oral liquid dosage forms containing furosemide and pantoprazole, based on the formulative procedures undertaken by the local pharmaceutical sector.

Tablets present in pharmacies will be used to prepare these extemporaneous preparations

2- To test the stability (by measuring the concentration of active material), organoleptic properties including taste, odor and smell, dose uniformity, shelf life and suspension properties of these formulations.

3- In the case of aspirin, we aim at studying the rate of degradation in aqueous solutions and suggest methods to decrease the degradation.

4- To suggest formulative solutions related to problem that are thought to arise during the preparation of the above mentioned liquids. These solutions will be based on preformulation studies that take into account the physicochemical properties of the drugs, the need for specific suspending agents and the pH of the preparation

Chapter two:

Literature Review

2.1 Literature review:

Boscolo O. (2019) et al., developed and studied the physicochemical and microbiological stability of omeprazole (a proton pump inhibitor) liquid oral formulations used as therapeutic agents in many acid-related disorders for pediatric use. Furthermore, stability was validated by the high-performance liquid chromatography (HPLC) method for the analysis of omeprazole in the studied formulations. Oral liquid suspensions of omeprazole were prepared at 2 mg/mL using crushed omeprazole pellets (formulation A) and pure omeprazole (formulation B) with a complete vehicle including humectant, suspending, sweetening, antioxidant, and flavoring agents. Samples were stored at 4°C and 25°C. The omeprazole content of each formulation was analyzed in triplicate using micro-HPLC at 0, 3, 7, 14, 30, 60, 90, 120, and 150 days. Other parameters were also determined, such as appearance, pH, resuspendibility, and viscosity. Microbiological studies were conducted according to the United States Pharmacopeia (USP) guidelines for non-sterile products. Formulation A stayed physicochemically and microbiologically stable at refrigerated (4°C) conditions for at least 150 days, and it only stayed stable for 14 days at 25°C. At least 90 days of physicochemical and microbiologically stable conditions at refrigerated (4°C) conditions, but it is not recommended to store at 25°C for more than 1 day. The proposed analytical method was suitable for the study of the stability of different formulations. [19]

Milic J. et al. (2017) explored the stability of omeprazole in pediatric suspension in order to determine the most suitable suspension. Three formulations were prepared and stored under refrigerated conditions and at room temperature for 30 days. The contents of omeprazole and preservatives were determined by a liquid chromatographic method. Obtained results demonstrated that an extemporaneously compounded vehicle consisting of xanthan gum 0.3%, sodium bicarbonate 8%, compound hydroxybenzoate solution APF 1%, and purified water to 100% is an adequate suspending vehicle for preparing individually compounded omeprazole oral liquid formulations. This formulation can be considered stable for 30 days when stored in an amber glass bottle, refrigerated at 2-8 C, and therefore, has significant potential as a viable alternative to commercially available capsules when that dosage form is found to be inappropriate. [20]

Shadi Baniasadi et al. (2012) set up extemporaneous compounding and determined the stability and quality of omeprazole suspension, which is not commercially available in Iran. Omeprazole 2

mg/mL was prepared using sodium bicarbonate base, placed in 120 mL glass bottles and stored at 5°C for 28 days. Samples were collected on days 1, 7, 14, 21, and 28 after preparation for analysis by high performance liquid chromatography (HPLC) and assessment of appearance, odor, and Ph. Omeprazole was stable for up to 28 days in the liquid formulations. No substantial changes in the appearance, odor, or pH of any liquid were observed. Their extemporaneous unit is the first compounding service in Iran where oral liquids such as omeprazole suspension can be prepared according to standard protocols. [21]

Makeen H. et al. (2020) were taken up to perform the stability study of extemporaneous omeprazole oral suspension frequently used in a referral hospital to determine the shelf life. Stability studies were performed by keeping the freshly constituted preparations in small containers at 2°C–8°C and 25°C 5°C; samples were withdrawn at 0, 7, 14, 21, and 28 days and assayed by the spectrophotometric method at 301 nm. The percent degradation or stability was calculated for each preparation, and the data was extrapolated to find out the shelf life. It was found that the shelf life (t 90%) of omeprazole oral suspension, prepared extemporaneously, is 32 days at room temperature (25 °C 5 °C) and 54 days in the refrigerator (2 °C 8 °C). [22]

Shoosanglertwijit J. et al. (2011) prepared extemporaneous furosemide suspensions from commercial furosemide tablets using two compounded suspending vehicles, compounded suspending vehicle 1 and compounded suspending vehicle 2. Compounded suspending vehicle 1 consisted of xanthan gum 0.25 g, glycerin 10 mL, syrup USP 50 mL, parabens concentrate 1 mL, and purified water to 100 mL. Compounded suspending vehicle 2 consisted of sodium carboxymethyl cellulose 0.1 g, glycerin 5 mL, sorbitol solution 20 mL, syrup USP 50 mL, parabens concentrate 1 mL, and purified water to 100 mL. And determined the physical, chemical, and microbiological stability of these preparations. Two formulations of extemporaneous furosemide suspensions were prepared from commercially available furosemide 40-mg tablets using two compounded suspending vehicles. Three samples of each formulation were stored in glass bottles protected from light and kept at three controlled temperatures: 4 °C, room temperature (30 °C), and 45 °C. A sample was removed from each bottle immediately after preparation and at 7, 14, 30, 45, and 60 days. The stability-indicating HPLC was used to analyze furosemide. The stability of furosemide suspensions was determined by calculating the percentage of the initial concentration remaining on each test day. At least 93% of the initial furosemide concentration remained in both

compounded furosemide suspensions for up to 60 days. Both formulations had no changes in appearance (color and consistency) or odor. Extemporaneously compounded furosemide suspensions, 2 mg/mL, were stable for at least 60 days when stored in glass bottles protected from light at three controlled temperatures. [23]

Dentinger P. et al. (2002) investigated the stability of a 2 mg/ml pantoprazole suspension made from a tablet and an 8.4% sodium bicarbonate solution. A modified stability indicator high-performance liquid chromatographic (HPLC) method was used to determine pantoprazole concentrations. The solution remained stable for 62 days at 2-8 °C in amber polyethylene terephthalate bottles. After each test interval, the oral drink retained more than 90% of the initial pantoprazole concentration. In either sample, there was no discernible change in color or odor, and no evident microbiological growth. [24]

Thaweethamcharoen T. et al. (2014) evaluated the stability of 3 extemporaneous oral liquid formulations such as 2 mg/ml syrup of furosemide, 2 mg/ml suspension of spironolactone, and 10 mg/ml suspension of hydrochlorothiazide, which were stored in the refrigerator (5 3oC). The physical, chemical, and microbiological stability were evaluated for 1 year, 2 months, and 1 month for furosemide syrup, spironolactone suspension, and hydrochlorothiazide suspension, respectively. The ultra-performance liquid chromatography (UPLC) technique was used for analysis of furosemide, spironolactone, and hydrochlorothiazide concentration in the preparation. At least 90 percent of the initial furosemide concentration remained after 360 days in furosemide syrup. Spironolactone and hydrochlorothiazide suspension declined to less than 90 percent in 60 days and 30 days, respectively. There were no detectable changes in color, odor, pH, and the microbiological tests were negative in all preparations. [25]

Aspirin was shown to be degraded in aqueous solutions [26, 27, and 29]. Germuth found that a 10 % of aspirin hydrolyzed at room temperature in one day in aqueous solutions. [26] Furthermore, Blaug showed that the stability of aspirin in water could be increased by the addition of polyethylene glycol or sorbitol. [28] These reports pointed to the fact that aspirin, as an ester molecule, is subjected to hydrolysis when dissolved in water, and that decreasing the polarity of the solution, or increasing the viscosity will decrease the rate of degradation.

Chapter three:

Materials, Methods and Experiments.

3.1.1 Chemicals and Materials:

Furosemide and pantoprazole kindly provided by Jerusalem Pharmaceutical Company, Palestine.

Acetylsalicylic acid kindly provided by Birzeit Pharmaceutical Company, Palestine.

Al-Quds University- Palestine), Xanthan gum, Carboxymethyl cellulose (CMC), NaOH, Milli-Q water, Salicylic acid, Acetic acid, Propylene glycol, distilled water, Sugar.

Pantover®, Fucid® kindly provided by pharmacies**.**

3.1.2 Instruments and Equipment:

UV-Spectrophotometer (JENWAY), was used to measure the absorbance.

PH- meter (HANNA)

Conductivity-meter (HANNA)

3.2 Methods

In this study, we prepare extemporaneous preparation of oral liquids of two drugs, furosemide and pantoprazole. We also examined the stability of a third drug, aspirin, by following the rate of drug hydrolysis.

In the first part, the suspensions were made by three different methods to simulate the work done in local pharmacies. These methods were chosen according to a survey made in pharmacies where we questioned the pharmacists on how they prepared oral liquids of these two drugs. The methods practiced were of three types:

1- Grinding tablets of the required amount of active ingredient, then dispersing in water
2- Grinding tablets with the required amount of active ingredient, then dispersing in syrup
3- Grinding tablets of the required amount of active ingredient, then dispersing in suspending agents with syrup. This third method was practiced by a minority of pharmacies.

The main aim of this study was to make a comparison between these two methods by analyzing samples taken from these preparations on daily basis, and examining the concentration of the active ingredient in these daily samples.

The results of the analysis were expressed as "yield %" which was calculated as:

% yield = actual concentration/theoretical concentration x 100%.

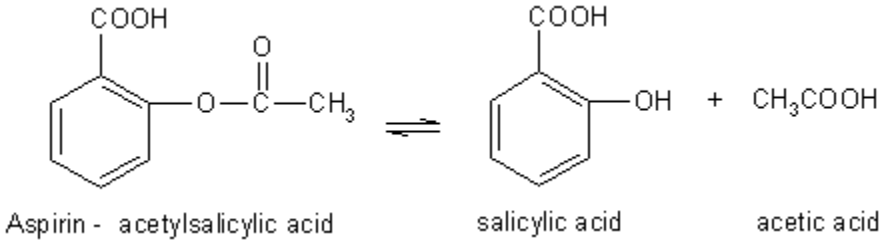
The theoretical concentration is the concentration of drug expected to be obtained in the sample (sample withdrawn after proper shaking), based on the assumption that the preparation is homogeneous.

The concentrations of furosemide and pantoprazole prepared were based on the mean pediatric dose present in practice. For Furosemide it was

2 mg / ml [30], and for Pantoprazole it was 1.6 mg/ml [31]

In the second part of experiments, we followed the hydrolysis pattern of aspirin (See reaction below) [32] by conductivity measurements. The concept of this experiment was to check the stability of aspirin suspensions made in local pharmacies by methods similar to these mentioned above. The focus in our preliminary experiments was to examine the feasibility of increasing the stability of aspirin in aqueous environments (decreasing hydrolysis rates), mainly by reducing the polarity of the aqueous phase with the addition of propylene glycol. [27]

Reaction of aspirin hydrolysis:



As seen in the reaction, the products of hydrolysis are more polar than the aspirin itself. The hydrolysis reaction yields two acids which will increase the conductivity of the solution .This was examined by conductivity meter and a standard curve was constructed to simulate the % of aspirin hydrolysis.

In these experiments, we prepared aqueous Aspirin solutions, containing pediatric dose of aspirin, then conductivity was measured on daily basis to follow up with the rate of aspirin hydrolysis for

12 days. Afterwards, we prepared aqueous solutions of aspirin containing 10% propylene glycol and examined the results of conductivity for the same period.

3.3 Experiments: part 1

3.3.1 Preparation and testing of Furosemide Suspensions

3.3.1.1 Furosemide suspensions in water

Furosemide 2 mg/ml suspensions in water were prepared by triturating 10 tablets of 40 mg furosemide, mixing with distilled water, and diluting to a final volume of 300 mL with distilled water. The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 1, 2, 3, 7, 8, 10, 13, 20, and 23 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL sample diluted with 10 mL of 0.1 M NaOH to a final volume of 250 ml of distilled water was removed for analysis.

Furosemide concentrations were measured by using a UV-Spectrophotometer (JENWAY), and 271 nm was selected as the quantitative wavelength.

3.3.1.2 Furosemide suspensions in Syrup:

Simple syrup preparation:

Simple syrup 85% according to USP was prepared by dissolving 850 g of sucrose into 1000 ml distilled water.

Furosemide 2 mg/ml suspension in syrup was prepared by triturating 10 tablets of 40mg furosemide, mixing with simple syrup and diluting to a final volume of 300 mL with syrup. The suspension was transferred to six amber glass bottles with child resistant caps, three bottles were stored in the refrigerator (4°C) and others were stored at room temperature. At 0, 1, 2, 3, 7, 8, 10 ,13, 20, and 23 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL

sample diluting with 10 mL 0.1 M NaOH to a final volume of 250 ml with distilled water was removed for analysis.

In general, suspensions are prepared as 2% of suspending agent. Different grams was prepared starting from 2g /100ml going down with 1g/100ml, 0.5g/100ml until 0.2/100ml which gave the best result for analysis because others gave very dense results .

3.3.1.3 Furosemide suspensions in Syrup using Xanthan gum 0.2g/100ml:

Furosemide suspensions in syrup using Xanthan gum, 0.2 g/100 ml, were prepared by triturating 10 tablets of 40 mg furosemide, mixing with 0.4 g of xanthan gum and 80 ml of simple syrup, 85%, up to a final volume of 00 ml with distilled water.

The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 1, 3, 6, 9, 13, 14, 16, and 21 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL sample diluted with 10 mL of 0.1 M NaOH to a final volume of 250 ml of distilled water was removed for analysis.

Furosemide concentrations were measured by using a UV-Spectrophotometer (JENWAY), and 271 nm was selected as the quantitative wavelength.

3.3.1.4 Furosemide suspensions in Syrup using Xanthan gum 0.5g/100ml:

Furosemide 2mg/ml suspension in syrup using xanthan gum, 0.5 g/100 ml was prepared by triturating 10 tablets of 40 mg furosemide, mixing with 0.5 g of xanthan gum and 120 ml of simple syrup, 85%, up to a final volume of 300 ml with distilled water.

