IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Advancements In Traditional And Novel Therapeutics For Thyroid Disorders: A Comprehensive Review Of Neuroendocrine Regulation And Drug Delivery Systems.

[1]MOHIT KUMAR CHAUHAN , [2]DR. ANSHUL SINGH

[1]RESEARCH SCHOLAR , [2]ASSISTANT PROFESSOR

[1]DEPARTMENT OF CHEMISTRY,

[1]BABA MASTNATH UNIVERSITY, ROHTAK, INDIA

Abstract: Thyroid disorders, encompassing hypothyroidism and hyperthyroidism, are critical global health challenges that significantly impact metabolic and systemic functions. This review decisively examines both established and innovative therapeutic strategies for managing these conditions, with a particular emphasis on treatments for hypothyroidism and hyperthyroidism. For hypothyroidism, levothyroxine tablets are the gold standard therapy, delivering reliable hormone replacement. Combination therapy using levothyroxine and liothyronine is an effective alternative for patients who continue to experience symptoms despite standard treatment. Furthermore, novel delivery methods, including soft gel and liquid formulations, as well as injectable and rectal preparations of levothyroxine, have been successfully developed to address specific patient needs, such as enhanced bio availability and absorption. Emerging therapeutic systems, such as implantable drug delivery technologies are poised to revolutionize treatment adherence and ensure precise hormone release. In the realm of hyperthyroidism management, traditional antithyroid drug therapies serve as the cornerstone of treatment. Rectal administration of these drugs provides a practical option for patients unable to tolerate oral medications. Additionally, injectable formulations offer vital flexibility in clinical management, particularly for acute cases. This paper deliberates the latest advancements in both standard and alternative therapies, firmly highlighting the evolving landscape of thyroid disorder management. It aims to inform clinicians and researchers about cutting-edge approaches to optimize patient care, effectively addressing gaps in current therapeutic practices for hypothyroidism and hyperthyroidism.

Index Terms - Hypothyroidism, Hyperthyroidism, Rectal administration, liothyronine and bio-availability

I. INTRODUCTION

The neuroendocrine and neurological systems are essential for controlling and sustaining homeostatic in the human organism. The neuroendocrine system maintains homeostasis by accurately secreting and delivering hormones to specific locations via the blood stream, whereas the neurological system enables swift transmission of information throughout various body organs via the brain, spinal cord, and nerves. The two systems consistently interact and influence one another, collaboratively functioning to preserve equilibrium[1-7]. Neuroendocrine hormones are crucial for controlling physiological activities and significantly influence several systems including metabolism, reproduction, electrolyte homeostasis, along with growth and development. Various glands throughout the body are essential for the synthesis and control of these hormones. The thyroid gland, situated in the front region of the neck, is essential for the synthesis, storage, in addition to secretion of thyroid hormones, namely triiodothyronine (T3) and thyroxine (T4). T3 is the active type of thyroid hormone, with a typical daily output of roughly 30 µg, whereas T4 is produced at about 100 µg. Both molecules possess biological activity; however, thyroid receptors demonstrate a tenfold greater affinity for T3 than for

T4. The daily synthesis of T3 by the thyroid gland is insufficient to fulfill the body's need. Consequently, approximately 80% of daily T3 is produced via the conversion of T4 to T3 via deiodination, facilitated by iodothyronine deiodinases. The principal difference between T3 and T4 is in the quantity of iodine atoms present[8-12]. Thyroid hormones are synthesized when the thyroid gland is activated by thyroid-stimulating hormone (TSH). In addition to their function in regulating metabolism and growth, thyroid hormones are crucial for supporting physical, mental, and cardiovascular health. Under typical circumstances, the synthesis of thyroid hormones is meticulously controlled by the hypothalamic-pituitary-thyroid (HPT) axis via a negative feedback mechanism[13-20]. When plasma concentrations of T4 and T3 are diminished, the hypothalamus secretes thyrotropin-releasing hormone (TRH). TRH upsurges the release of TSH from the pituitary gland, which induces the thyroid gland to generate T3 and T4. Elevated levels of T3 and T4 subsequently suppress TRH synthesis, reducing TSH production and effectively closing the feedback loop. The predominant thyroid problems are hyperthyroidism and hypothyroidism. Hyperthyroidism is defined by the overproduction and excessive secretion of thyroid hormones, whereas hypothyroidism is marked by inadequate hormone production. The incidence of these disorders varies between 2% and 6% of the population, highlighting their prominence. It is essential to ascertain that these illnesses and their therapies can significantly impact patients' long-term health[21-24]. This article offers a systematic examination of traditional therapy strategies and novel drug delivery innovations essential for the treatment of thyroid disorders, as evidenced by the literature.

