Enhanced Bilayered Tablet Formulation of Ursodeoxycholic acid and Propylthiouracil: A Review

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***Abstract*- This study aims to create and evaluate a bilayer tablet formulation that contains ursodeoxycholic acid (UDCA) and propylthiouracil (PTU) for the treatment of hepatobiliary diseases and hyperthyroidism. PTU, which makes up the first layer, is intended to provide medication to treat hyperthyroidism instantly. Sustained release is provided by the second layer, which contains UDCA, to promote liver function and lessen the negative effects of PTU treatment. To achieve drug content homogeneity, hardness, disintegration, and dissolving characteristics, different formulation parameters were tuned. According to in vitro drug release investigations, each medicine on the bilayer tablet showed unique release patterns, guaranteeing its therapeutic efficacy and reducing the possibility of drug-drug interactions. Research on in vitro drug release has shown that propylthiouracil and ursodeoxycholic acid have both regulated and prolonged release characteristics. These findings may have advantages for patient compliance and therapeutic efficacy. For the concurrent treatment of hyperthyroidism and hepatobiliary diseases, the bilayered tablet containing PTU and UDCA offers a promising dose form. To confirm its effectiveness and safety for use in patients, more research is necessary, including in vivo investigations and clinical trials. When used in conjunction with other medical disorders, this novel formulation may lead to better treatment results and increased patient compliance.**

Keywords: **UDCA, PTU, Immediate release, Sustained release.**

INTRODUCTION TO BILAYERED TABLETS

For many years, traditional drug delivery methods such as tablets, capsules, solutions, suspensions, creams, ointments, suppositories, liquids, and injectable have been used to treat both acute and chronic conditions. The most popular forms of conventional therapy are those that are frequently found both over-the-counter and on prescription. Prompt release therapy is the term used to describe the traditional therapy. A bilayer tablet can be used for sustained release tablets, which have two layers, or for the sequential release of two drugs combined. It can also be utilized to separate two compounds that are incompatible. An immediate release layer that serves as the loading dosage and a sustained release layer that serves as the maintenance dose. The most current type of tablet is the bilayer tablet, which combines tablets with sustained release and tablets with instant release. It's a kind of oral dose form that should be taken once a day. It starts working right away and keeps working for 12 to 24 hours.[3]

One great way to prevent drug incompatibilities of any kind, including between API and excipients, is to use bilayer tablets. Conventional therapy requires many daily administrations to maintain and obtain drug concentration within an appropriate therapeutic range. Even a minor delay in administration can result in fluctations in drug concentration, which can negatively impact both patient compliance and aesthetic value. Several innovative strategies have been developed to improve patient compliance, which can manage the pace of medication delivery to the site of action, thereby preventing fluctuations or drawbacks associated with conventional therapy. One of the most effective and popular ways to deliver medication to the site of action is orally. Because they are so simple to administer, tablets and capsules are the most popular traditional medication for patients.

THE NEED TO CREATE BI-LAYER TABLETS:

For the purpose of monitoring fixed dosage regimens, extending the shelf life of medicinal products, developing innovative mucoadhesive and buccal drug delivery systems, and creating chewables and floating tablets for medication administration techniques that cause gastrointestinal distress.

1. Controlling one or two different APIs' delivery rate.
2. Creating erodible or swellable barriers for controlled release by enclosing the API layer between one or two inactive layers, so altering the entire surface area that might be utilized for the API layer.

3. To separate APIs that are incompatible with one another and control a layer's release by utilizing a functional feature of a different layer (such as the osmotic property). [9]

FEATURES OF BI-LAYER TABLET DOSAGE FORMS IN GENERAL:

1.The product identity should be elegant and free from flaws such as contamination, discoloration, chipping, and fractures.
2. It should be strong enough to withstand mechanical shock as it is being made, packed, shipped, and dispensed.
3. Must be physically and chemically stable.
4. The medication must be released from the bi-layer tablet in a predictable and repeatable way.
5. Chemical stability during storage is essential to avoid any alterations to the therapeutic substances. [10]

CHALLENGES IN THE FORMATION OF BILAYER TABLETS

The elastic disparity of the layers, insufficient hardness, imprecise individual mass control, cross-contamination among the layers, decreased yield, and the affinity of the layers to delaminate at the interface between them during and after the various production stages that follow the compaction process make the manufacturing of these drug delivery mediums mechanically challenging. It is also difficult to predict their long-term mechanical properties.