The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 1, 5, 6, 8, 13, 18, 16, and 21 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL sample diluted with 10 mL of 0.1 M NaOH to a final volume of 250 ml of distilled water was removed for analysis.

Furosemide concentrations were measured by using a UV-Spectrophotometer (JENWAY), and 271 nm was selected as the quantitative wavelength.

3.3.1.5 Furosemide suspensions in Syrup using 0.2g/100ml Carboxymethyl cellulose (CMC):

Furosemide suspensions in syrup using 0.2 g/100 ml of carboxymethyl cellulose were prepared by triturating 10 tablets of 40 mg furosemide, mixing with 0.2 g of carboxymethyl cellulose and 120 ml of simple syrup, 85% up to a final volume of 300 ml with distilled water.

The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 2, 5, 8, 12, 13, 15 and 21 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL sample diluted with 10 mL of 0.1 M NaOH to a final volume of 250 ml of distilled water was removed for analysis.

Furosemide concentrations were measured by using a UV-Spectrophotometer (JENWAY), and 271 nm was selected as the quantitative wavelength.

3.3.1.6 Standard drug solution

A stock standard solution equivalent to 0.5 mL of furosemide was prepared by dissolving 50 mg of pure drug in water and diluting it to 100 mL in a calibrated flask with NaOH 0.1M.

Different aliquots (0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 mL) of 1 mg/mL Pantoprazole solution were accurately measured and transferred into a series of 100 mL volumetric flasks and the volume made up to the mark with water. Then all dilutions were scanned between 200-400 nm against a blank, which shows the maximum absorbance at 290 nm.

3.3.2 Preparation and testing of Pantoprazole Suspensions

3.3.2.1 Pantoprazole suspensions in water

A suspension of pantoprazole 1.6 mg/mL in water was prepared by triturating 12 tablets of 40 mg pantoprazole, mixing with distilled water, and diluting to a final volume of 300 mL with distilled water. The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles with 50ml were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 1, 3, 10, 13, 25, 27, 45, and 46 days, each bottle was inverted and shaken

manually to ensure a uniform suspension, and a 1 mL sample diluted with distilled water to a final volume of 100 ml volumetric flask was removed for analysis.

Pantoprazole concentrations were measured by using a UV-Spectrophotometer (JENWAY) and 290 nm was selected as the quantitative wavelength.

3.3.2.2 Pantoprazole suspensions in syrup

Simple syrup preparation:

Simple syrup 85% according to USP was prepared by dissolving 850 g of sucrose into 1000 ml distilled water.

A suspension of pantoprazole 1.6 mg/mL in syrup was prepared by triturating 12 tablets of 40 mg pantoprazole, mixing with simple syrup, and diluting to a final volume of 300 mL with syrup. The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles with 50ml were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 1, 3, 10, 13, 25, 27, 45, and 46 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL sample diluted with distilled water to a final volume of 100 ml volumetric flask was removed for analysis.

Pantoprazole concentrations were measured by using a UV-Spectrophotometer (JENWAY) and 290 nm was selected as the quantitative wavelength.

3.3.2.3 Pantoprazole suspensions in syrup using Xanthan gum 0.2g/100ml

Pantoprazole 1.6 mg/mL suspension in syrup using Xanthan gum 0.2 g/100 ml was prepared by triturating 12 tablets of 40 mg pantoprazole, mixing with 0.2 g of xanthan gum and 120 ml of simple syrup 85% up to a final volume of 300 ml with distilled water.

The suspension was transferred to six amber glass bottles with child-resistant caps; three bottles with 50ml were stored in the refrigerator (4°C), and the others were stored at room temperature. At 0, 1, 2, 7, 8, 16, and 45 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1 mL sample diluted with distilled water to a final volume of 100 ml volumetric flask was removed for analysis.

Pantoprazole concentrations were measured by using a UV-Spectrophotometer (JENWAY) and 290 nm was selected as the quantitative wavelength.

3.3.2.4 Pantoprazole suspensions in syrup using Carboxymethyl cellulose (CMC) 0.2g/100ml

Pantoprazole 1.6 mg /mL suspensions in syrup using Carboxymethyl cellulose (CMC) 0.2g/100ml was prepared by triturating 12 tablets of 40 mg pantoprazole, mixing with 0.2 g of Carboxymethyl cellulose and 120 ml of simple syrup 85% up to a final volume of 300 ml with distilled water.

The suspension was transferred to six amber glass bottles with child resistant caps, three bottles with 50ml were stored in the refrigerator (4°C) and others were stored at room temperature. At 0, 1, 2, 7, 8 ,16 and 45 days, each bottle was inverted and shaken manually to ensure a uniform suspension, and a 1mL sample diluting with distilled water to a final volume of 100 ml volumetric flask was removed for analysis.

Pantoprazole concentrations were measured by using a UV-Spectrophotometer (JENWAY) and 290 nm was selected as the quantitative wavelength.

3.3.2.5 Standard drug solution

A stock standard solution equivalent to 1mg/mL Pantoprazole was prepared by dissolving 100 mg of pure drug in water and diluting to 100 mL in calibrated flask with water, and a 1mL stock standard solution diluting with distilled water to a final volume of 100 ml volumetric flask was removed for analysis.

Different aliquots (0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0 , 7.0 mL) of 1 mg/mL Pantoprazole solution were accurately measured and transferred into a series of 100 mL volumetric flasks and volume made up to the mark with Milli-Q water. Then all dilutions were scanned between 200-400 nm against blank, which shows the maximum absorbance at 290 nm.

3.3 Experiments: part 2

3.3.3 Preparation and analysis of aspirin aqueous solutions

Preparation of aspirin, SA, AA solutions:

Nine solutions with different concentrations of aspirin, salicylic acid (SA) and acetic acid (AA) diluting to 100 mL in calibrated flask with Milli-Q were prepared as shown in table to read the conductivity:

Table (3.1): Construction of calibration curve

Solution No.	**Aspirin (g)**	**SA (g)**	**Acetic acid (g)**	**Acetic acid(mL)**	**Q-Water (mL)**
1	0.2	0	0	0	Up to 100
2	0.178	0.015	0.007	7	Up to 100
3	0.1584	0.030	0.01408	14	Up to 100
4	0.138	0.0455	0.0211	21	Up to 100
5	0.108	0.0607	0.0281	28	Up to 100
6	0.099	0.076	0.0352	35	Up to 100
7	0.0792	0.091	0.042	42	Up to 100
8	0.0594	0.1062	0.0492	49	Up to 100
9	0.0396	0.12144	0.056	56	Up to 100

3.3.3.1 Follow up of the conductivity aspirin aqueous solution with time

0.2 g of aspirin was weighted and diluted to a volume of 100 ml in a volumetric flask with Milli-Q water, and the dissolution was done by heating at 50 °C with stirring and, after that, cooling to room temperature to read conductivity for thirty days.

3.3.3.2 Aspirin with 10 % propylene glycol (PG):

1 L of (900 mL Milli-q water and 100 mL propylene glycol) was used as solvent

Table (3.2) Construction of calibration curve with 10% PG

Solution No.	**Aspirin (g)**	**SA (g)**	**Acetic acid (g)**	**Acetic acid(mL)**	**RO water + PG10% (mL)**
1	0.2	0	0	0	Up to 100
2	0.178	0.015	0.007	7	Up to 100
3	0.1584	0.030	0.01408	14	Up to 100
4	0.138	0.0455	0.0211	21	Up to 100
5	0.108	0.0607	0.0281	28	Up to 100
6	0.099	0.076	0.0352	35	Up to 100
7	0.0792	0.091	0.042	42	Up to 100

8	0.0594	0.1062	0.0492	49	Up to 100
9	0.0396	0.12144	0.056	56	Up to 100

3.3.3.3 Aspirin with 10% propylene glycol (PG) per time

0.2 g of aspirin was weighted and diluted to a volume of 90 ml Milli-Q Water with 10 ml PG volumetric, and the dissolution was done by heating at 50 °C with stirring and, after that, cooling to room temperature to read conductivity for thirty days.

Chapter four:

Results and Discussion.

4. Data analysis of the results

In this study we focused on elucidating the differences between different methods of preparation of extemporaneous formulations. These methods that are performed by local pharmacies. The objective was to see how homogeneous and stable these formulations are. So two drugs were chosen; furosemide and pantoprazole that are popular for extemporaneous preparations for children. The oral preparations were prepared as mentioned previously and samples were taken periodically and analyzed. In the results below, the 'yield %" is calculated as: (actual amount in the sample/expected amount) X 100%.

We also calculated the "range" for each preparation, which is obtained by measuring the difference between the highest value (sample concentration) and lowest value of the daily samples. The smaller the range, the more uniform and stable is the preparation.

Each experiment was done in triplicates.

4.1 Sample analysis of furosemide suspensions:

4.1.1 Calibration curve of furosemide

Concentration	UV Absorption
0	0
0.02	1.107
0.004	0.235
0.0008	0.063
0.00016	0.035

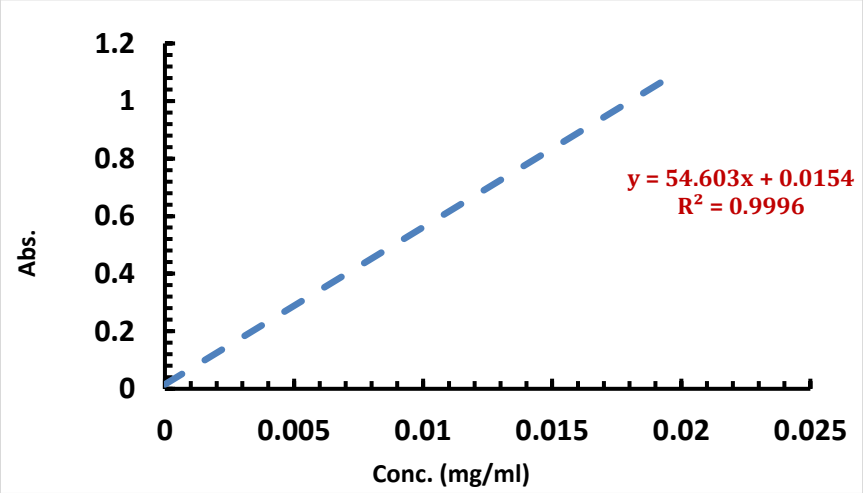


Figure (4.1.1): calibration curve of furosemide

4.1.2 Furosemide suspension in water at room temperature:

Table (4.1.2): results of sample analysis of Furosemide dispersed in water at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time /day	0	1	2	3	7	8	10	13	20	23
F.W.RT 1	0.286	0.428	0.518	0.434	0.398	0.432	0.33	0.442	0.392	0.419
F.W.RT 2	0.287	0.415	0.499	0.432	0.378	0.411	0.311	0.412	0.39	0.421
F.W.RT 3	0.301	0.415	0.501	0.461	0.387	0.43	0.354	0.454	0.388	0.399
C mg/ml 1	0.005	0.008	0.009	0.008	0.007	0.008	0.006	0.008	0.007	0.007
C mg/ml 2	0.005	0.007	0.009	0.008	0.007	0.007	0.005	0.007	0.007	0.007
C mg/ml 3	0.005	0.007	0.009	0.008	0.007	0.008	0.006	0.008	0.007	0.007
%yield 1	61.83	94.50	115.1	95.83	87.59	95.37	72.02	97.66	86.21	92.39
%yield 2	62.20	91.41	110.7	95.37	83.01	90.56	67.67	90.79	85.76	92.85
%yield 3	65.40	91.41	111.2	102.0	85.07	94.91	77.51	100.4	85.30	87.82
% average	63.15	92.44	112.3	97.74	85.22	93.62	72.40	96.29	85.76	91.02
SD	1.965	1.784	2.390	3.708	2.293	2.653	4.933	4.952	0.458	2.785

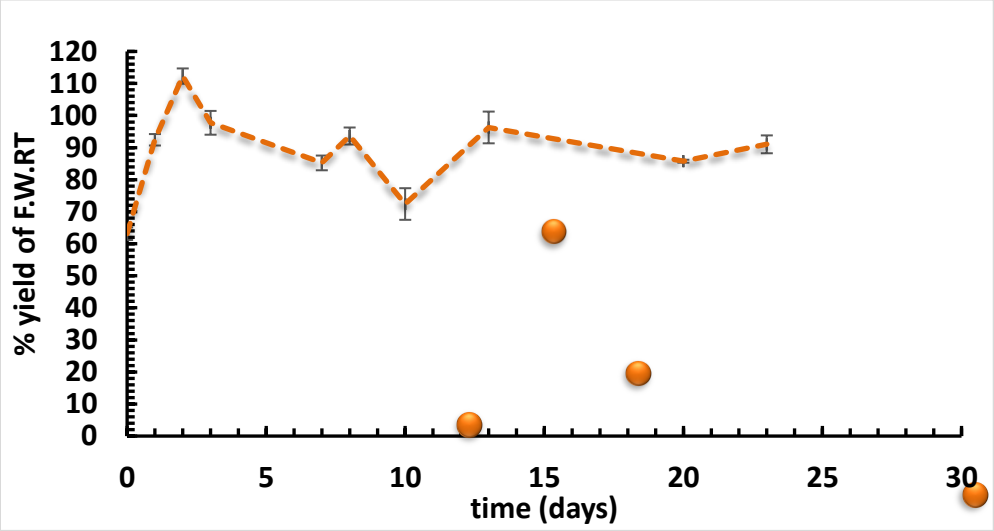


Figure (4.1.2): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in water and preserved for the duration of the study at room temperature

It is seen in table 4.1.2 and figure 4.1.2 how the concentration of furosemide is different from sample to sample. It is very important to notice the fluctuation pattern present between the daily doses. For example: in the first day a patient receives about 60% of the prescribed dose, while on day 2 he receives about 110% of the dose. The range calculated was 45.8.