1. HYPOTHYROIDISM

Hypothyroidism is a serious medical disorder marked by insufficient production of thyroid hormones, which undermines the body's everyday physiological requirements. Precise identification of this condition is crucial and can be accomplished using blood tests that assess T3, T4, and TSH concentrations. This disorder is categorized into three main types: primary hypothyroidism, originating from thyroid gland dysfunction; secondary hypothyroidism, resulting from inadequate TSH secretion by the pituitary; and tertiary hypothyroidism, caused by insufficient TSH secretion from the hypothalamus. In instances of primary hypothyroidism, T3 and T4 levels are diminished, although TSH levels, produced by the pituitary gland to stimulate thyroid function, are augmented. Conversely, secondary and tertiary hypothyroidism demonstrates diminished levels of T3, T4, and TSH[25-31]. Hypothyroidism is an extensively health problem prevailing all around the globe, impacting roughly 5% of the population, with an estimated extra 5% likely undiagnosed. Primary hypothyroidism comprises around 95% of cases, whilst secondary and tertiary forms represent the remaining occurrences. Individuals with hypothyroidism exhibit many symptoms such as fatigue, sensitivity to cold, depression, bradycardia, and constipation. These symptoms are sometimes erroneously ascribed to alternative medical diseases, leading to deferment in the diagnosis and treatment of the underlying hypothyroidism. Delays may result in significant problems including infertility, hypertension, neuromuscular dysfunction, dyslipidemia, and cognitive impairment[32-35]. The reasons of hypothyroidism are varied; still, iodine deficiency is the most prevalent, especially in impoverished nations. The reduction in T3 and T4 synthesis directly leads to an autoimmune condition termed “Hashimoto's thyroiditis,” which progressively deteriorates thyroid function and is proliferating worldwide. Hypothyroidism may result from a specific therapy, presenting a significant consideration for patients. Radioactive iodine therapy is an efficient non-surgical method that reduces or eliminates an overactive thyroid gland. Thyroidectomy, the surgical excision of a portion or the entirety of the thyroid gland, is an essential procedure for addressing disorders such as hyperthyroidism, thyroid malignancies, or goiter. Recognizing that both treatment alternatives may result in hypothyroidism underscores the necessity for vigilant monitoring and the possible need for subsequent hormone replacement therapy. The treatment options for hypothyroidism are currently restricted and require immediate attention. **Table 1** presents a summary of traditional pharmacological treatments for hyperthyroidism.

Table1: Anoverviewofexistingtechnologiesforthetreatmentofhypothyroidism

Formulation	Advantages	Disadvantages/Limitations
Levothyroxine Tablet	Long history of medical use. Simple and convenient for patients. Generally well tolerated.	Variable bioavailability. Reduced absorption (due to interactions with food and drugs). Patient non-compliance.
Levothyroxine andLiothyronine	Euthyroidism restoration in rats.	In patients, no clear advantage was observed over the standard treatment with LEVO alone.
Levothyroxine Soft Gel and Liquid	No food-drug interactions. Improved bioavailability and patient adherence.	Insufficient evidence due to limited number of studies.
Levothyroxine injections(IM and SC)	Enhanced patient compliance. Sustained drug release. Avoiding drug malabsorption.	Lack of data on long-term TSH variability. Limited data (case reports).
Rectal formulations	Simple and does not require any special equipment. For the treatment of patients in who moral administration is not possible. To improve bioavailability, T4 level scan be maintained in patients by administering suppositories at a dose 1.8 times higher than that of the tablet.	Limited data (6 patients). Lower bioavailability compared to oral route.