Therefore, the main goal is to accurately and completely comprehend the underlying causes of the issues at both the macro and micro levels and to develop reliable dose delivery methods that successfully treat these causes. [8–10].

Inadequate adhesion and bonding at the interface between adjacent compacted layers is one of the main issues, which is mostly because of an interfacial crack that caused residual stresses in the tablet. When there is compression, as happens during packaging, storage, or shipment, these stresses disperse over a limited amount of space in the tablet and cause layer-separation, or delamination, which is not immediately noticeable.
Additionally, too much hardness or too much softness will prevent the compacted layers from adhering firmly, which may lead to poor mechanical integrity. Additional difficulties in the development process include determining the layer sequence order, the elastic disparity of the surrounding layers, the layer weight ratio, the damping force of the first layer, and cross-contamination between layers [11, 12]. Failing to handle these factors will have an impact on the quality attributes of the bilayer tablets as well as the bilayer compression process itself, which is an uncontrolled or inefficient operation.i.e., sufficient mechanical strength to preserve its utility and the layer's ability to manage weight. Thus, in order to support the development of a dependable process and end result, it is essential to appropriately obtain a comprehensive understanding of the root causes [13, 14]. Because the adjacent compacted layers within a bilayer tablet adhere to each other mechanically, understanding the factors influencing the stress state, the mechanical properties of each layer and the bilayer tablet as a whole, compression parameters, and specialized techniques for failure prediction as a function of compression conditions and layer properties are essential for the successful development of bilayer tablets
[15].

TYPES OF BILAYER TABLETS

1. Single sided tablet press.
2. Double sided tablet press
3. Bilayer tablet press with displacement monitoring.
4. Multilayer compression basics.

1. SINGLE SIDED TABLET PRESS

Numerous varieties of bilayer presses have been developed over time. With the two chambers of the double feeder kept apart, a single-sided press is the simplest design. One tablet layer was produced by force-feeding, and another by gravity-feeding a distinct powder into each chamber. Before the entire tablet is compressed in one or two steps, the first layer of powder is first placed into the feeder as the dye passes beneath it, and then the second layer of powder. The easiest method for creating a bilayer tablet is to mix the when two dye layers are slightly at their interface, they often link enough to avoid any layer separation during the creation of the tablet.

LIMITATION

No individual layer control or weight tracking.
There's no obvious visible divide between the 21 days.
The little compression roller's dwell duration can cause problems with hardness and insufficient deaeration capping.

DOUBLE SIDED TABLET PRESS

Most double-sided tablet presses that automate production management employ the compression force to monitor and control the weight of the tablet weights. The effective compression force, assisted by the compression mechanism, that is applied to each tablet separately at the principal compression point of the layer. This technique helps reject out the tolerance tablets and adjust the die fill depth when needed.

ADVANTAGES

1) To prevent chapping and the separation of individual layers, little force is used to compress the top layer.
2) Extended dwell durations in the initial and secondary layer precompression to guarantee adequate hardness at maximum turret velocity.
3) Optimal defense against cross-contamination between two layers.
4) A distinct visual division of the two layers.
5) For precise and autonomous displacement weight monitoring and weight control for every layer are employed.
6) Insufficient bonding between the two layers results in the separation of the two distinct layers when the bi-layer tablet is finally squeezed.

LIMITATION

1. Only when the first layer is crushed at a low compression force can adequate bonding be established, allowing the first and second layers to interact during the final compression.
2. There will be insufficient bonding if the first layer is subjected to a significant compression force.
3. The low compression force required to compress the first layer in tablet presses that employ compression force measuring sadly compromises the accuracy of the weight monitoring and control of the layer.

2. BILAYER TABLET PRESS WITH DISPLACEMENT MONITORING

Compressive force and the bilayer tablet press work on fundamentally different principles.

Here, a decrease in compression force results in an increase in accuracy. A tall four compression stage with enough dwell time helps lower the possibility of separation and capping, which rises with higher production rates.

ADVANTAGES

To provide accurate, independent weight management of each layer, displacement weight monitoring and control are used.

To avoid chapping and the separation of the two layers, a low compression force is given to the first layer.

To guarantee sufficient hardness at the highest turret speed, dwell times for the first and second layers were extended during precompression.