4.1.3 Furosemide suspension in water at 4°C:

Table (4.1.3): results of sample analysis of Furosemide dispersed in water at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time /day	0	1	2	3	7	8	10	13	20	23
F.W. 4°C 1	0.364	0.454	0.371	0.377	0.458	0.391	0.279	0.397	0.317	0.274
F.W. 4°C 2	0.389	0.399	0.366	0.391	0.478	0.389	0.267	0.374	0.311	0.247
F.W. 4°C 3	0.324	0.45	0.365	0.403	0.464	0.374	0.299	0.345	0.333	0.281
C mg/ml 1	0.006	0.008	0.007	0.007	0.008	0.007	0.005	0.007	0.006	0.005
C mg/ml 2	0.007	0.007	0.006	0.007	0.008	0.007	0.005	0.007	0.005	0.004
C mg/ml 3	0.006	0.008	0.006	0.007	0.008	0.007	0.005	0.006	0.006	0.005
%yield 1	79.80	100.41	81.41	82.78	101.32	85.98	60.34	87.36	69.04	59.20
%yield 2	85.53	87.82	80.26	85.98	105.90	85.53	57.60	82.09	67.67	53.02
%yield 3	70.65	99.49	80.03	88.73	102.70	82.09	64.92	75.45	72.71	60.80
% average	78.66	95.90	80.57	85.83	103.31	84.53	60.96	81.63	69.81	57.67
SD	7.506	7.020	0.736	2.979	2.350	2.127	3.701	5.965	2.603	4.110

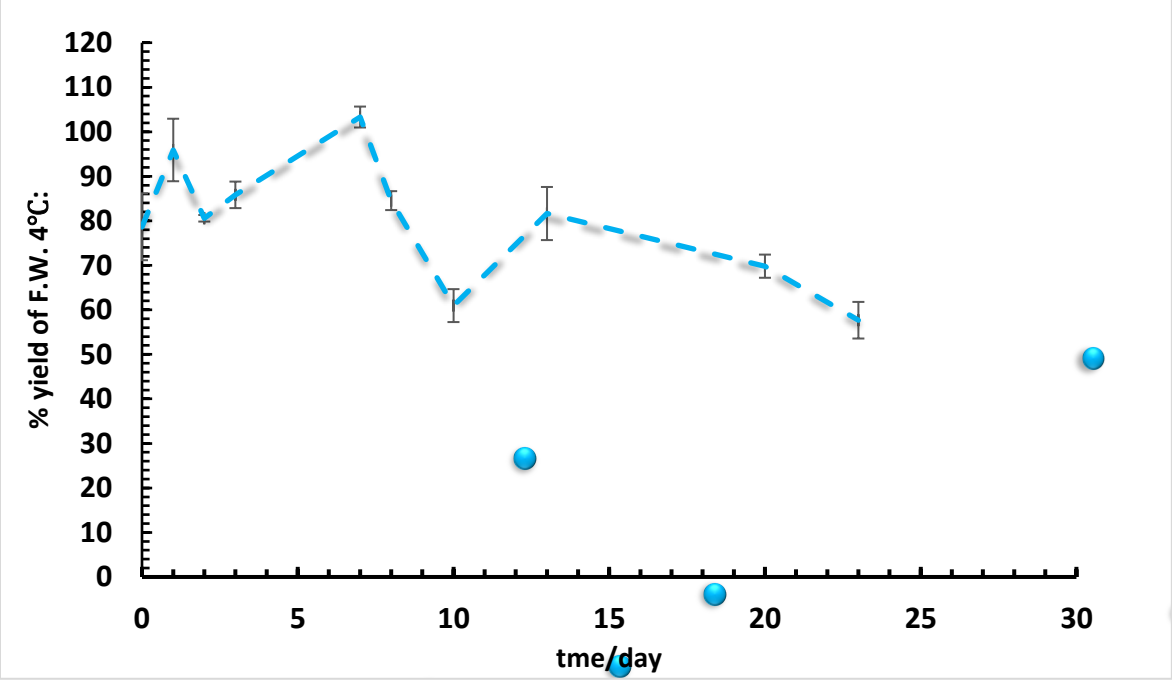


Figure (4.1.3): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in water and preserved for the duration of the study at 4°C

As seen in figure 4.1.3, high differences between sample concentrations is obtained when preserving the furosemide preparation at 4 C. the low solubility of furosemide, which is also decreased with lowering temperature might also contribute to these results. The range is 45.6

4.1.4 Furosemide suspension syrup at Room temperature:

Table (4.1.4): results of sample analysis of Furosemide dispersed in syrup at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	1	2	3	7	8	10	13	20	23
F.S.RT 1	0.3564	0.4264	0.426	0.443	0.382	0.425	0.323	0.354	0.393	0.342
F.S.RT 2	0.3454	0.424	0.42	0.432	0.378	0.41	0.314	0.361	0.378	0.358
F.S.RT 3	0.3164	0.4301	0.441	0.41	0.391	0.464	0.321	0.354	0.39	0.364
C mg/ml 1	0.006	0.007	0.007	0.008	0.007	0.007	0.006	0.006	0.007	0.006
C mg/ml 2	0.006	0.007	0.007	0.008	0.007	0.007	0.005	0.006	0.007	0.006
C mg/ml 3	0.005	0.008	0.008	0.007	0.007	0.008	0.006	0.006	0.007	0.006
%yield 1	77.31	93.44	93.35	97.27	83.21	93.12	69.61	76.76	85.75	73.99
%yield 2	74.77	92.89	91.97	94.74	82.29	89.66	67.54	78.37	82.29	77.68
%yield 3	68.09	94.30	96.81	89.66	85.28	102.1	69.15	76.76	85.05	79.06
% average	73.39	93.54	94.04	93.89	83.59	94.97	68.77	77.29	84.36	76.91
SD	4.763	0.708	2.493	3.873	1.535	6.425	1.089	0.932	1.830	2.621

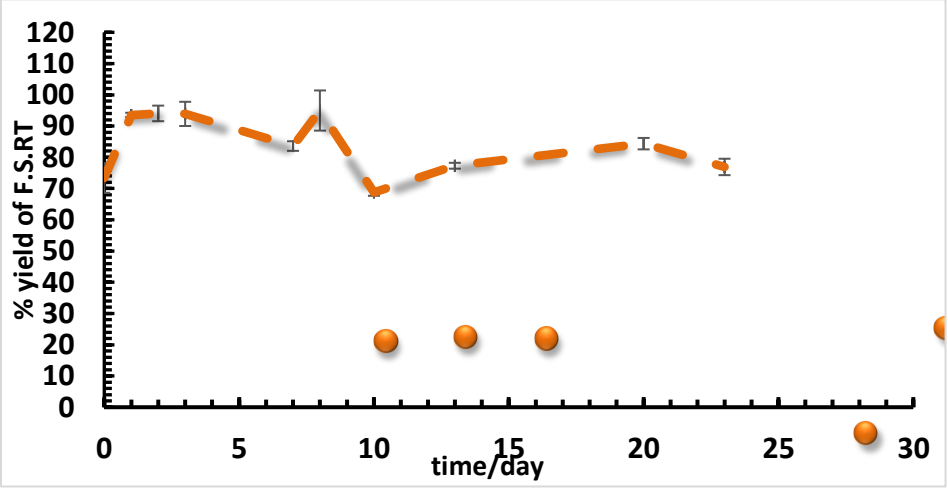


Figure (4.1.4): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in syrup and preserved for the duration of the study at R.T

The range for furosemide preparation after addition of syrup was 26. Less fluctuation in yield is apparent with the use of syrup, probably cause by increasing the viscosity of the liquid

4.1.5 Furosemide suspension syrup at 4°C:

Table (4.1.5): results of sample analysis of Furosemide dispersed in syrup at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	1	2	3	7	8	10	13	20	23
F.S.4C 1	0.357	0.370	0.180	0.405	0.404	0.444	0.356	0.393	0.372	0.343
F.S.4C 2	0.348	0.378	0.210	0.357	0.412	0.454	0.321	0.387	0.364	0.341
F.S.4C 3	0.322	0.366	0.201	0.389	0.432	0.410	0.344	0.376	0.381	0.330
C mg/ml 1	0.006	0.006	0.003	0.007	0.007	0.008	0.006	0.007	0.007	0.006
C mg/ml 2	0.006	0.007	0.004	0.006	0.007	0.008	0.006	0.007	0.006	0.006
C mg/ml 3	0.006	0.006	0.003	0.007	0.008	0.007	0.006	0.007	0.007	0.006
%yield 1	78.25	81.06	37.68	89.19	88.96	98.12	77.97	86.44	81.63	75.00
%yield 2	76.09	83.10	44.55	78.20	90.79	100.41	69.96	85.07	79.80	74.54
%yield 3	70.23	80.28	42.49	85.53	95.37	90.33	75.22	82.55	83.70	72.02
% average	74.86	81.48	41.57	84.31	91.71	96.29	74.39	84.69	81.71	73.85
SD	4.147	1.454	3.524	5.595	3.302	5.280	4.072	1.974	1.947	1.602

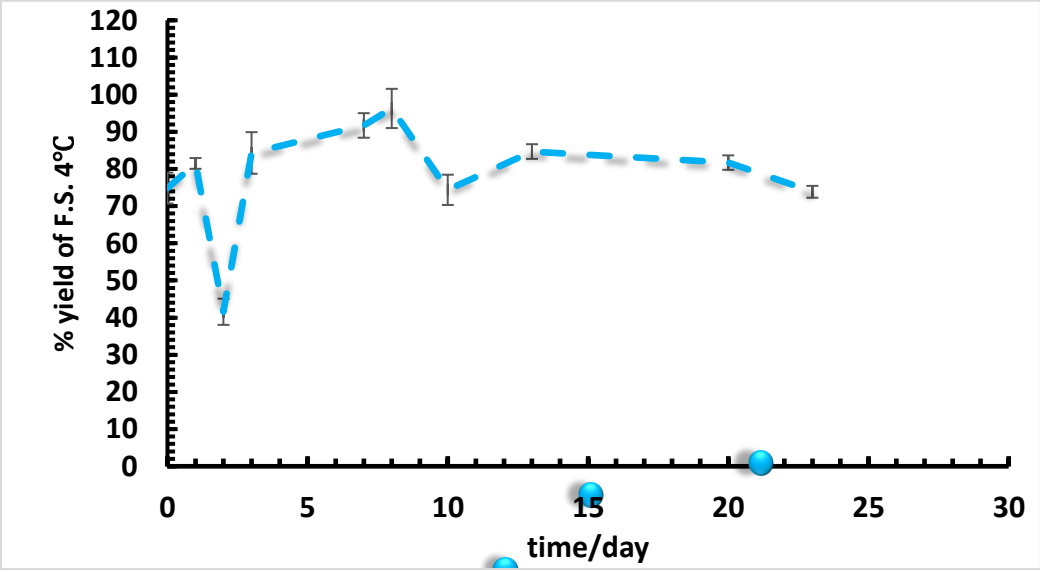


Figure (4.1.5): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in syrup and preserved for the duration of the study at 4°C

In this preparation, the range was 50. This is thought to be a result of the decreased solubility of furosemide in low temperature. Also, noting that it was hard to shake-well the preparation while it is cold.

4.1.6 Furosemide suspension in syrup using Xanthan gum 0.5g/100ml at 4°C:

Table (4.1.6): results of sample analysis of Furosemide dispersed in xanthan gum 0.5 g/100 ml suspension at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	1	5	6	8	13	18	2
X.0.5.4C1	0.321	0.466	0.335	0.378	0.337	0.343	0.422	0.343
X.0.5.4C2	0.311	0.259	0.341	0.359	0.342	0.344	0.388	0.37
X.0.5.4C3	0.354	0.374	0.383	0.37	0.35	0.335	0.343	0.343
C mg/ml 1	0.006	0.008	0.006	0.007	0.006	0.006	0.007	0.006
C mg/ml 2	0.005	0.004	0.006	0.006	0.006	0.006	0.007	0.006
C mg/ml 3	0.006	0.007	0.007	0.006	0.006	0.006	0.006	0.006
%yield 1	69.96	103.15	73.16	83.01	73.62	75.00	93.08	75.00
%yield 2	66.84	54.86	73.76	77.91	73.99	74.45	84.59	80.44
%yield 3	76.76	81.37	83.44	80.44	75.83	72.38	74.22	74.22
% average	71.19	79.79	76.79	80.45	74.48	73.94	83.97	76.55
SD	5.068	24.186	5.769	2.550	1.185	1.382	9.446	3.392

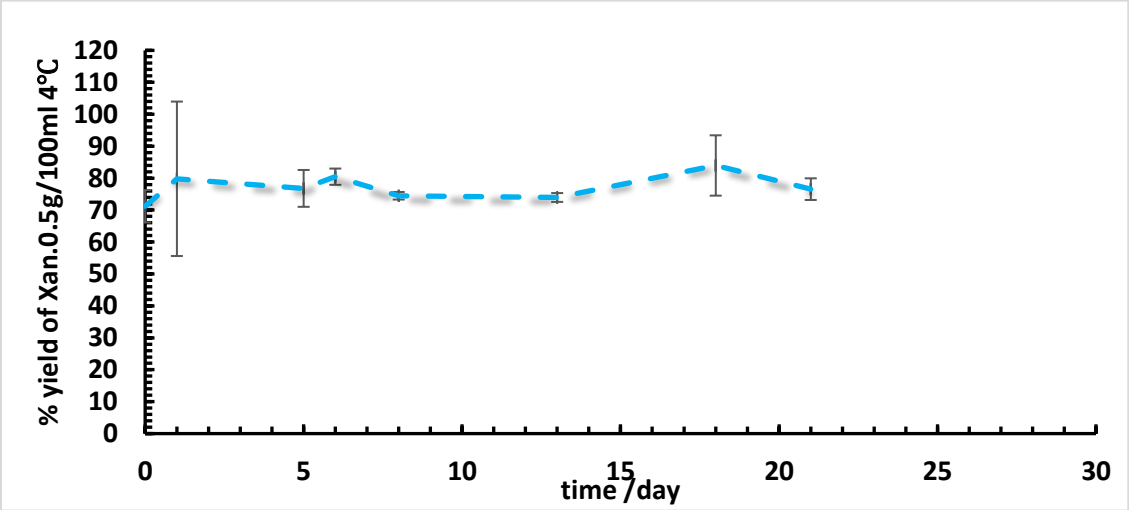


Figure (4.1.6): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in xanthan gum 0.5g/100ml suspension and preserved for the duration of the study at 4°C