1.1.STANDARD MANAGEMENT OF HYPOTHYROIDISM

The conventional treatment for hypothyroidism is replacement therapy utilizing levothyroxine sodium (LEVO sodium), a synthetic analogue of the endogenous thyroid hormone T4. This medication efficiently normalizes TSH (thyroid-stimulating hormone) values. Although LEVO sodium is primarily delivered as an oral tablet, numerous other formulations have been investigated in scholarly literature and thoroughly evaluated in clinical trials[36-39]. The subsequent sections will present a thorough discussion of these different formulations. Additionally, Table 1 provides a concise overview of the standard formulas employed in the management of hypothyroidism.

1.1.1. LEVOTHYROXINETABLETS

The most efficacious treatment for hypothyroidism is the daily administration of LEVO sodium. This synthetic sodium salt of the levorotatory isomer of T4 possesses an identical chemical structure to the hormone endogenously synthesized by the body. LEVO sodium is offered in multiple strengths—25 μg, 50 μg, 75 μg, and 100 μg—facilitating accurate dosing customized to individual requirements. The initial dosage of LEVO sodium is determined by the patient's body weight and rounded to the nearest 25 μg. Patients must be meticulously monitored, with a review conducted three months post-treatment commencement to avert rebound hyperthyroidism resulting from enormously high dosages. Subsequent to this evaluation, the dosage of LEVO sodium is modified in accordance with test findings and the patient's clinical response. Although LEVO sodium tablets are the conventional mode of administration, it is important to acknowledge that this medication is also offered in liquid form and through injection. A soft gel capsule formulation has just received approval from both the European Medicines Agency and the American Food and Drug Administration, offering enhanced choices for patient adherence[41-44]. LEVO salt pills should be administered first thing in the morning empty stomach to guarantee adequate absorption in the small intestine. Consuming the medication with meals or specific drugs might markedly impede absorption, resulting in inadequate hormone levels. Foods and drugs that may pose complications include dietary fibre, caffeine, grapefruit juice, iron, calcium, and proton pump inhibitors. The bioavailability of LEVO sodium ranges from 60% to 80%, with a half-life of roughly 6 to 7 days. Patient non-compliance with oral LEVO sodium treatment is a considerable issue, frequently stemming from non-adherence to the drug schedule or neglect of specific administration directives from healthcare providers, leading to suboptimal therapeutic results. Studies have shown that supervised once-weekly oral thyroxine administration can significantly improve adherence among patients[45-47]. This method is both effective and innocuous, without any toxicity when compared to daily medication, considering the half-life of thyroxine. Consequently, weekly dosing represents a viable alternative that warrants serious consideration for those encountering compliance difficulties.

1.1.2. LEVOTHYROXINE AND LIOTHYRONINE

Recent studies have clearly presented the potential advantages of combining liothyronine and levothyroxine (LEVO) for individuals who are experiencing symptoms despite monotherapy with LEVO, even when their TSH levels are within the normal range. Escobar-Morreale conducted a thorough evaluation demonstrating that treatment with LEVO, either alone or in combination with liothyronine, can influence euthyroidism in both animal models and humans. In stringent animal tests, thyroidectomized rats were administered subcutaneous infusions of LEVO, synthetic T3 (liothyronine), or a combination thereof. The findings conclusively demonstrated that neither liothyronine nor LEVO alone could restore euthyroidism; however, the combination therapy of liothyronine and LEVO was successful in attaining this condition in rats. It is essential to acknowledge the significant biochemical disparities between human and rat models concerning the secretion, transport, and metabolism of thyroid hormones. In humans, thyroid-binding globulin (TBG) functions as the principal serum transport protein, while transthyretin fulfills this role in rats[48-51]. The disparities highlight that the mechanisms governing tissue thyroid hormone levels—whether via deiodination or other metabolic pathways—are particular to both tissue type and species.Moreover, the regulation of iodothyronine uptake and release in organs and tissues exhibits considerable variation. Contrary to expectations, the review's findings unequivocally demonstrated that, in humans, the combination therapy of LEVO and liothyronine did not confer any further advantage over normal treatment with LEVO alone. Until further conclusive studies are conducted, LEVO shall continue to be the primary treatment for hypothyroidism in people.