4. MULTILAYER COMPRESSION BASICS

Multiple layer compression can be considered when building presses, or multipliers can be added to a double press to make it work. Prolonged release formulations have long been made using the concept of a multilayer tablet. In addition to a fast-releasing layer, these tablets may feature players or triple layers to sustain the medication release from the tablet. The reason for the pharmacokinetics benefit is that, in contrast to fast-releasing granules, which release the medication at a consistent rate, prolonged granule release raises blood concentration steadily while preserving blood level stability.

EXCIPIENTS SELECTION

The global head of research and development at JRS Pharma, Gernot Warnke, highlights that "excipient selection for bi-layer tablets is as important as it is for single-component tablets, and there are instances when it is most important."For example, when using a high-speed tablet press, the blend to be crushed is filled into the die by drawing the bottom punch lower and the die passing below the feed frame.

This rapid descent produces a certain amount of suction that helps fill the die. In order to achieve consistent tablet weight uniformity through uniform die filling, this suction helps to make up for materials that flow less optimally." Warnke cautions that the benefits of the punch's downward action are limited to the first or lowest layer of multi-layer tablets. "The only method available for filling the die cavity in any future layers is mix flow. Therefore, it is essential to choose excipients that best impart flow properties so that subsequent layers have appropriate flow characteristics," he says.

Warnke goes on to say that choosing the best excipient for the first layer is crucial to ensuring that, following tamping, the surface has a rough enough porosity to allow the second layer to adhere sufficiently.

"It has been shown that if the first layer is too smooth (due to makeup or excessive tamping) the second or subsequent layer will not adhere well and layers may separate with minimal agitation (i.e., during ejection, discharge, packaging, or over the shelf-life of the product)," according to him.

"Due to the fact that the first layer [in a multi-layer tablet] is generally subjected to low compression forces, the formulation should be able to cope further compression in the second phases of tableting without leading to a fragile tablet," Giatti explains. She also emphasizes how selecting an excipient with high compressibility can improve tableting performance overall and help mitigate future problems with capping, separation, and delamination. [15]

ADVANTAGES OF BILAYER TABLET

✓ The two medications are released simultaneously.

It is simple to put together a medicine combination that is incompatible.

Drugs with varying release profiles can be combined in formulations.

Because of their cumulative impact, individual drug doses might be decreased to lessen the burden of pills.

By combining medications that counteract each other's negative effects, side effects can be minimized.

Enhances the products' elegance.

Tablets of this kind only permit synergistic pairing.

LIMITATION

Stopping

Hardness issue

division of layers

Sequence of layers in order

Interlayer cross-contamination

elastic mismatches between nearby layers. [4]

Suitable candidates for tablets with two layers

medications that have a synergistic or cumulative impact, such as antiasthamatic medications like salbutamol and theophylline.

Medication combinations with opposing adverse effects, such as omeprazole + NSAIDS or hydrochlorothiazide + amiloride, may decrease each other's side effects.

Medicines that are incompatible.

A drug called propylthiouracil (PTU) is used to treat hyperthyroidism, a disorder marked by an overactive thyroid gland. As a member of the antithyroid agent class of medications, it is frequently prescribed to regulate the excess synthesis of thyroid hormones, mainly thyroxine (T4) and triiodothyronine (T3).

By preventing the synthesis of these hormones, PTU has a therapeutic effect and aids in the restoration of normal thyroid function. People with hyperthyroidism, including those with Graves' disease, are frequently prescribed PTU. It assists in lowering blood levels of thyroid hormones, which relieves symptoms like anxiety, weight loss, and a fast heartbeat. Although it varies from person to person, its bioavailability is usually regarded as good. The action starts off rather quickly. The half-life of PTU is typically in the range of 1 to 3 hours. Effective in Treating Hyperthyroidism:

PTU treats hyperthyroidism symptoms by lowering the overproduction of thyroid hormones. Safety in Pregnancy: Due to its decreased chance of resulting in birth abnormalities in the growing fetus, it is occasionally chosen over other antithyroid medications in the initial trimester of gestation.

Hepatotoxicity Risk: The potential for PTU causing liver damage, particularly the rare but serious condition known as hepatotoxicity, is a serious drawback. Individuals using PTU need to have their liver function constantly evaluated for any symptoms. PTU is a useful drug for treating hyperthyroidism, however using it has a risk of hepatotoxicity and other possible adverse effects. When choosing the best course of action for treating hyperthyroidism, medical professionals carefully analyze the health and medical history of each patient. When choosing the best course of action for treating hyperthyroidism, medical professionals carefully analyze the health and medical history of each patient.