A rather stable and homogeneous preparation was obtained using xanthan gum. The range was 13. However, the yield was always less than 100%, which is thought to be a result of occlusion effect of the suspending agent

4.1.7 Furosemide suspension in syrup using Xanthan gum 0.5g/100ml at R.T:

Table (4.1.7): results of sample analysis of Furosemide dispersed in xanthan gum 0.5 g/100 ml suspension at R.T Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	1	5	6	8	13	18	21
X 0.5 RT1	0.357	0.496	0.405	0.376	0.366	0.319	0.328	0.33
X.0.5.RT2	0.308	0.376	0.44	0.388	0.354	0.32	0.336	0.349
X.0.5.RT3	0.293	0.401	0.394	0.412	0.347	0.318	0.337	0.334
C mg/ml 1	0.006	0.009	0.007	0.007	0.006	0.006	0.006	0.006
C mg/ml 2	0.005	0.007	0.008	0.007	0.006	0.006	0.006	0.006
C mg/ml 3	0.005	0.007	0.007	0.007	0.006	0.006	0.006	0.006
%yield 1	78.20	110.02	89.19	82.55	80.26	69.50	71.56	72.02
%yield 2	66.98	82.55	97.20	85.30	77.51	69.73	73.39	76.37
%yield 3	63.55	88.27	86.67	90.79	75.91	69.27	73.62	72.94
% average	69.58	93.62	91.02	86.21	77.90	69.50	72.86	73.77
SD	7.662	14.494	5.499	4.196	2.200	0.229	1.129	2.293

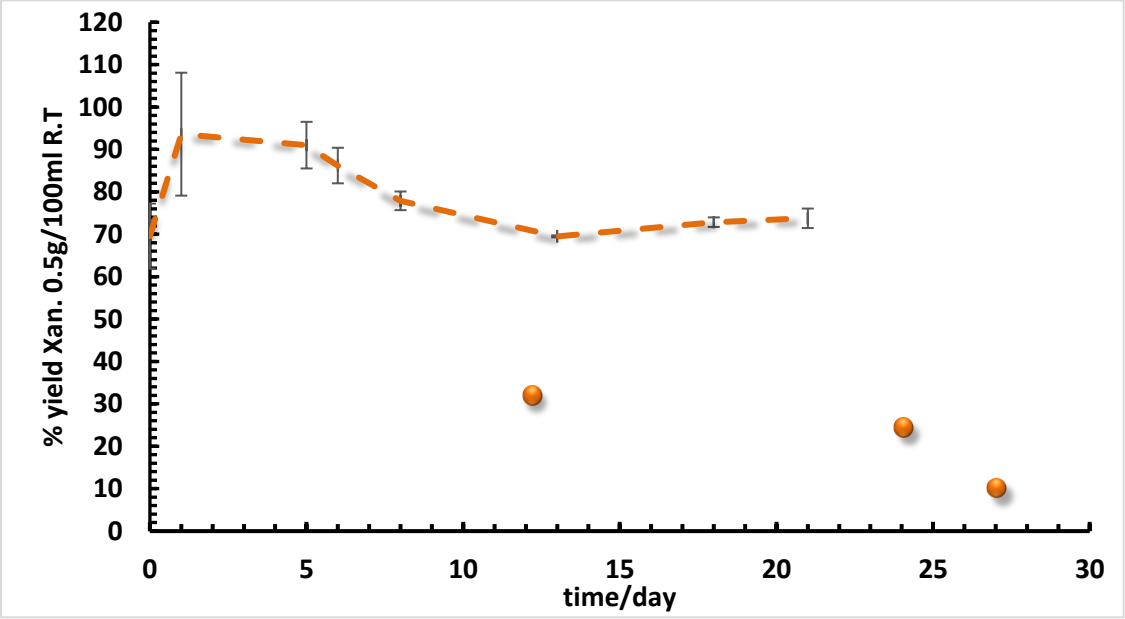


Figure (4.1.7): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in xanthan gum 0.5g/100ml suspension and preserved for the duration of the study at R.T

Range = 25.1

4.1.8 Furosemide suspension in syrup using Xanthan gum 0.2g/100ml at 4°C:

Table (4.1.8): results of sample analysis of Furosemide dispersed in xanthan gum 0.2g /100 ml suspension at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	1	3	6	9	13	14	16	21
X.0.2.4C1	0.398	0.412	0.34	0.327	0.325	0.325	0.298	0.362	0.348
X.0.2.4C2	0.341	0.366	0.334	0.351	0.357	0.342	0.364	0.347	0.349
X.0.2.4C3	0.37	0.366	0.358	0.387	0.335	0.35	0.343	0.353	0.37
C mg/ml 1	0.007	0.007	0.006	0.006	0.006	0.006	0.005	0.006	0.006
C mg/ml 2	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006
C mg/ml 3	0.006	0.006	0.006	0.007	0.006	0.006	0.006	0.006	0.006
%yield 1	87.59	90.79	74.31	71.33	70.88	70.88	64.69	79.35	76.14
%yield 2	74.54	80.26	72.94	76.83	78.20	74.77	79.80	75.91	76.37
%yield 3	81.18	80.26	78.43	85.07	73.16	76.60	75.00	77.29	81.18
% average	81.10	83.77	75.22	77.74	74.08	74.08	73.16	77.51	77.90
SD	6.525	6.080	2.859	6.913	3.748	2.923	7.719	1.728	2.844

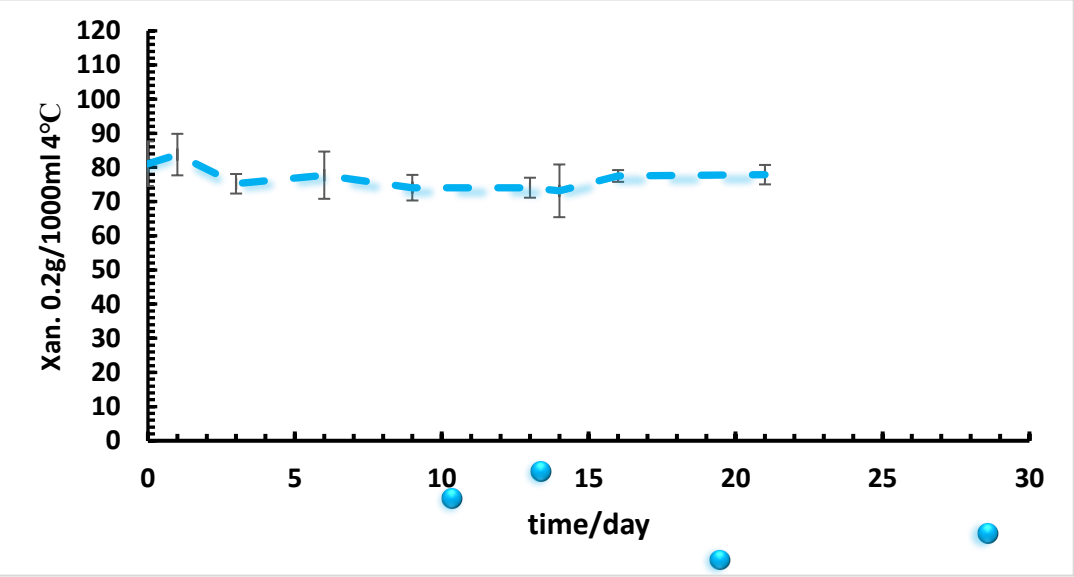


Figure (4.1.8): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in xanthan gum 0.2g/100ml suspension and preserved for the duration of the study at 4°C

4.1.9 Furosemide suspension in syrup using Xanthan gum 0.2g/100ml at R.T:

Table (4.1.9): results of sample analysis of Furosemide dispersed in xanthan gum 0.2g /100 ml suspension at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	1	3	6	9	13	14	16	21
X.0.2RT1	0.358	0.365	0.372	0.366	0.329	0.349	0.254	0.353	0.333
X0.2RT2	0.397	0.384	0.36	0.365	0.335	0.37	0.315	0.337	0.349
X.0.2.RT3	0.378	0.383	0.354	0.357	0.335	0.353	0.328	0.366	0.37
C mg/ml 1	0.006	0.006	0.007	0.006	0.006	0.006	0.004	0.006	0.006
C mg/ml 2	0.007	0.007	0.006	0.006	0.006	0.006	0.005	0.006	0.006
C mg/ml 3	0.007	0.007	0.006	0.006	0.006	0.006	0.006	0.006	0.006
%yield 1	78.43	80.03	81.63	80.26	71.79	76.37	54.62	77.29	72.71
%yield 2	87.36	84.38	78.89	80.03	73.16	81.18	68.59	73.62	76.37
%yield 3	83.01	84.15	77.51	78.20	73.16	77.29	71.56	80.26	81.18
% average	82.93	82.86	79.35	79.50	72.71	78.28	64.92	77.06	76.75
SD	4.465	2.448	2.098	1.129	0.793	2.553	9.045	3.325	4.248

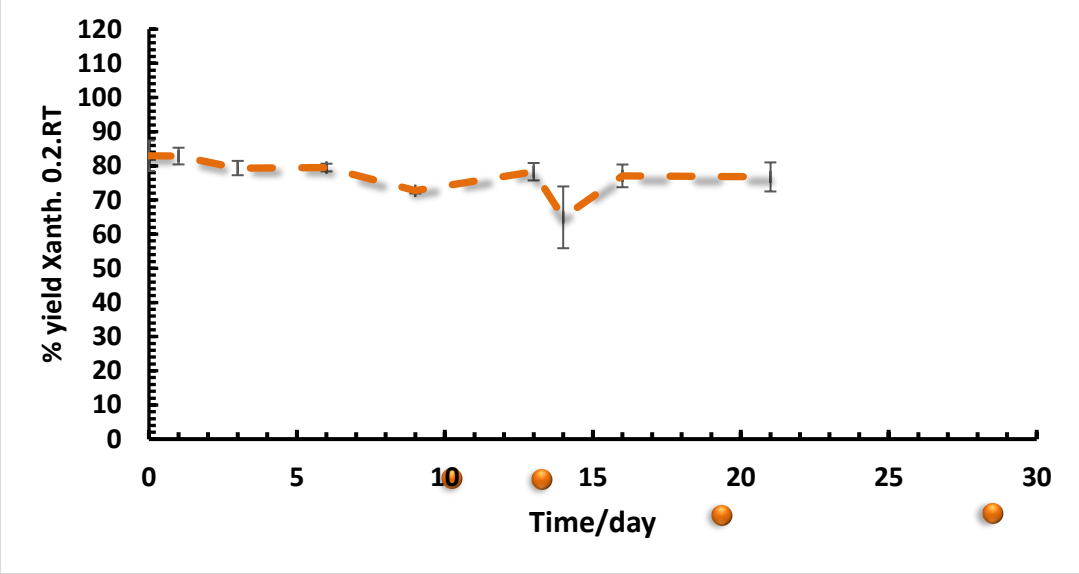


Figure (4.1.9): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in xanthan gum 0.2g/100ml suspension and preserved for the duration of the study at R.T

4.1.10 Furosemide suspension in syrup using CMC.0.2g/100ml at 4°C:

Table (4.1.10): results of sample analysis of Furosemide dispersed in CMC 0.2g /100 ml suspension at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	2	5	8	12	13	15	21
C.0.2.4C1	0.301	0.251	0.321	0.34	0.372	0.413	0.363	0.334
C.0.2.4C2	0.288	0.25	0.3	0.28	0.415	0.424	0.419	0.376
C.0.2.4C3	0.281	0.266	0.336	0.38	0.367	0.403	0.292	0.306
C mg/ml 1	0.005	0.004	0.006	0.006	0.007	0.007	0.006	0.006
C mg/ml 2	0.005	0.004	0.005	0.005	0.007	0.007	0.007	0.007
C mg/ml 3	0.005	0.005	0.006	0.007	0.006	0.007	0.005	0.005
%yield 1	63.38	53.93	69.96	74.31	81.63	91.02	79.57	72.94
%yield 2	62.40	53.71	65.15	60.57	91.48	93.54	92.39	82.55
%yield 3	60.80	57.37	73.39	83.47	80.49	88.73	63.32	66.53
% average	62.20	55.00	69.50	72.78	84.53	91.10	78.43	74.00
SD	1.301	2.052	4.140	11.522	6.041	2.405	14.571	8.066