1.1.3. LEVOTHYROXINE IN SOFT GEL AND LIQUID FORMULATIONS

Since the mid-nineteenth century, levothyroxine (LEVO) has been the primary treatment for hypothyroidism and plays essential role in patient care these days. Their efficacy in sustaining appropriate T3 and T4 levels within a therapeutic range is well-documented; yet attaining ideal results may occasionally pose difficulties. The issues mostly arise from LEVO's pharmacokinetic characteristics and the multiple factors affecting its dosage.

To improve patient adherence, it is crucial to consider the unique daily dose schedule related to LEVO. Non-

compliance may result in inadequate serum concentrations, potentially causing severe side consequences from poorly treated hypothyroidism[52-57]. A significant 2021 review by Nagy Endre examined whether soft gel and liquid formulations including pre-dissolved thyroxine could provide enhanced bioavailability relative to conventional pills. Comprehending the distinctions among these formulations can be advantageous. Tablets necessitate disintegration and dissolution prior to absorption, whereas soft gel capsules liquefy before absorption, and liquid forms facilitate direct absorption. This observation indicates that patients may gain advantages from liquid or soft gel formulations, particularly when frequent dose modifications are necessary due to gastrointestinal variability. Moreover, for individuals who struggle to ingest tablets at least 30 minutes before to meals, liquid or soft gel formulations offer a more convenient alternative, as they do not interfere with food intake. The assertion that liquid and soft gel formulations improve bioavailability is encouraging; nevertheless, additional study is required to validate this due to the restricted scope of existing trials[58]. A substantial potential exists to investigate alternate drug delivery methods in the treatment of hypothyroidism to address the problems linked to the oral administration of LEVO. This research is to examine diverse studies that have explored alternative effective delivery techniques, thereby adding to the continuous enhancement of treatment procedures.

1.1.4. LEVOTHYROXINE INJECTIONS

An efficacious remedy for severe instances of non-compliance is the giving of weekly intramuscular injections of LEVO sodium. This approach has reliably demonstrated effectiveness in normalizing thyroid levels in hypothyroid patients, highlighting the usefulness of intramuscular injections for administering LEVO salt. Multiple studies affirm that IM injections are a strong alternative to address patient non-compliance. Moreover, the oral absorption of LEVO sodium is frequently inconsistent, leading to aberrant thyroid levels even in adherent patients. Consequently, LEVO injections emerge as the superior option for this cohort[59-61]. Groener validated this method by documenting successful results with once-weekly subcutaneous LEVO injections for patients unable to attain optimal thyroid levels after oral LEVO sodium therapy. This study distinctly underscores the deficiencies of oral administration while validating the merits of subcutaneous delivery.

1.1.5. RECTALFORMULATIONS

Rectal administration via suppositories offers a highly effective alternative to oral drug delivery, especially for individuals unable to ingest drugs orally, including the young and old. Kashiwagura conducted a study to systematically assess the clinical efficacy of LEVO suppositories in thyroidectomized rats. The findings demonstrated that the bioavailability of the LEVO suppository was inferior to that of oral LEVO, presumably attributable to the particular formulation employed. This suppository was designed to be prepared without specialized equipment, allowing for its use in hospitals or community pharmacies. The process entailed the fusion of a 1:1 blend of Witepsol H-15 and Witepsol E−75 with the pharmaceutical agent, yielding a final drug concentration of 75 μg per 1.35 g of suppository. To improve bioavailability, it is crucial to optimize the formulation and production techniques of these suppositories. Although rectal administration successfully circumvents first-pass metabolism, a considerable benefit in hypothyroidism treatment, it is essential to acknowledge that this route may not enhance patient adherence[62-66]. A considerable number of patients favor the ease of oral pills compared to rectal suppositories, and others may encounter difficulties with the insertion procedure.