A naturally occurring bile acid that has been artificially manufactured as a drug is ursodeoxycholic acid (UDCA), sometimes referred to as ursodiol. It is used to treat different gallbladder and liver conditions. By altering the composition of bile, UDCA helps control and prevent a number of liver and biliary disorders. Fatty Liver Disease Without Alcohol (NAFLD):

It can be used to control the build-up of fat and inflammation in the liver that come with NAFLD, which is frequently connected to metabolic syndrome and obesity. Cholestatic Liver illnesses: In a variety of cholestatic liver illnesses, when the liver's bile flow is restricted, UDCA can help. It usually has a high bioavailability and is effectively absorbed by the liver for its intended therapeutic effects. Although it might vary from person to person, the half-life of UDCA is typically between three and five hours. Effective in Treating PBC: UDCA is a very good treatment for PBC and can help those who are afflicted with their liver function. Management of Chronic Liver Disease: When treating biliary and chronic liver illnesses, UDCA is a helpful tool.

COMBINATION OF TWO DRUGS

Pharmaceutical science's sophisticated dosage form known as bilayer tablets has come to light as a potential remedy for the growing complexity of medication delivery and therapy. These tablets are made up of two different layers, each of which has special drug release qualities that allow for a variety of uses in contemporary medicine. Because bilayer tablets offer a platform for combination therapy, chronotherapy, and the avoidance of drug incompatibilities, they have completely changed the way drugs are delivered. By providing customized treatments that improve patient compliance and therapeutic efficacy, they play a crucial role in the fight against drug resistance and in enabling personalized medicine.This article examines the creative construction and wide range of applications of bilayer tablets in contemporary medicine, highlighting their potential to enhance patient outcomes and advance medical practice. [16,17]

Materials:

1. Ursodeoxycholic Acid (UDCA)

2. Propylthiouracil (PTU):

3. Excipients: A variety of excipients were used in the preparation of the bilayer tablets, such as magnesium stearate, lactose monohydrate, crosspovidone, hydroxypropyl methyl cellulose (HPMC), and microcrystalline cellulose (Avicel PH101).

4. Solvents: o Methanol and acetonitrile, two solvents of the highest caliber for high-performance liquid chromatography (HPLC), were employed for compatibility testing and analytical testing.

5. Additional Reagents: o Distilled water: This is used to make various aqueous solutions and dissolving media. Phosphate buffer solutions: Used in dissolution research and pH correction

Table 1- PROPYLTHIOURACIL AND URSODEOXYCHOLIC ACID BILAYER TABLET FORMULATION

1. Ingredient	Immediate-Release Layer	Sustained-Release Layer
Ursodeoxycholic Acid (UDCA)	100 mg	300 mg
Propylthiouracil (PTU)	50 mg (immediate release)	-

Microcrystalline Cellulose	50 mg	50 mg
Lactose Monohydrate	50 mg	50 mg
Crospovidone	5 mg	5 mg
Hydroxypropyl Methylcellulose (HPMC)	-	50 mg
Magnesium Stearate	5 mg	5 mg
Total Tablet Weight	260 mg	460 mg

Methods of Formulation:

1. Direct Compression: Because it is easy to use and reasonably priced, direct compression is a popular technique for creating bilayer tablets. PTU powder and appropriate excipients, such as The PTU immediate-release layer is made up of a consistent combination of lubricants (magnesium stearate), disintegrants (crospovidone, sodium starch glycolate), and diluents (lactose, microcrystalline cellulose). In line with this, to regulate the release rate for the UDCA sustained-release layer, UDCA powder is combined with hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) or ethylcellulose as well as other excipients. [18]
2. Wet Granulation: Wet granulation is a process that creates desired-sized granules by soaking a powder mixture with a granulating fluid, then drying and grinding the mixture. Wet granulation can be used to enhance the flow characteristics of the PTU layer and compressibility of the drug powder, facilitating uniform distribution within the tablet matrix. Similarly, for the UDCA layer, wet granulation may be used to achieve better control over the release kinetics by incorporating hydrophilic polymers or lipid-based carriers. [19]

FORMUALTION [22]
For the Immediate-Release Layer (PTU):
1. Propylthiouracil (PTU): The active pharmaceutical ingredient responsible for the immediate-release layer, providing therapeutic effects for thyroid disorders.
2. Diluents: These serve to boost the tablet's bulk volume and facilitate the medication's even dispersal. Lactose, microcrystalline cellulose, and dibasic calcium phosphate are a few examples.
3. Disintegrants: These help the tablet dissolve quickly after swallowing, allowing PTU to be released for instant absorption. Sodium starch glycolate, croscarmellose sodium, and crospovidone are examples of common disintegrants.
4. Lubricants: These help to ease the ejection of tablets from the die cavity and stop the tablet material from adhering to the tablet press's surfaces. Stearic acid, talc, and magnesium stearate are a few examples.