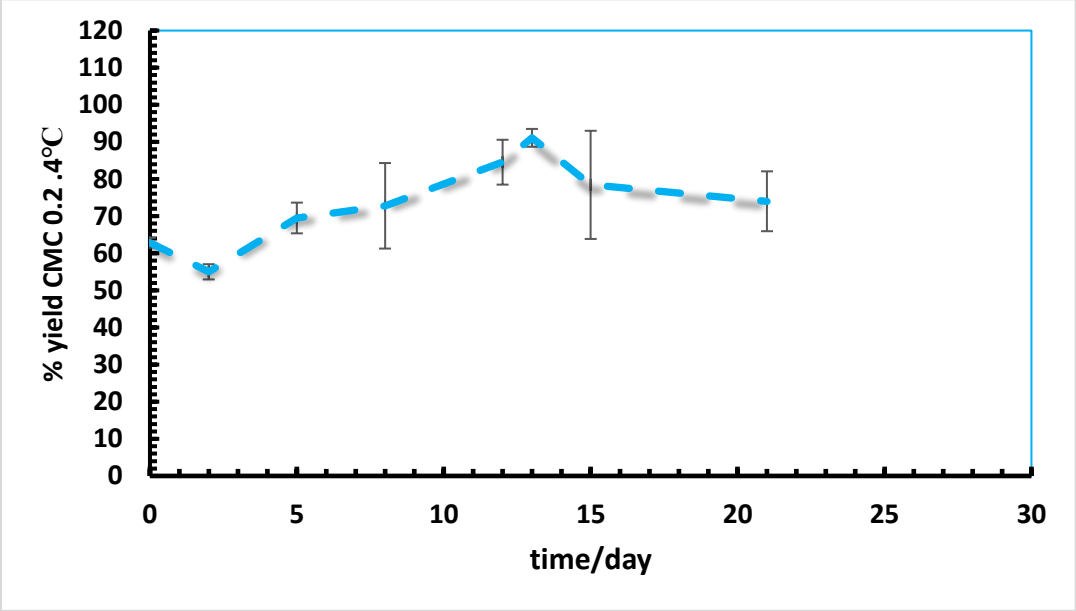


Figure (4.1.10): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in CMC 0.2g/100ml suspension and preserved for the duration of the study at 4°C

4.1.11 Furosemide suspension in syrup using CMC.0.2mg/100ml at RT:

Table (4.1.11): results of sample analysis of Furosemide dispersed in CMC 0.2g /100 ml suspension at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Time/day	0	2	5	8	12	13	15	21
C.0.2.RT1	0.305	0.226	0.387	0.389	0.342	0.374	0.382	0.365
C.0.2.RT2	0.298	0.278	0.35	0.313	0.35	0.379	0.368	0.339
C.0.2.RT3	0.277	0.299	0.366	0.37	0.337	0.426	0.332	0.405
C mg/ml 1	0.005	0.004	0.007	0.007	0.006	0.007	0.007	0.006
C mg/ml 2	0.005	0.005	0.006	0.005	0.006	0.007	0.006	0.006
C mg/ml 3	0.005	0.005	0.006	0.006	0.006	0.008	0.006	0.007
%yield 1	66.30	48.21	85.07	85.53	74.77	82.09	83.92	80.03
%yield 2	64.69	60.12	76.60	68.13	76.60	83.24	80.72	74.08
%yield 3	59.89	64.92	80.26	81.18	73.62	94.00	72.48	89.19
% average	63.63	57.75	80.64	78.28	75.00	86.44	79.04	81.10
SD	3.336	8.603	4.248	9.054	1.501	6.567	5.905	7.611

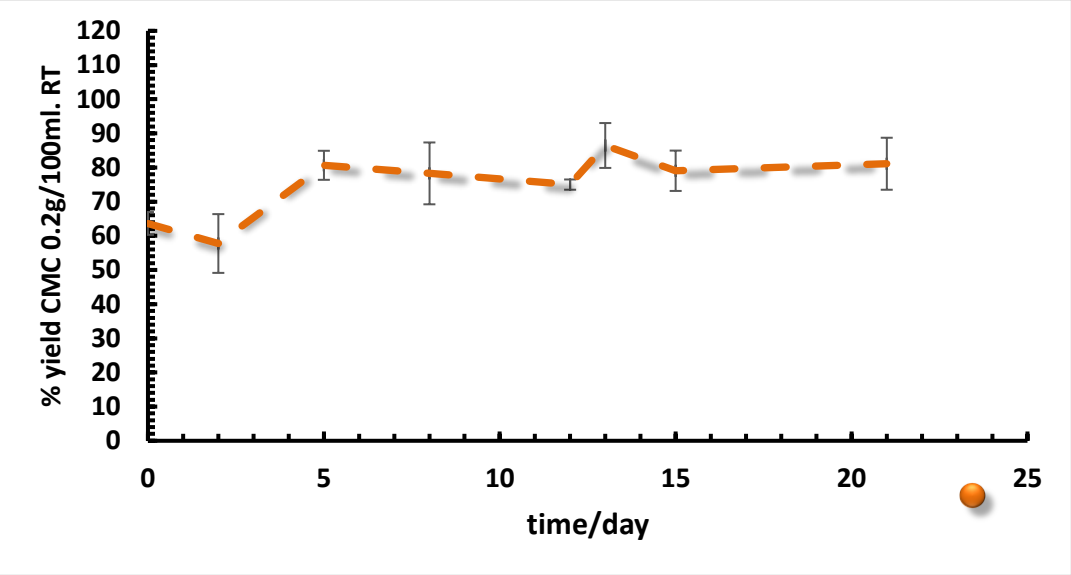


Figure (4.1.11): Percentage yield (actual/expected X100%) of samples taken from Furosemide tablets dispersed in CMC 0.2g/100ml suspension and preserved for the duration of the study at R.T

Table 4.1.12: A summary of the "range" of the different preparations

Preparation	Range
Furosemide in water at R.T	45.8
Furosemide in water at 4°C	45.6
Furosemide in syrup at R.T	26
Furosemide in water at 4°C	50
Furosemide Suspension with 0.5% xanthan gum at R.T	25.1
Furosemide Suspension with 0.5% xanthan gum at 4°C	13
Furosemide Suspension with 0.2% xanthan gum at R.T	10.7
Furosemide Suspension with 0.2% xanthan gum at 4°C	18
Furosemide Suspension with 0.2% CMC at 4°C	36
Furosemide Suspension with 0.2% CMC at R.T	23.3

It can be observed that Xanthan gum served as a better suspending agent, as it yielded lower range values than CMC. Also, the yield was higher for xanthan gum than CMC. The highest yield values were obtained using Xanthan gum at 0.2% and storing at room temperature. Using 0.5% xanthan gum lowered the yield values, possibly because of the thicker nature of the suspension produced. It was noted at the preparation stages that this higher concentration of xanthan gum took longer time to disperse in the suspension. We conclude here that the preparation of furosemide without a suspending agent will yield a non-homogeneous suspension and will not provide the correct dose to the patient. Adding a suspending agent, in this case xanthan gum at 0.2 gm/100ml.

4.2 Pantoprazole analysis:

4.2.1 Calibration Curve:

Table (4.2.1): Calibration Curve of Pantoprazole

Conc. (µg)	Conc. (mg)	Abs.
0	0	0
5	0.005	0.192
10	0.01	0.354
20	0.02	0.741
30	0.03	1.172
40	0.04	1.537
50	0.05	1.971

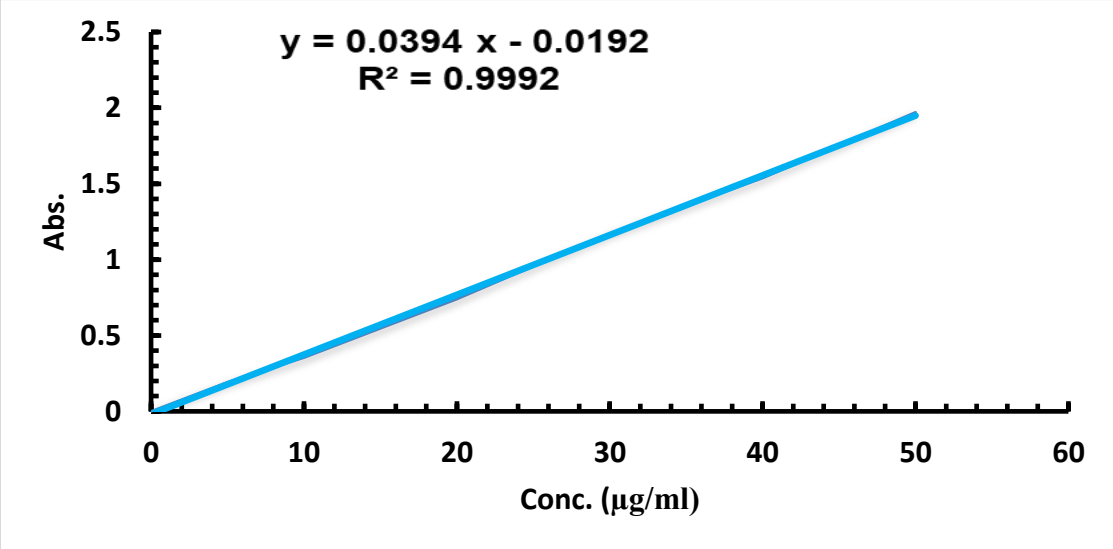


Figure (4.2.1): Calibration Curve of Pantoprazole

4.2.2 Pantoprazole suspension in water at RT:

Table (4.2.2): results of sample analysis of Pantoprazole dispersed in water at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Days	0	1	3	10	13	25	27	45	46
P.w.RT1	0.544	0.591	0.602	0.612	0.59	0.637	0.574	0.553	0.601
P.w.RT2	0.631	0.601	0.618	0.628	0.622	0.656	0.624	0.598	0.623
P.w.RT3	0.618	0.528	0.608	0.612	0.618	0.661	0.632	0.574	0.623
C1 mg/ml	1.429	1.549	1.577	1.602	1.546	1.665	1.506	1.452	1.574
C2 mg/ml	1.650	1.574	1.617	1.643	1.627	1.714	1.632	1.566	1.630
C3 mg/ml	1.617	1.389	1.592	1.602	1.617	1.726	1.653	1.506	1.630
% yield 1	89.34	96.80	98.54	100.13	96.64	104.09	94.10	90.77	98.38
% yield 2	103.1	98.4	101.1	102.7	101.7	107.1	102.0	97.9	101.9
% yield 3	101.1	86.8	99.5	100.1	101.1	107.9	103.3	94.1	101.9
(AVG)	97.85	93.99	99.70	100.9	99.81	106.3	99.81	94.26	100.7
SD	7.444	6.278	1.282	1.465	2.766	2.009	4.986	3.572	2.015

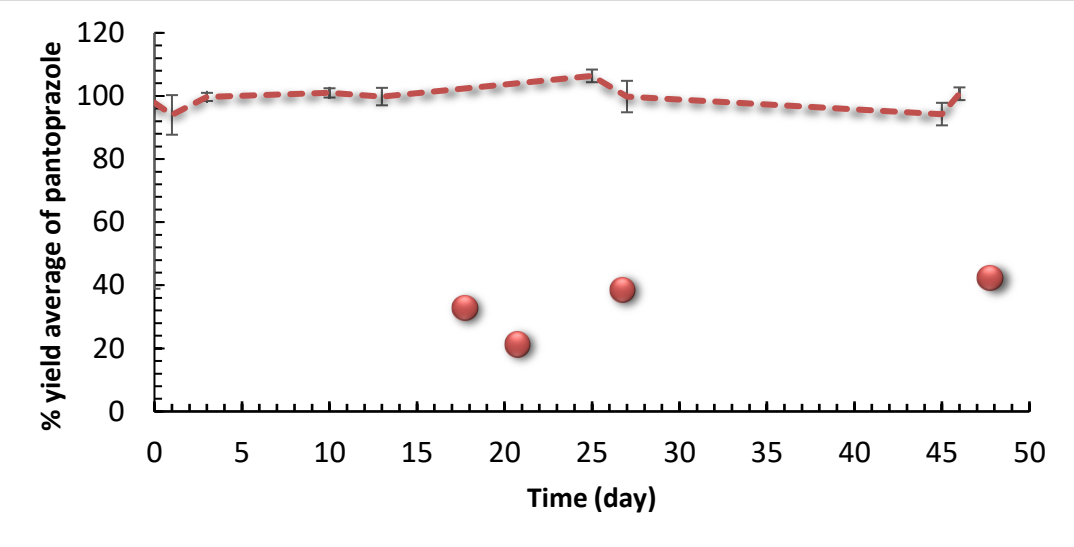


Figure (4.2.2): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in water and preserved for the duration of the study at R.T

4.2.3 Pantoprazole suspension in water at 4°C:

Table (4.2.3): results of sample analysis of Pantoprazole dispersed in water at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield.

Days	0	3	10	13	25	27	45	46
P.w.°C1	0.649	0.657	0.626	0.678	0.613	0.651	0.557	0.633
P.w.°C2	0.677	0.62	0.633	0.69	0.653	0.645	0.52	0.652
P.w.°C3	0.644	0.651	0.634	0.682	0.644	0.608	0.558	0.684
C1 mg/ml	1.696	1.716	1.638	1.770	1.605	1.701	1.462	1.655
C2 mg/ml	1.767	1.622	1.655	1.800	1.706	1.686	1.369	1.704
C3 mg/ml	1.683	1.701	1.658	1.780	1.683	1.592	1.465	1.785
% yield 1	106.0	107.3	102.3	110.6	100.3	106.3	91.40	103.5
% yield 2	110.4	101.4	103.5	112.5	106.6	105.4	85.5	106.5
% yield 3	105.2	106.3	103.6	111.2	105.2	99.49	91.56	111.5
(AVG)	107.2	105.0	103.1	111.4	104.0	103.7	89.50	107.2
SD	2.821	3.150	0.691	0.969	3.329	3.694	3.435	4.089

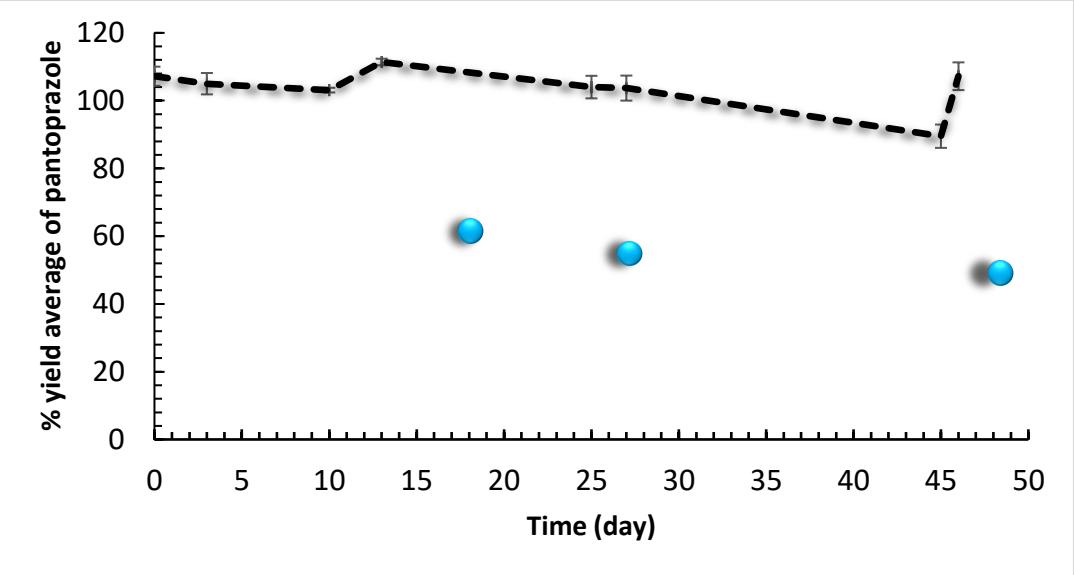


Figure (4.2.3): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in water and preserved for the duration of the study at 4°C

4.2.4 Pantoprazole suspension in syrup at RT:

Table (4.2.4): results of sample analysis of Pantoprazole dispersed in syrup at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield.