1.2.ALTERNATIVE THE RAPEUTIC DELIVERY SYSTEMS FOR HYPOTHYROIDISM

1.2.1. Trans dermal drug delivery systems

The conventional topical drug delivery technique mainly aims for the localized effects instead of systemic absorption. A study by Azerbayjani examined the possibility of systemic effects by the topical administration of levothyroxine (LEVO) using smart polymeric nanofibers. The researchers utilized the electrospinning process to create a sustained topical administration system using blends of poly-N-isopropyl acrylamide (PNIPAM) and polyvinyl alcohol (PVA). **Table 2** provides a summary of transdermal drug delivery systems

employed for the administration of pharmaceuticals in the treatment of hypothyroidism. The research encompassed an examination of the interactions between the polymers and LEVO, succeeded by assessments of the permeation of LEVO sodium from the polymeric nanofibers utilizing confocal microscopy and excised human skin. Despite the polymeric nanofibers effectively maintaining and extending the penetration of LEVO, the amount that pierced the skin was inadequate to produce a systemic effect *in vivo*. Transdermal drug delivery devices are considered efficient and are frequently utilized for medication administration. These systems bypass the first-pass metabolism linked to oral administration, therefore improving bioavailability and reducing pharmacological interactions. Furthermore, these devices can prolong the release profile of pharmaceuticals, thus enhancing patient compliance. The transdermal delivery method may provide considerable benefits in the management of hypothyroidism by reducing difficulties typically associated with oral administration of LEVO. Subsequent research by Padula examined the transdermal delivery of LEVO sodium by evaluating its physicochemical properties and *in vitro* penetration. Multiple formulations incorporating cyclodextrins or organic solvents as solubilizing agents were examined, using Somatoline as a reference formulation. The epidermis of a rabbit's ear was utilized as a model for *in vitro* permeation investigations due to its relative resemblance to human skin in passive settings. The results demonstrated that transdermal delivery of LEVO shows potential for localized therapeutic effects; however, systemic drug delivery produced suboptimal outcomes, as the permeated concentration was considerably below the therapeutic threshold necessary for effective drug levels[67-69]. Microneedle (MN) arrays are a minimally invasive approach that can circumvent the stratum corneum barrier, hence improving the effectiveness of transdermal medication administration. In this context, Ghazi and Al-Mayahy created LEVO-loaded hyaluronic acid (HA) dissolving microneedles for transdermal delivery. The HA-based MN arrays exhibited exceptional insertion efficacy in both Parafilm M and human skin models when a force of 32 N per array was applied. *In vitro* experiments have shown that 96–98% of the administered LEVO was progressively released over a 60-minute period. The scientists noted that the MN array commenced disintegration roughly 5 minutes after implantation and attained total dissolution within 60 minutes. Furthermore, the *ex vivo* permeation investigation demonstrated that the utilization of the MN array markedly improved the transdermal administration of LEVO in comparison to control samples, which included an aqueous drug solution and a polymeric needle-free film.

Table2:An overview of novel technologies for the treatment of hypothyroidism

Formulation	Advantages	Disadvantages/Limitations
Trans dermal drug delivery systems	Sustained and prolonged penetration of LEVO Avoiding the first-pass effect. Improving bioavailability and reducing interactions. Improving patient adherence.	The amount of LEVO that penetrated the skin was insufficient to cause a systemic effect *in vivo* (topical formulations). Enhanced trans dermal delivery of LEVO using micro needles was only demonstrated *ex vivo.*
Osmotic pumps or subcutaneously implanted pellets	Prolonged drug release. Bypassing first pass metabolism. Increased patient compliance. Continuous release of T3 in rodents over a predefined period.	*In vitro* and *in vivo* data only. No clinical (human) studies have been completed yet.
Subcutaneous poly (caprolactone) implants	Prolonged drug release. Bypassing first pass metabolism. Increased patient compliance.	