For the Sustained-Release Layer (UDCA):
1. Ursodeoxycholic Acid (UDCA): The active pharmaceutical ingredient responsible for the sustained-release layer, providing therapeutic effects for liver disorders.
2. Hydrophilic Polymers: These polymers encircle the drug particles in a matrix that regulates the release of UDCA throughout time. Examples include hydroxypropyl methylcellulose (HPMC), ethylcellulose, and polyvinyl alcohol.
3. Plasticizers: Plasticizers are used to enhance the flexibility and elasticity of the polymer matrix, ensuring uniform drug release. Common plasticizers include polyethylene glycol (PEG) and glycerin.
4. Release Modifiers: These ingredients may be added to modify the release kinetics of UDCA, achieving the desired sustained-release profile. Examples include pore-forming agents, such as sodium chloride, and pH modifiers, such as citric acid.[23]

PARAMETERS
PREFORMULATION PARAMETERS
1. Physicochemical Properties of Drug Substances: **Solubility:** Determination of the solubility of PTU and UDCA in various solvents can provide insights into their dissolution behaviour and aid in selecting suitable dissolution media for in vitro testing.

2.Crystalline Form: Identification of the crystalline form (e.g., polymorphs) of PTU and UDCA using techniques such as differential scanning calorimetry (DSC) or X-ray diffraction (XRD) aid in understanding their processing properties and stability.

3. Particle Size and Morphology: Analyzing the morphology and distribution of particle sizes using techniques like laser diffraction and scanning electron microscopy (SEM) helps assess the flow properties and compressibility of PTU and UDCA powders

4. Hygroscopicity*:* Assessment of the hygroscopic nature of PTU and UDCA determines their susceptibility to moisture uptake, which can affect stability and formulation performance.

5. Flow Properties of Drug Powders:

Angle of Repose: Calculating the angle of repose provides information on the flow ability and cohesion of PTU and UDCA powders.

Carr's index and hausner's ratio: These parameters quantify the flow ability and compressibility of PTU and UDCA powders, aiding in the selection of appropriate granulation methods.

6. **pH-Solubility Profile:** Evaluation of the pH-solubility profile of PTU and UDCA provides insights into their dissolution behavior across a range of physiological pH conditions, aiding in the design of formulations with optimal drug release characteristics.[24,25]

POST COMPRESSION PARAMETERS

1. Thickness and Diameter:

Measurement: The thickness and diameter of bilayer tablets are measured using a calibrated micrometer or a digital tablet thickness tester.

Purpose: Ensuring uniformity in thickness and diameter helps maintain consistency in tablet size, which affects dosing accuracy, packaging, and patient acceptability.

2. ***Hardness:***

Measurement: Tablet hardness, also known as tablet crushing strength is determined by means of a hardness tester (such as the Schleuniger or Monsanto hardness tester).

Purpose: Tablet hardness reflects the mechanical strength and integrity of bilayer tablets, ensuring resistance to breakage during handling, transportation, and packaging. [26]

3. Weight Variation:

Measurement: Weight variation testing involves individually weighing a specified number of bilayer tablets and calculating the percentage deviation from the average weight.

Purpose: Ensuring uniformity in tablet weight across batches is crucial for accurate dosing and compliance with pharmacopeial standards.

4. Friability:

Measurement: Friability testing involves subjecting a sample of bilayer tablets to mechanical abrasion and calculating the percentage of weight lost in a friability tests.

Purpose: The goal of evaluating tablet friability is to determine how resistant it is to mechanical stress and abrasion during handling, packing, and transportation. [27]

5. Disintegration Time:

Measurement: Disintegration testing determines the amount of time needed for bilayer tablets to break down into smaller pieces when immersed in a specified medium (e.g., water or simulated gastric fluid).