Days	0	1	3	10	13	25	27	45	46
P.w.RT1	0.617	0.627	0.559	0.626	0.661	0.577	0.535	0.331	0.367
P.w.RT2	0.567	0.558	0.541	0.546	0.556	0.365	0.542	0.299	0.344
P.w.RT3	0.589	0.578	0.592	0.559	0.549	0.556	0.554	0.299	0.337
C1 mg/ml	1.615	1.640	1.468	1.638	1.726	1.513	1.407	0.889	0.980
C2 mg/ml	1.488	1.465	1.422	1.435	1.460	0.975	1.424	0.808	0.922
C3 mg/ml	1.544	1.516	1.551	1.468	1.442	1.460	1.455	0.808	0.904
% yield 1	100.9	102.51	91.72	102.3	107.9	94.57	87.91	55.55	61.26
% yield 2	92.99	91.56	88.86	89.66	91.24	60.95	89.02	50.48	57.61
% yield 3	96.48	94.73	96.95	91.72	90.13	91.24	90.93	50.48	56.50
(AVG)	96.80	96.27	92.51	94.57	96.43	82.25	89.29	52.17	58.46
SD	3.975	5.632	4.103	6.810	9.952	18.53	1.524	2.931	2.490

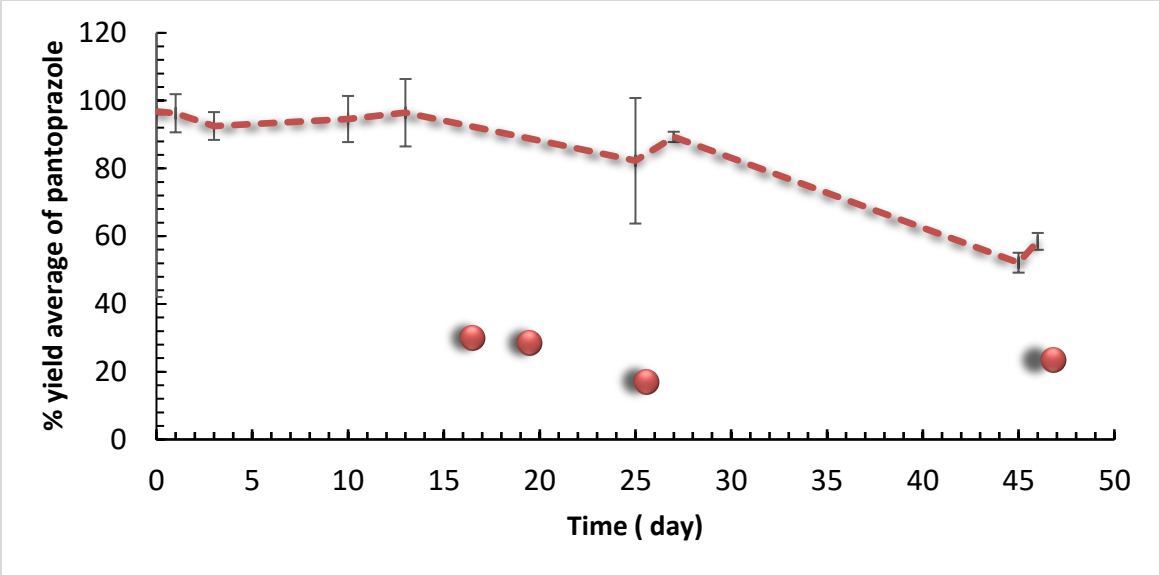


Figure (4.2.4): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in syrup and preserved for the duration of the study at R.T

4.2.5 Pantoprazole suspension in syrup at 4°C.

Table (4.2.5): results of sample analysis of Pantoprazole dispersed in syrup at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield.

Days	0	3	10	13	25	27	45	46
P.w.°C1	0.608	0.575	0.582	0.595	0.547	0.61	0.489	0.642
P.w.°C2	0.546	0.628	0.588	0.566	0.631	0.645	0.508	0.675
P.w.°C3	0.509	0.594	0.582	0.666	0.616	0.646	0.508	0.653
C1 mg/ml	1.592	1.508	1.526	1.559	1.437	1.597	1.290	1.678
C2 mg/ml	1.435	1.643	1.541	1.485	1.650	1.686	1.338	1.762
C3 mg/ml	1.341	1.556	1.526	1.739	1.612	1.688	1.338	1.706
% yield 1	99.49	94.26	95.37	97.43	89.82	99.81	80.62	104.9
% yield 2	89.66	102.7	96.32	92.83	103.1	105.4	83.63	110.1
% yield 3	83.79	97.27	95.37	108.69	100.8	105.5	83.63	106.6
(AVG)	90.98	98.06	95.69	99.65	97.91	103.6	82.62	107.2
SD	7.935	4.259	0.550	8.161	7.107	3.252	1.740	2.665

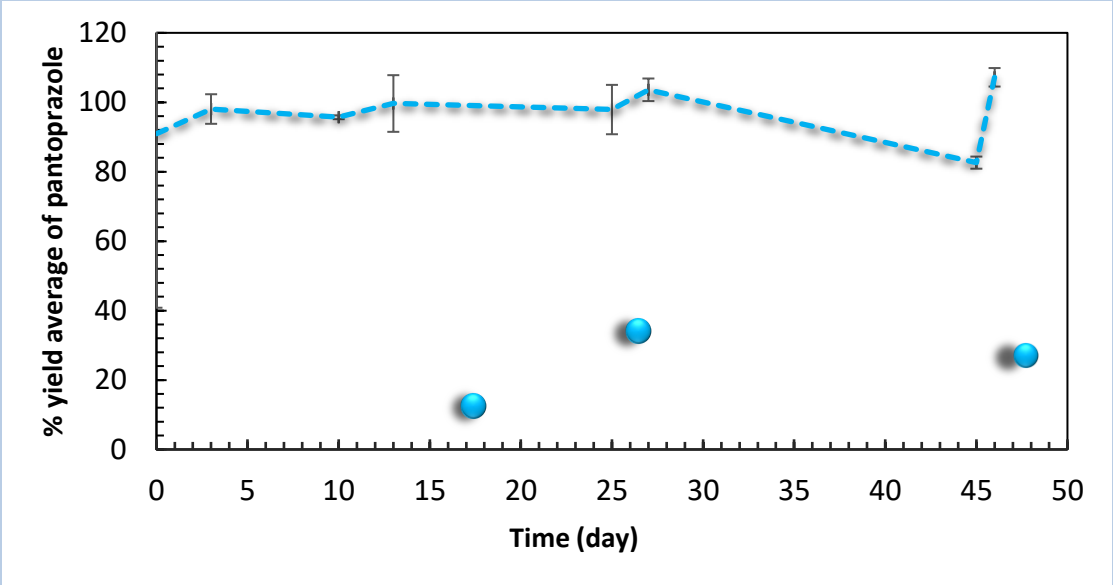


Figure (4.2.5): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in syrup and preserved for the duration of the study at 4℃

4.2.6 Pantoprazole suspension in syrup using xanthan gum at R.T:

Table (4.2.6): results of sample analysis of Pantoprazole dispersed in xanthan gum suspension at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Days	0	1	2	7	8	16	45
P.X.RT1	0.599	0.608	0.558	0.516	0.61	0.595	0.518
P.X.RT2	0.566	0.6	0.606	0.591	0.626	0.578	0.574
P.X.RT3	0.621	0.581	0.555	0.613	0.632	0.605	0.505
C1 mg/ml	1.569	1.592	1.465	1.358	1.597	1.559	1.363
C2 mg/ml	1.485	1.572	1.587	1.549	1.638	1.516	1.506
C3 mg/ml	1.625	1.523	1.457	1.605	1.653	1.584	1.330
% yield 1	98.06	99.49	91.56	84.90	99.81	97.43	85.22
% yield 2	92.83	98.22	99.18	96.80	102.3	94.73	94.10
% yield 3	101.6	95.21	91.09	100.3	103.3	99.02	83.15
(AVG)	97.48	97.64	93.94	93.99	101.8	97.06	87.49
SD	4.391	2.200	4.540	8.067	1.804	2.165	5.816

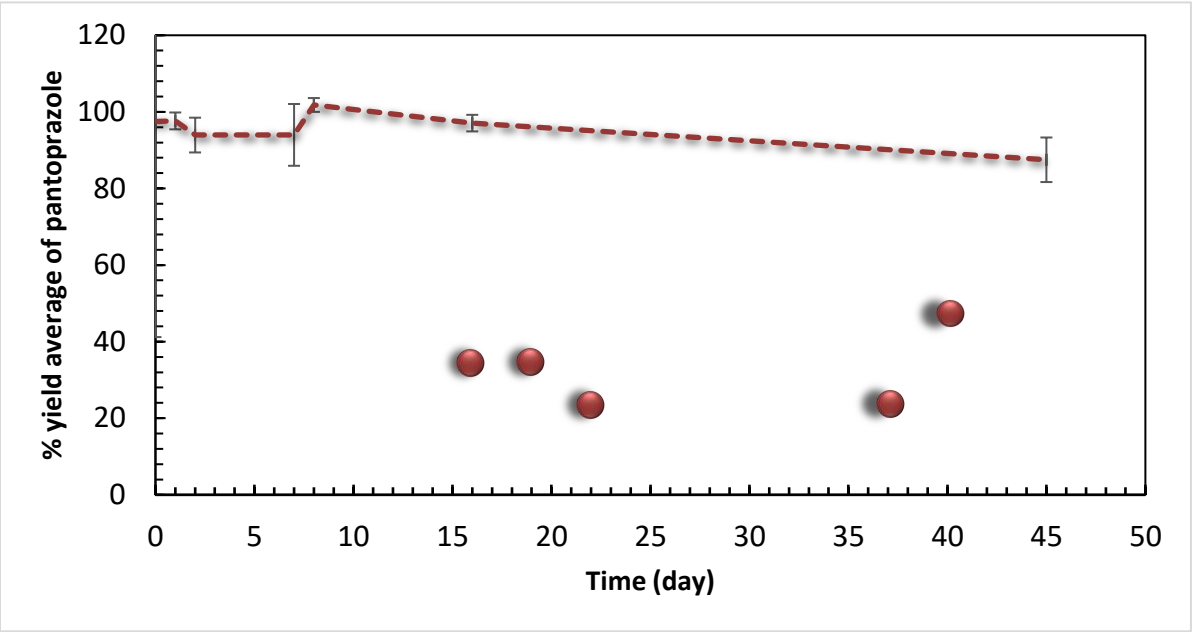


Figure (4.2.6): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in xanthan gum suspension and preserved for the duration of the study at R.T.

4.2.7 Pantoprazole suspension in syrup using xanthan gum 0.2 g/100ml at 4°C.

Table (4.2.7): results of sample analysis of Pantoprazole dispersed in xanthan gum suspension at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Days	0	1	2	7	8	16	45
P.X.°C1	0.656	0.586	0.625	0.627	0.625	0.605	0.615
P.X.°C2	0.615	0.613	0.64	0.627	0.625	0.606	0.538
P.X.°C3	0.621	0.606	0.599	0.619	0.73	0.608	0.552
C1 mg/ml	1.714	1.536	1.635	1.640	1.635	1.56	1.6
C2 mg/ml	1.610	1.605	1.673	1.640	1.635	1.587	1.414
C3 mg/ml	1.625	1.587	1.569	1.620	1.902	1.592	1.450
% yield 1	107.1	96.00	102.2	102.5	102.2	101	102
% yield 2	100.6	100.3	104.6	102.5	102.2	99.18	88.39
% yield 3	101.6	99.18	98.06	101.2	118.8	99.49	90.61
(AVG)	103.1	98.49	101.6	102.1	107.7	100.1	95.3
SD	3.513	2.223	3.291	0.733	9.616	55.59	49.93

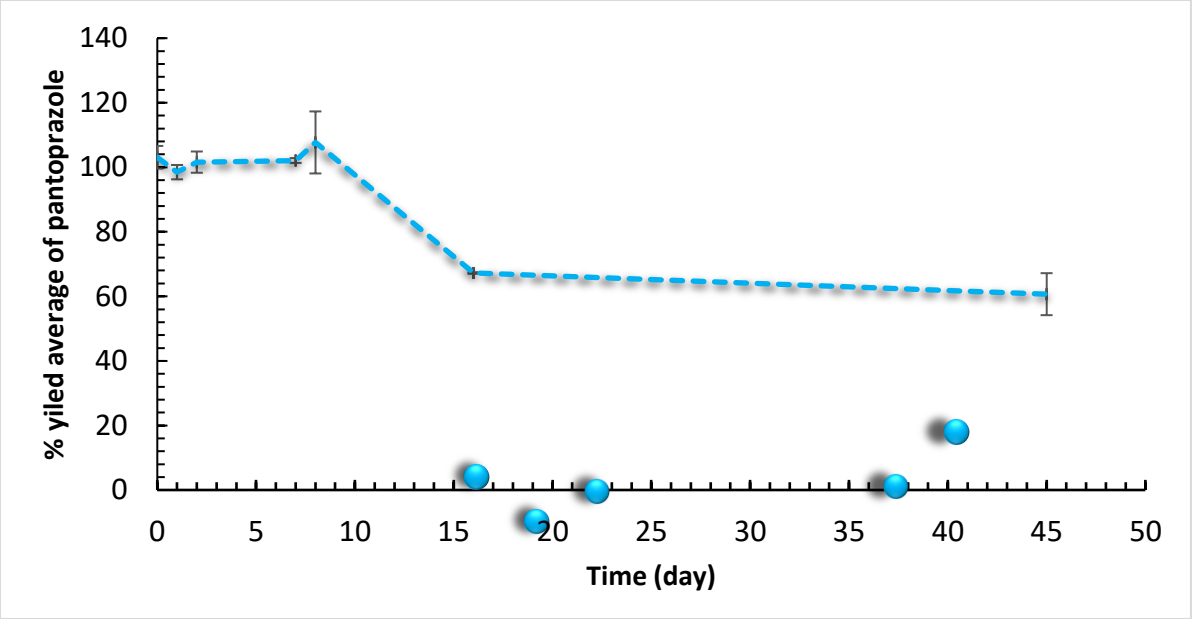


Figure (4.2.7): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in xanthan gum suspension and preserved for the duration of the study at 4°C.