	Sustained LEVO release over atleast 100 days.	
ProNeura®	Prolonged drug release. Bypassing first pass metabolism. Increased patient compliance. Continuous T3 release in beagle dogs and thyroidectomised rats over 6 months.	
LEVO-loaded porous silicon membrane	Prolonged drug release. Bypassing first pass metabolism. Increased patient compliance. Sustained drug release for 14 days.	
Subcutaneous implant containing a nanochannel membrane	Linear release profile for more than 15 days.	
Injectable formulations	Prolonged drug release. Bypassing first pass metabolism. Increased patient compliance. *In situ*-forming gel (PLGA-PEG-PLGA) with a minimum burst release.	

1.2.2. IMPLANTABLE DRUG DELIVERY SYSTEMS

Implantable drug delivery systems are exceptionally efficient in facilitating prolonged medication release within the body. These devices can be engineered in diverse shapes, materials, and pharmaceutical combinations for purposes like contraception and the management of chronic conditions. They have manifold benefits in contrast to the oral administration methods, such as extended release, evasion of first-pass metabolism, and enhanced patient adherence. Research indicates that pellet systems and osmotic pumps can administer T3 in accurately controlled dosages when subcutaneously implanted in mice for the treatment of hypothyroidism. The ALZET osmotic micro pump functions by pulling water into its reservoir, so providing a steady drug release. Innovative Research of America's pellet technology has a biodegradable matrix for sustained T3 release, as confirmed by animal experiments[70-72]. Moreover, biodegradable implants composed of poly(caprolactone) have exhibited prolonged release of LEVO for more than 100 days, with release rates affected by the polymer's composition. Pharmaceutical companies are improving T3 administration techniques. Titan Pharmaceuticals' ProNeura®, a solid rod composed of ethylene-vinyl acetate and T3, has demonstrated successful release over a six-month period in both canines and thyroidectomized rats. Kashanian have created an LEVO-loaded porous silicon membrane that achieves 87% drug release within two weeks. Geninatti developed an advanced subcutaneous implant featuring a nanochannel membrane for prolonged hormone release, exhibiting linear release for more than 15 days *in vitro*. Although these advancements are encouraging, additional study is necessary to validate the safety and effectiveness of these implantable technologies.