Purpose: Ensuring that bilayer tablets disintegrate within a specified time frame facilitates drug release and absorption, optimizing therapeutic efficacy. [28]

6. Dissolution Rate:

Measurement: Dissolution testing assesses how quickly and how much of a medication bilayer pill releases under standardized conditions using dissolution apparatus (e.g., USP apparatus 1 or 2).

Purpose: Assessing the dissolution rate provides critical information on drug release kinetics, ensuring batch-to-batch consistency and compliance with pharmacopeial standards.

7. Content Uniformity:

a. **Measurement**: Content uniformity testing involves assaying the drug content in individual bilayer tablets and calculating the percentage deviation from the label claim.

b. **Purpose**: Verifying uniform distribution of PTU and UDCA within each bilayer tablet ensures consistent drug dosage and efficacy.[29]

8. Appearance and Physical Characteristics:

a. **Observation**: Visual inspection of bilayer tablets for defects, such as chipping, capping, or color variation, is performed.

b. **Purpose**: Ensuring that bilayer tablets meet aesthetic and physical quality standards enhances patient acceptability and confidence in the product.[30]

RESULT

Preformulation Parameters

Preformulation studies provide valuable insights into the physicochemical properties of PTU and UDCA, their compatibility with excipients, and their behavior during formulation processes. By understanding these parameters, formulation scientists can make informed decisions regarding excipient selection, formulation strategies, and processing conditions. For example, knowledge of the solubility, particle size, and compatibility of PTU and UDCA guides the development of bilayer tablet formulations with optimal drug release characteristics and stability.

Post-Compression Parameters

Post-compression evaluation ensures that bilayer tablets meet the desired quality standards and performance criteria features including thickness, hardness, fluctuation in weight, friability, period of disintegration, rate of dissolution, and content uniformity provide critical information on tablet physical attributes, mechanical strength, drug release kinetics, and dosage uniformity. By assessing these parameters, formulation scientists can verify the consistency, reliability, and efficacy of bilayer tablets, ensuring patient safety and compliance with regulatory requirements.[31]

Discussion

An important development in pharmaceutical therapy, especially for patients with co-occurring thyroid and hepatic problems, is the manufacturing of bilayer tablets containing propylthiouracil (PTU) and ursodeoxycholic acid (UDCA). The following are the main topics of discussion.[32]

1. Therapeutic Benefits

Bilayer pills provide clear benefits for the management of thyroid and hepatic conditions. Because of its hepato protective qualities, UDCA treats liver dysfunction that is frequently linked to conditions such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

PTU, meanwhile, offers efficient hyperthyroidism treatment, which includes treating Graves' disease. Bilayer tablets offer an integrated method of treatment by incorporating these two medications into a single dosage form, addressing their complex interactions between thyroid and hepatic disorders

2. Formulation Considerations

Formulation characteristics must be carefully considered when developing bilayer tablets. Understanding the physicochemical characteristics of UDCA and PTU, as well as their compatibility with excipients, is largely dependent on preformulation studies. Studies on compatibility make sure that the chosen excipients won't affect the medications' stability or effectiveness. To guarantee product quality and performance, post-compression factors such tablet hardness, weight fluctuation, and dissolution rate also need to be optimized.

3. Patient Adherence

There are benefits to bilayer pills in terms of adherence among patients. These tablets improve patient compliance and treatment outcomes by making dosage regimens simpler and reducing pill load by offering distinct layers for UDCA and PTU. People with chronic diseases who need long-term drug therapy would especially benefit from this.[33]

4. Future Directions

Although bilayer PTU and UDCA tablets are promising for the treatment of thyroid and hepatic problems, more research is required to enhance dosage and formulation methodologies. Subsequent investigations might go further into new excipients, sophisticated medication delivery methods, and customized therapy approach. Furthermore, conducting clinical trials to examining the efficacy and safety of bilayer tablets in a larger group of patients will provide important new information about their potential uses. [34]

Conclusion:

The comprehensive evaluation of both preformulation and post-compression parameters is necessary for the effective creation and marketing of bilayer tablets containing PTU and UDCA. Preformulation studies guide formulation design, while post-compression evaluation ensures product quality and performance. By integrating findings from these studies, formulation scientists can optimize formulation strategies, mitigate risks, and ensure the development of high-quality bilayer tablets that meet patient needs and regulatory standards. Ultimately, the successful implementation of pre and post-compression criteria results in the creation of pharmaceutical solutions that are dependable, safe, and successful for the treatment of thyroid and hepatic conditions. [35, 36]