4.2.8 Pantoprazole suspension in syrup using CMC 0.2g/100ml at 4°C:

Table (4.2.8): results of sample analysis of Pantoprazole dispersed in CMC suspension at 4°C. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Days	0	1	2	7	8	16	45
P.CMC.4°C1	0.655	0.607	0.674	0.633	0.68	0.655	0.645
P.CMC.4°C2	0.678	0.634	0.621	0.638	0.673	0.642	0.651
P.CMC.4°C3	0.677	0.651	0.711	0.653	0.685	0.647	0.658
C1 mg/ml	1.711	1.589	1.759	1.655	1.775	1.711	1.686
C2 mg/ml	1.770	1.658	1.625	1.668	1.757	1.678	1.701
C3 mg/ml	1.767	1.701	1.853	1.706	1.787	1.691	1.719
% yield 1	106.9	99.3	110.0	103.5	110.9	106.9	105.4
% yield 2	110.6	103.6	101.6	104.3	109.8	104.9	106.3
% yield 3	110.4	106.3	115.8	106.6	111.7	105.7	107.4
(AVG)	109.3	103.1	109.1	104.8	110.8	105.8	106.4
SD	2.062	3.520	7.176	1.651	0.956	1.040	1.032

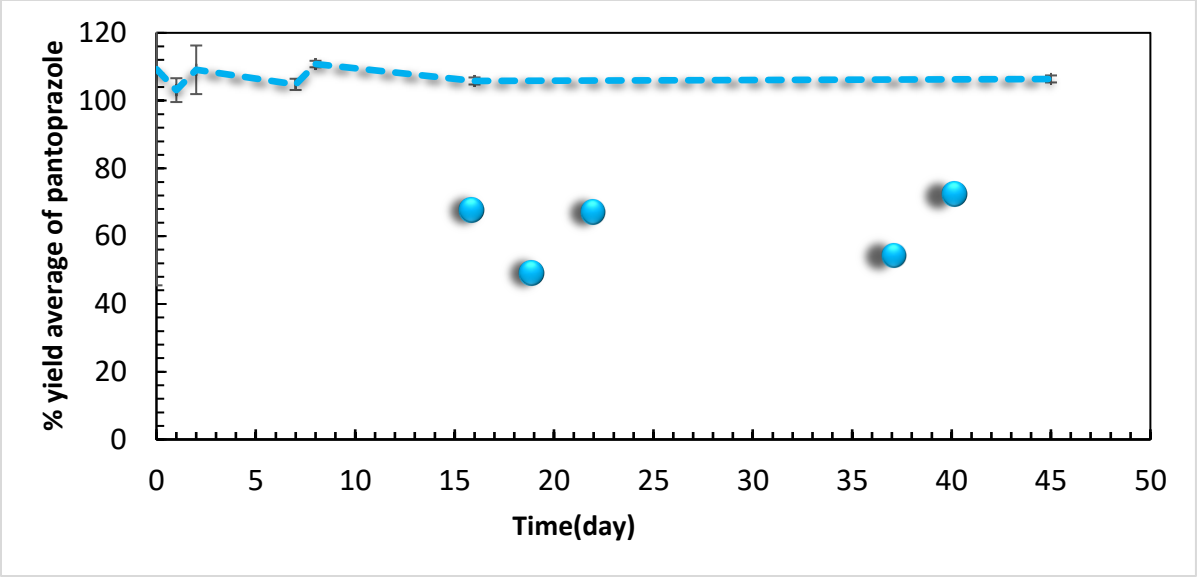


Figure (4.2.8): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in CMC suspension and preserved for the duration of the study at 4°C.

4.2.9 Pantoprazole suspension in syrup using CMC 0.2g/100ml at R.T:

Table (4.2.9): results of sample analysis of Pantoprazole dispersed in CMC suspension at R.T. Shown are the concentrations obtained from three samples each day, the % yield and the average % yield

Days	0	1	2	7	8	16	45
P.CMC.RT1	0.627	0.608	0.665	0.562	0.631	0.671	0.709
P.CMC.RT2	0.655	0.628	0.636	0.683	0.693	0.649	0.594
P.CMC.RT3	0.654	0.662	0.687	0.687	0.67	0.655	0.655
C1 mg/ml	1.640	1.592	1.737	1.475	1.650	1.752	1.848
C2 mg/ml	1.711	1.643	1.663	1.782	1.808	1.696	1.556
C3 mg/ml	1.709	1.729	1.792	1.792	1.749	1.711	1.711
% yield 1	102.5	99.5	108.5	92.20	103.1	109.5	115.5
% yield 2	106.9	102.7	103.9	111.4	113.0	106.0	97.3
% yield 3	106.8	108.1	112.0	112.0	109.3	106.9	106.9
(AVG)	105.4	103.4	108.2	105.2	108.5	107.5	106.6
SD	2.520	4.331	4.058	11.269	4.972	1.804	9.127

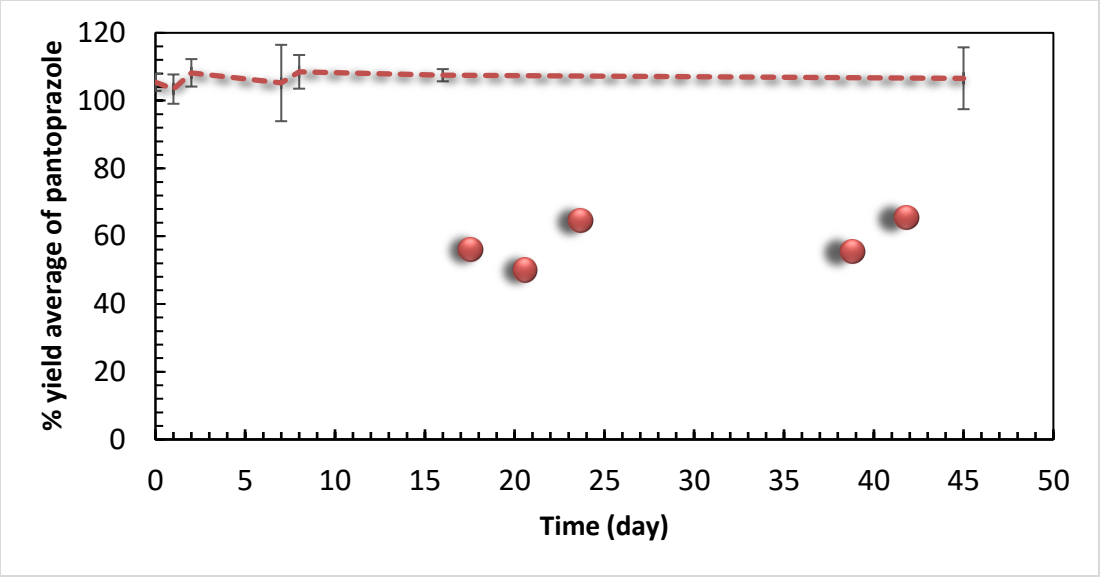


Figure (4.2.9): Percentage yield (actual/expected X100%) of samples taken from pantoprazole tablets dispersed in CMC suspension and preserved for the duration of the study at R.T.

4.2.10: A summary of the "range" of the different preparations

Preparation	range
Pantoprazole in water at RT	8
Pantoprazole in water at 4°C	22
Pantoprazole in syrup at RT	44
Pantoprazole in syrup at 4°C	25.5
Pantoprazole Suspension with 0.2% xanthan gum at RT	14.5
Pantoprazole Suspension with 0.2% xanthan gum at 4°C	13
Pantoprazole Suspension with 0.2% CMC at 4°C	6
Pantoprazole Suspension with 0.2% CMC at RT	5

It is observed, in contrast to Furosemide, that pantoprazole in water alone yielded a homogeneous aqueous preparation, with yields close to 100% and low range values. This could be attributed to the good solubility of the compound in water. Adding syrup decreased the yield and elevated the range values. It is worth of mentioning that we observed a color change in syrups of pantoprazole, which could be attributed to the decomposition of the drug however, using CMC as a suspending agent, with the addition of syrup, elevated the yield values and lowered the range. This is interesting as xanthan gum was better for furosemide. We conclude that pre-formulation studies are essential since each drug has its optimum formula and excipients

4.3 Aspirin analysis: (part 2)

In this part we followed the degradation of aspirin by measuring the increase in the conductivity of the solution. We also evaluated the effect of the addition of propylene glycol to the solution, which is assumed to decrease the level of degradation by decreasing the polarity of the solvent.

The first step was to construct a calibration curve, which can relate the % of aspirin degradation to the conductivity. As aspirin degrades it produces equimolar concentrations of salicylic acid and acetic acid. Accordingly, a 10 % degradation will yield a 10% increase of both acids in solution and so forth. These solution were prepared to simulate aspirin degradation, for example a solution with 90% aspirin and 10% of both acetic and salicylic acids will stand for 10% aspirin degradation and so on. The exact amount used are mentioned in the Methods section

4.3.1 Conductivity Reading of Aspirin Solutions (calibration Curve):

Solution NO.	% Aspirin	% Salicylic Acid	% Acetic acid	Conductivity Reading (µs) at 25℃)
1	100	0	0	605
2	90	10	10	706
3	80	20	20	793
4	70	30	30	832
5	60	40	40	910
6	50	50	50	967
7	40	60	60	1130
8	30	70	70	1370
9	20	80	80	1500

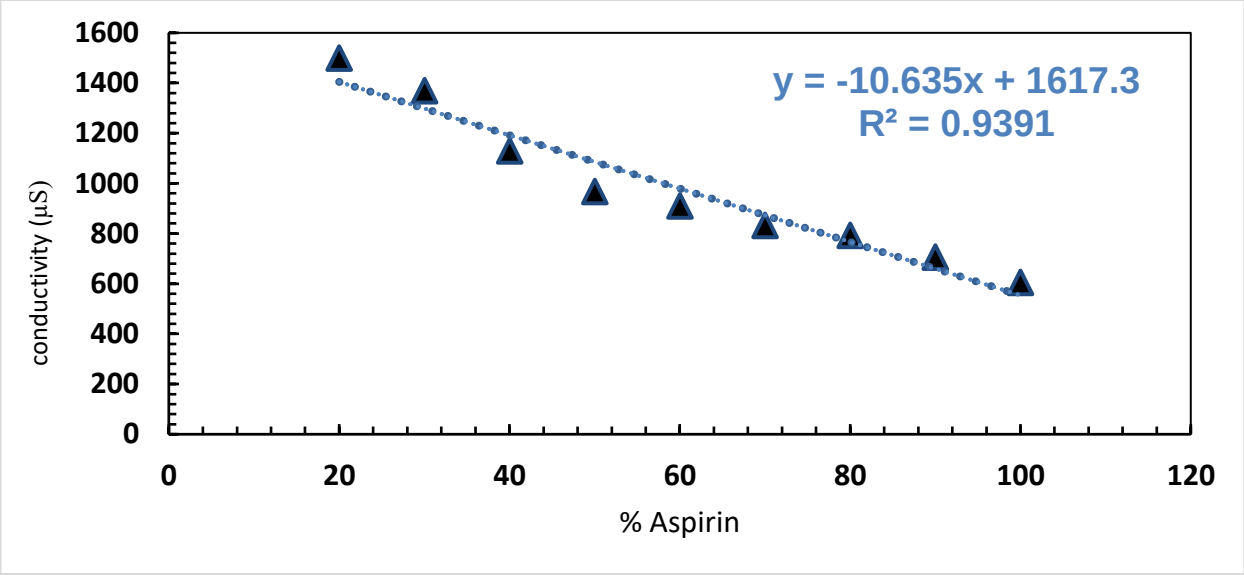


Figure (4.3.1) Calibration curve of aspirin

It is clearly seen that as more Aspirin is hydrolyzed, the conductivity increases in a linear manner. This will allow using this calibration curve to calculate the % of aspirin degradation based on the conductivity

4.3.2 Aspirin degradation in aqueous solutions:

Table (4.3.2): concentrations results of aspirin % with water by reading its conductivity every day.