1.2.3. INJECTABLE PREPARATIONS

The subcutaneous administration of levothyroxine (LEVO) offers an effective method for the prompt delivery of accurate dosages because to its quick absorption properties. When administered as an aqueous solution, LEVO's half-life is roughly 2 hours. This approach is appropriate for emergencies, but it may not be optimal for routine dosage, as it requires multiple injections to withstand sufficient therapeutic T3 levels. Researchers have investigated *in situ*-forming gels and depot-forming injectable formulations to enhance the treatment of hypothyroidism. These novel formulations may improve patient outcomes by decreasing the absorption rate of LEVO and prolonging its half-life. Kamali conducted a study examining the application of the triblock copolymer PLGA-PEG-PLGA in the development of *in situ*-forming gels (ISFG) designed to reduce the first burst release of LEVO. The researchers significantly mitigated the issue of burst release by selecting PLGA-PEG-PLGA instead of conventional PLGA. The hydrogen bonding between N-methyl-pyridone (NMP) and PEG molecules evidently restricted the rapid diffusion of NMP, resulting in a more regulated release profile. The thermosensitive characteristics of PLGA-PEG-PLGA were crucial in reducing the first burst.A notable benefit of this triblock formulation is that it does not necessitate surgical implantation; it remains liquid at ambient temperature and transforms into a gel upon injection. NMP functions as a solvent because of the instability of PLGA-PEG-PLGA in aqueous environments[73,74]. The thermosensitive response initiates this shift, facilitating efficient gel formation. Various weight ratios of the triblock were assessed to further diminish burst release, demonstrating that the use of PLGA-PEG-PLGA resulted in decreased initial LEVO release; while preserving the biocompatibility and biodegradability of both the copolymer and the solvent over a 21-day delivery period. Despite LEVO's longstanding role as a primary treatment for hypothyroidism, attaining optimal therapeutic results is hindered by issues including inconsistent bioavailability, malabsorption, food-drug interactions, and patient non-compliance. Preliminary tactics have been formulated to improve drug absorption and promote patient compliance through many formats, including liquid solutions, soft gel capsules, injections, and rectal formulations. Nevertheless, stronger clinical evidence is required to substantiate their efficacy. Moreover, researchers have achieved significant progress in transdermal and implanted delivery devices intended for prolonged drug release, which have been evaluated both *in vitro* and *in vivo*. These encouraging results suggest substantial promise for enhanced patient outcomes; however, it is crucial to acknowledge that human clinical trials remain essential for further assessment of these strategies[75]. Ongoing exploration and innovation in medication delivery systems have significant potential for improving hypothyroidism treatment and promoting patient compliance.

2. HYPERTHYROIDISM

Hyperthyroidism is a significant ailment marked by the overproduction and release of thyroid hormones, with Graves' disease as the most common illness. This autoimmune condition induces excessive thyroid hormone production and leads to thyroid gland enlargement, profoundly affecting the body's general health. Additional sources to hyperthyroidism encompass toxic multinodular goiter and single toxic adenoma. The impact of surplus thyroid hormones is significant, affecting several organs and systems. Patients often experience concerning symptoms, including tachycardia, involuntary weight loss, and tremors in the extremities. Additionally, individuals may encounter troubling physical symptoms such as heart palpitations, sleep disruptions, heat intolerance, frequent urination, heightened bowel movements, nausea or vomiting, dyspnea, and excessive perspiration[76-79]. If hyperthyroidism is left untreated, the repercussions might be severe. Severe cardiovascular complications, such as atrial fibrillation, embolic stroke, and congestive heart failure, represent a substantial risk, especially for individuals over 60, who face an elevated danger. Consequently, patients suffering with hyperthyroidism encounter an increased risk of early mortality.

Additionally, hyperthyroidism may result in thyrotoxic periodic paralysis, characterized by muscle paralysis caused by elevated intracellular potassium levels. Furthermore, elevated amounts of thyroid hormones can result in osteoporosis and adversely affect the reproductive health of both genders. Males may develop gynecomastia, whereas females frequently encounter irregular menstrual cycles and reduced fecundity. Tackling hyperthyroidism is essential for protecting overall health and wellness.

2.1. STANDARD MANAGEMENT OF HYPERTHYROIDISM

Standard treatment modalities for hyperthyroidism encompass anti-thyroid medications (ATDs), radioactive iodine therapy, and thyroidectomy. Thyroidectomy is the most established and favoured treatment for Graves' illness. It is essential to acknowledge that individuals who have undergone a complete thyroidectomy will necessitate levothyroxine (LEVO) therapy. The previously mentioned LEVO drug delivery systems are exceptionally effective for individuals who have undergone total thyroidectomy[80,81]. Moreover, radioactive iodine therapy (RIT) serves as a potent alternative for the treatment of hyperthyroidism. This technique entails the precise ablation of the thyroid gland utilizing radioactive iodine (^{131}I) at dosages ranging from 150 to 200 microcuries per gram, provided over a period of up to 18 weeks. The ^{131}I is administered orally, in either pill or liquid form, resulting in a notable thyroid uptake rate of roughly 60% in patients. Radioactive iodine therapy is contraindicated for those who are pregnant, lactating, or intending to conceive[82]. This study will concentrate on the diverse drug delivery methods for the treatment of thyroid disorders, excluding surgical interventions and radiation ablation of the thyroid gland. **Table 3** provides a detailed summary of the standard pharmacological approaches for the treatment of hyperthyroidism.