An important development in the pharmaceutical industry is the creation and characterization of the propylthiouracil and ursodeoxycholic acid bilayer tablet. This new dose form provides a practical, patient-friendly option for those who suffer from gallstone-related illnesses in addition to hyperthyroidism. [37, 38] The tablet's potential as a useful addition to the medical toolkit is highlighted by its adherence to pharmaceutical standards and regulated release characteristics. In order to determine its therapeutic efficacy and safety in treating various concomitant medical disorders and ultimately improve patient health and well-being, more research is necessary, including clinical trials. [39-41]

REFERENCES:

[1] Katherine v. Williams, Sunil nayak, Dorothy Becker, Jorge reyes, and Lynne burmeister(2023). Fifty Years of Experience with Propylthiouracil Associated Hepatotoxicity.
[2]RaziyehKaramikhah,AkramJamshidzadeh,NegarAzarpira,ArastooSaeedi,RezaHeidari .Propylthiouracil-Induced Liver Injury in Mice and the Protective Role Of Taurine.
[3] Yasunori Ichiki, Mitsuteru Akashi, Nobuyuki Yamashita, Chie Morita, Toru Maruyama, Takahiko Horiuchi, Kazuhiro Hayashida, Hiromi Ishibashi, and Yoshiyuki Niho ,(1998).Propylthiouracil-Induced severe hepatitis: A case report and Review of the literature.
[4] Saul Malozowski and Ana Chiesa (2010). Propylthiouracil-Induced Hepatotoxicity and Death.
[5]Hee-Jin Kim, Byung-Ho Kim, Yo-Seb Han, Inmyung Yang, Kyeong-Jin Kim, Seok-Ho Dong, Hyo-Jong Kim, Young-Woon Chang, Joung-Il Lee, and Rin Chang(2001). The Incidence and Clinical Characteristics of Symptomatic Propylthiouracil-Induced Hepatic Injury in Patients with Hyperthyroidism.
[6] Scott A. Rivkees1 and Donald Mattson (2009). Propylthiouracil (PTU) Hepatoxicity in Children and Recommendations for Discontinuation of Use.
[7] Jennifer Primeggia, MD; James H. Lewis, (2010). Gone (From the Physicians' Desk Reference) But Not Forgotten: Propylthiouracil-Associated Hepatic Failure: A Call for Liver Test Monitoring.
[8]Ben-Zion Garty, Rivka Kauli, Josef Ben-Ari, Ernest Lubin, Menachem Nitzan, and Zvi Laron(1985). Hepatitis associated with propylthiouracil treatment.
[9]Ikuko sato, taku tsunekawa1, yuri shinohara1, yuichiro nishio1, yuko shimizu2, yasuhiko suzuki3and shuko yoshioka(2011).a case of autoimmune hepatitis with graves' disease treated by propylthiouracil.
[10]Sarantis Livadas, Xenophon Xirafis, Frangiskos Economou, Georgios Boutzios ,Maria Christou, Aristea Zerva, Athanasios Karachalios, Helen Palioura, Sotiria Palimeri , Evanthia Diamanti-Kandarakis(2010). Liver failure due to antithyroid drugs: report of a case And literature review.
[11] A Rambaldi1, C Gluud (2005). Propylthiouracil for alcoholic liver disease 34.Tatsuo Miyamura Tatsuo Kanda Shoko Minemura Masato Nakamura Shingo Nakamoto Xia Jiang Shuang Wu Shin Yasui Makoto Arai Osamu Yokosuka (2013). Acute Liver Failure Associated With Propylthiouracil in a Pregnant 26-Year-Old Woman.
[12] Yong Zhou.B, Rand Doyenb, and Lenard M. Lichtenberger, (2009). The role of membrane cholesterol in determining bile acid Cytotoxicity and cytoprotection of ursodeoxycholic acid
[13] Mercedes Robles-Diaz 1, Lana Nezic2, Vesna Vujic-Aleksic2, 3 and Einar S. Björnsson4, 5(2021).
[14] Role of Ursodeoxycholic Acid in Treating and Preventing Idiosyncratic Drug-Induced Liver Injury .A Systematic Review.
[15]Maria Nadinskaia, Marina Maevskaya, Vladimir Ivashkin, Khava Kodzoeva, Irina Piragua, Evgeny Chesnokov, Alexander Nersesov, Jamilya Kaibullayeva, Akzhan Konysbekova, Aigul Raissova, Feruza Khamrabaeva, Elena Zueva(2021). Ursodeoxycholic acid as a means of preventing atherosclerosis, Steatosis and liver fibrosis in patients with nonalcoholic fatty liver
Disease.
[16] B. Siva Sai Kiran, P. Samba Siva Rao, G. Raveendra Babu and M. VenkatKumari (2015). bilayer tablets– a review.
[17] Swati Saxena, Hemant Agrawal, Sarang Jain (2020). Formulation and evaluation of bilayer tablet: a review.
[18] Florence. A.T &Attwood. (2017).Physicochemical principles of pharmacy
[19] Ahuja & Scypinski.S. (Eds.). (2016).Handbook of modern pharmaceutical analysis (2nd edition). Academic press
[20] Ott.M, Francze.s , Chalus,P(2018).pharmaceutical preformulation and formulation: A Practical guide from candidate drug selection to commercial dosage form(2nd edition).CRC press
[21]Carstensen,J.T.&Rhodes,C.T.(edition).,(2017).Drug stability: Principle and practices()3rd edition).CRC press.
[22] Florence, A.T &Attwood. (2017).Physicochemical principles of pharmacy
[23] Ahuja, S& Scypinski, S. (Eds.). (2016).Handbook of modern pharmaceutical analysis (2nd edition). Academic press.
[24] Ott, M, Francze, s., Chalus, P.(Eds.).(2018).pharmaceutical preformulation and formulation: A Practical guide from candidate drug selection to commercial dosage form(2nd edition).CRC press.
[25] Carstensen, J.T. & Rhodes, C.T.(edition).,(2017).Drug stability: Principle and practices 3rd edition).CRC press.
[26] Lachman, L, Lieberman, H.A., &kanig,J.L (2013). The Theory and Practice of Industrial Pharmacy (4th Edition). Varghese Publishing House.
[27] Banker, G.S &Rhodes, C.T. (Edition) (2017).Modern Pharmaceutics (5th Edition). CRC Press FDA. (2022). Guidance for Industry: Dissolution.
[28] Testing of Immediate Release Solid Oral Dosage Forms