Time (day)	Conductivity (µS) at 25°C	% Remaining of aspirin
0	605	95.18
1	611	94.62
2	622	93.58
5	670	89.07
6	678	88.32
8	747	81.83
12	859	71.30

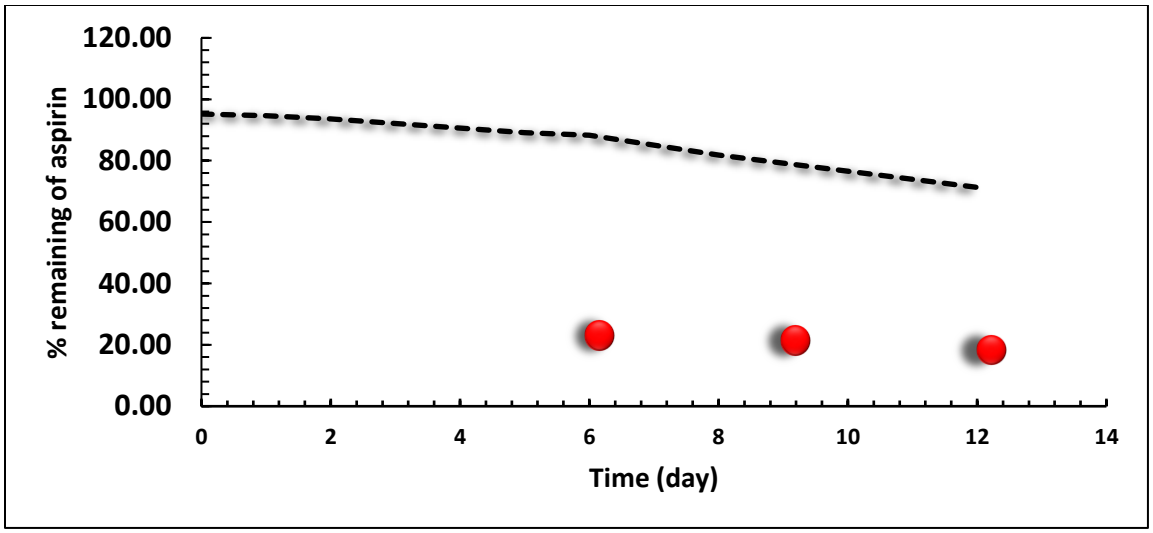


Fig 4.3.2: remaining aspirin (%) per time

4.3.3 Conductivity reading of solutions with PG 10% :(Calibration Curve):

Solution NO.	% Aspirin	% Salicylic Acid	% Acetic acid	Conductivity Reading (µs) at 25°C)
1	100	0	0	518
2	90	10	10	675
3	80	20	20	732
4	70	30	30	776
5	60	40	40	848
6	50	50	50	861
7	40	60	60	950
8	30	70	70	965
9	20	80	80	997

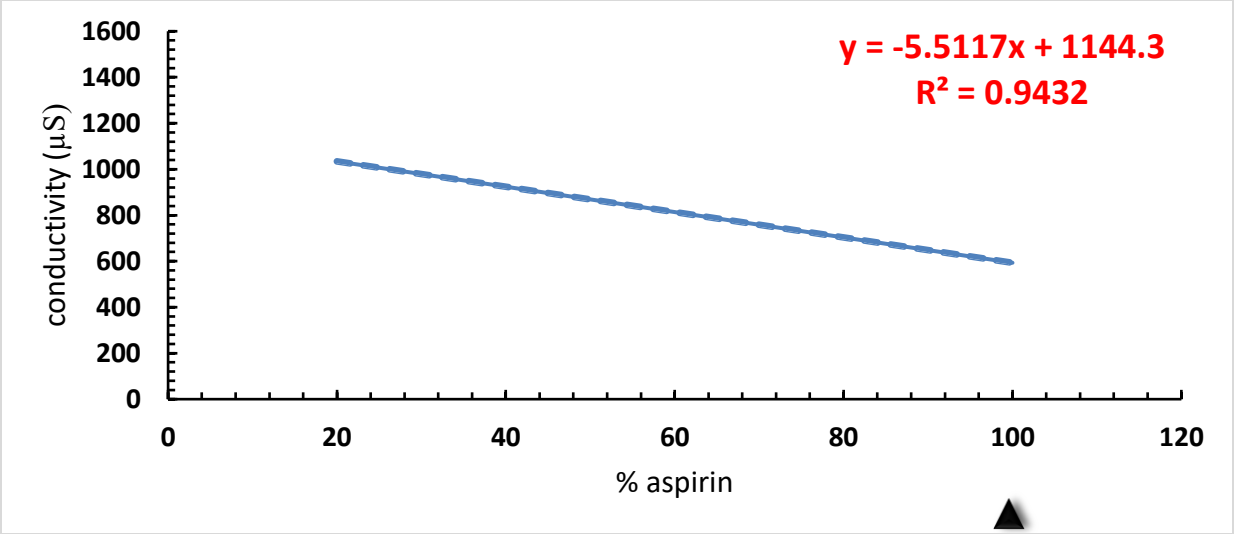


Figure (4.3.3) calibration curve of aspirin in water with 10% PG

Table (4.3.4) concentrations results of aspirin with 10% PG as a solvent by reading its conductivity every day.

Time (day)	Conductivity (µS) at 25°C	% remaining
0	518	100
1	530	97.9
2	541	95.9
5	550	94.2
6	559	92.6
8	575	89.7
12	596	85.9

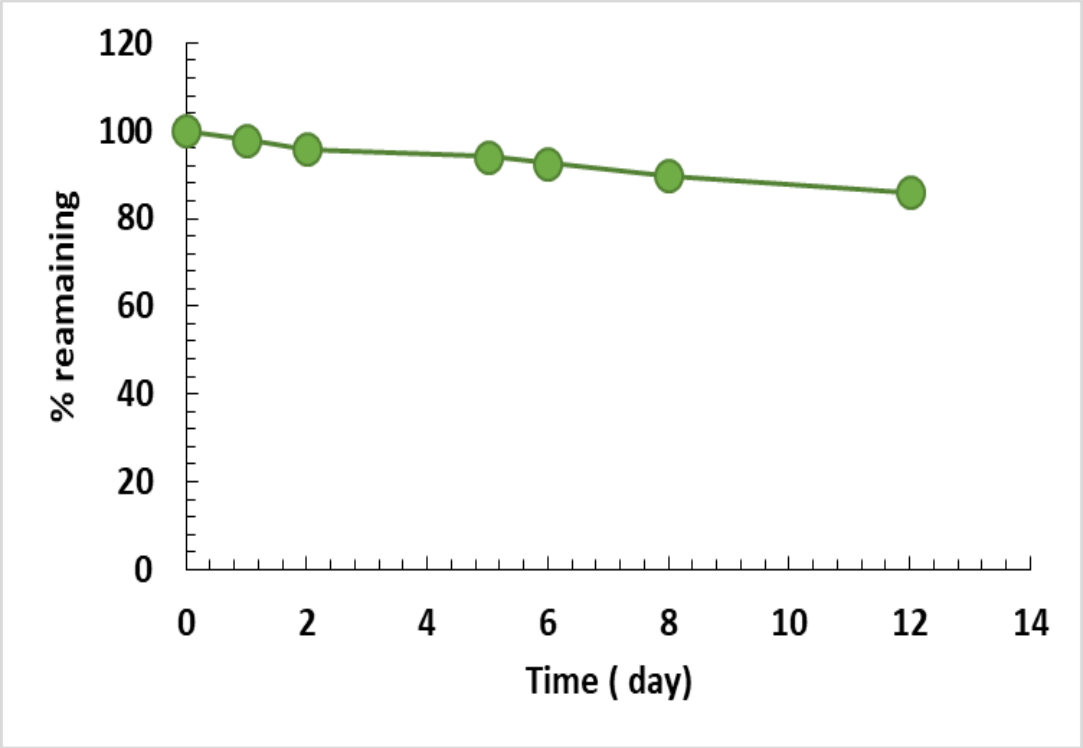


Figure 4.3.4: remaining aspirin % in solutions with PG

It is apparent form these results that PG retarded the degradation of aspirin in aqueous solutions. Compared to about 29% degradation of aspirin in water, PG led to about 14% degradation during the same time period. This should shed a light on the importance of such materials that increase the stability of aspirin in water.

Chapter five

Conclusion

5. Conclusion

It is concluded that pre-formulation studies are vital prior to the compounding of extemporaneous preparations. These studies should include testing of the physico-chemical properties of the active ingredient, such as solubility, pka, and stability in aqueous solutions. Formulative considerations taken into account should include using suspending agents, viscosity modifying agents, and materials that prevent the hydrolysis or increase the stability of the active ingredient when applicable. Oral liquids of Different drugs should not be prepared similarly. Preformulation studies must take place before preparing extemporaneous liquids. Not all suspending agents are equally suitable in stabilizing suspensions.Pharmacies that frequently prepare oral liquids must at least once perform stability studies

6. Future work

1- Long term stability studied of aspirin formulations.

2- Examination of effect of materials other than PEG...

3- Examination of other drugs than those tested in this study.

4- Expansion of preformulation aspect

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تحديد وتقييم استقرار التحضيرات الصيدلانية الارتجالية

إعداد: أنوار عرفات موسى أبو سنينة

المشرف: الدكتور طارق الجعبة

الملخص:

المقدمة والأهداف: التحضيرات الصيدلانية الارتجالية هي تلك التي يصنعها الصيدلي دون دراسة او مبدأ توجيهي، وعادة بتم تصنيعها باستخدام اشكال صيدلانية معدة مسبقا مثل الأقراص والكريمات. يتم تحضير هذه المستحضرات عند الحاجة إلى تغيير تركيز الدواء أو شكل جرعاته. أكثر الأنواع شيوعًا في فلسطين للتحضير كشكل صيدلاني هو السائل المعد للأطفال الذي يستخدم الأقراص كمواد أولية. ومع ذلك، هناك عدة مشاكل في هذه التحضيرات، أهمها ثبوتيتها وتجانسها. قد يكون توحيد الجرعة هي القضية الأكثر أهمية. أظهرت دراسة استقصائية أجريت في الصيدليات المحلية أنه لم يتم اتباع معيار واحد في هذه المستحضرات، ولم يتم إجراء دراسة لمراقبة الجودة حتى الآن للتحقق من صحة هذه المنتجات. أجريت هذه الدراسة لإجراء مقارنة واقتراح الحلول التركيبية من خلال تحليل التحضيرات المصنوعة بالطرق المتبعة في الصيدليات المحلية وبطرق أكثر دقة صيدلانياً. تم اختيار عقارين يستخدمان على نطاق واسع في التحضيرات الآنية؛ فوروسيميد وبانتوبرازول. كانت التجارب على هذين العقارين تهدف إلى فحص تجانس جرعة السوائل الفموية المحضرة. وتم أيضا اختيار عقار ثالث وهو الأسبرين لاختبار ثبوتيته، لأن العديد من الصيدليات تقوم بتحضيره كسائل فموي معلق في الماء دون مراعاة تأثير التحلل المائي للأسبرين على ثبات المنتج وتجانسه.

المنهجية: في الجزء الأول من الدراسة، تم استخدام أقراص فوروسيميد وبانتوبرازول لصنع دواء سائل عن طريق الفم من ثلاثة تركيبات مختلفة. كانت الطريقة الأولى هي إذابة الأقراص في الماء. الطريقة الثانية كانت عن طريق اذابته بالشراب المحلى. الطريقة الثالثة كانت باستخدام شراب مع عامل معلق، إما كربوكسي ميثيل السليلوز أو صمغ الزانثان، بتركيزات مختلفة. تم تخزين هذه التركيبات في درجة حرارة الغرفة أو عند 4 درجات مئوية وأخذت العينات بشكل دوري لتحليل تركيز المادة الفعالة. تم فحص تأثير نوع العامل المعلق وتركيزه على تجانس المستحضر. في الجزء الثاني من الدراسة، تم فحص تحلل الأسبرين في البيئة المائية من خلال قياس الموصلية الكهربائية. تقيس الموصلية الزيادة في تركيزات الأيونات حيث يتحلل الأسبرين إلى حمضين، حمض الأسيتيك وحمض الساليسيليك. في هذا الجزء، تم إنشاء منحنى معياري لمحاكاة النسبة المئوية لتحلل الأسبرين بقيم الموصلية ذات الصلة. تم إذابة الأسبرين في الماء وأجريت دراسة ثبوتيته بقراءة قيم الموصلية بشكل دوري. في دراسة أخرى، تم استخدام البروبيلين جليكول كمذيب مشترك لفحص قدرة البروبيلين جليكول على تقليل معدل تحلل الأسبرين.

النتائج والمناقشة: لوحظ عدم تجانس الفوروسيمد المحضر في الماء أو الشراب مقارنة بتلك المستحضرات المصنوعة باستخدام عامل معلق. أدى استخدام عامل معلق إلى زيادة استقرار وثبوتية التركيبة وتوحيده بشكل كبير، كما يتضح من القيم والنتاجات الفعلية. تُعزى هذه النتائج إلى قابلية الذوبان المنخفضة للفوروسيميد. تم الحصول على نتائج مختلفة في حالة البانتوبرازول، حيث أدى نشر الأقراص في الماء إلى تحضير متجانس. يمكن تفسير ذلك من خلال الذوبان الجيد للبانتوبرازول. ومع ذلك، فإن استخدام عامل معلق أدى إلى تقليل النطاق المحسوب، وهو مقياس التذبذب في تركيز الدواء في العينات اليومية. في الجزء الثاني من

الدراسة، تم توضيح التحلل المائي للأسبرين بوضوح، كما يتضح من زيادة الموصلية في محلول الأسبرين في كل مرة. كما ادى إضافة البروبيلين جليكول إلى تقليل معدل تحلل الأسبرين، ربما عن طريق تقليل قطبية المذيب.

الاستنتاجات: استنتج أن دراسات ما قبل الصياغة ضرورية قبل تركيب المستحضرات الارتجاليه. يجب أن تشمل هذه الدراسات فحص الخصائص الفيزيائية والكيميائية للمادة الفعالة، مثل الذوبان ,pka، والثبات في المحاليل المائية. وان يؤخذ بعين الاعتبار استخدام عوامل التعليق، وعوامل تعديل اللزوجة، والمواد التي تمنع التحلل المائي أو تزيد من ثبات المواد الفعالة عند الاقتضاء.