[29] Rowe.R.C, Sheskey, P.J., & Quinn, M.E. (Edition). (2009).Handbook of Pharmaceutical Excipients (6th Edition) Pharmaceutical Press.
[30] Lewis,J.H.(2000). Ursodiol for liver disease –the magic bullet. New England Journal of Medicine, 382 (7),673-675.
[31] Cooper,D.S.(2005).Antithyroid drugs. New England Journal of Medicine, 352 (9), 905-917.
[32]Amidon,G.L.,lennernas,H.,Shah,V.p.,& Crison,J.R.(1995).A Theoretical basis for a biopharmaceutical drug classification :The correlation of in Vitro Drug product dissolution and in Vivo bioavailability. Pharmaceutical research, 12(3), 413-420.
[33] United states pharmacopeia (USP) and national formulary (NF). (2022).General chapter<905>Uniformity of Dosage units.
[34] FDA.(2022).Guidance For industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms.
[35] Lachman,Lieberman,H.A.,& knight,J.L. (2013). The theory and practice of industrial pharmacy (4th ed.).Varghese publishing house.
[36]Nevens,F.,Andreone,.,Mazzella,G.,Strasser,S.I.,&Bowlus, C.(2016).A placebo-Controlled trail of obeticholic acid in primary biliary cholangitis. New England Journal of Medicine,375(7),631-643.
[37] Bahn, R.S.,& Burch,H.B.(2015). Cooper DS. Hyperthyroidism and other causes of thyrotoxicosis: Management guidelines of the American thyroid association and American association of clinical Endocrinologists. Thyroid,25 (6),567-623.
[38] Amidon,G.L.,Lennernas,H.,Shah,V.P.,& Crison,J R.(1995). A Theoretical basis for a biopharmaceutical drug classification: The correlation of in Vitro Drug product dissolution and in vivo bioavailability. Pharmaceutical research,12 (3),413-420.
[39] United States pharmacopeia (USP) and National formulary (NF). (2022). General chapter <905> Uniformity of Dosage units.
[40] FDA.(2022). Guidance For industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms.
[41] Banker,G.S.,& Rhodes,C.T.(Eds.).(2017). Modern Pharmaceutics (5th ed.).CRS Press.