Table3 :An overview of existing technologies for the treatment of hyperthyroidism.

Formulation	Advantages	Disadvantages/Limitations
Oral methimazole	High oral bioavailability (ca. 93%). Prolonged duration of action. Can be administered once-daily. Less ever side effects.	Risk of first trimester methimazole-induced embryo pathy.
Oral propylthiouracil	Generally used during the first trimester of pregnancy.	Lower oral bioavailability (ca. 80%) compared to methimazole. Requires higher doses compared to methimazole. Administered three times a day.
Oral carbimazole	Prodrug of methimazole. Oral bioavailability of ca. 90%.	Requires higher doses compared to methimazole.
Rectal formulations	Similar pharmacokinetic parametersto oral administration of methimazole and propylthiouracil. Highly effective to control serious cases of thyrotoxicosis and thyroid storm. For the treatment of patients who are unable to take the drug orally.	Insufficient evidence due to limited data and number of case studies.

Injectable formulations	Alternative parenteral route of administration (intravenous) of methimazole in certain rare cases.	Limited data (case reports).

2.1.1. ORAL ADMINISTRATION OF ANTI THYROID DRUGS

Anti thyroid medications (ATDs) are frequently employed in the management of hyperthyroidism and comprise thiamazole (methimazole), propylthiouracil, and carbimazole. These drugs are sent to the thyroid, where they impede iodide organification, oxidation, and the creation of hormones T4 and T3. Thiamazole, the chosen treatment for Graves' illness, possesses an oral bioavailability of 93% and a longer half-life compared to propylthiouracil, facilitating once-daily administration. Propylthiouracil exhibits a bioavailability of around 80%, whereas carbimazole is metabolized into thiamazole post-administration. Treatment modalities encompass titration, which modifies the ATD dosage progressively to sustain normal thyroid function, and the "block and replace" strategy, which employs elevated ATD doses in conjunction with levothyroxine. Although both techniques are efficacious, titration exhibits fewer adverse effects and is typically favoured. The initial dosage of thiamazole is contingent upon the severity of the condition: 10–15 mg daily for moderate instances and 20–40 mg for severe cases[83-87]. Carbimazole necessitates doses of 140% of thiamazole, whereas propylthiouracil is administered in doses ranging from 50 to 150 mg three times daily. Thyroid function is evaluated 4–6 weeks post-treatment initiation and then every 2–3 months. Upon achieving normal function, patients sustain a daily dosage of 5–10 mg of thiamazole for duration of up to 18 months. A significant drawback of ATD therapy is the elevated return rate of hyperthyroidism upon discontinuation of the medication[88,89].

2.1.2. RECTALADMINISTRATIONOFANTITHYROIDDRUGS

The rectal administration of methimazole with propylthiouracil has demonstrated efficacy as a feasible alternative to the oral route, akin to LEVO. Nabil effectively developed methimazole suppositories containing 60 mg of the medication by integrating it with Span 80 and cocoa butter. The pharmacokinetic parameters recorded for these suppositories were comparable to those associated with oral administration, so confirming the rectal route as an efficacious strategy for delivering antithyroid medications (ATDs). Moreover, propylthiouracil can be effectively administered rectally. Bartle demonstrated that glycerol ester-based suppositories (Whitepsol H-15) containing propylthiouracil attain T3 serum levels comparable to those achieved with oral treatment, notwithstanding the reduced bioavailability of rectal propylthiouracil[90-93]. Furthermore, the administration of propylthiouracil is not limited to suppositories; enemas have also demonstrated efficacy. Evidence suggests that propylthiouracil enemas distinctly decline T4 levels. Suppositories and enemas are especially beneficial in managing severe thyrotoxicosis and thyroid storm—critical disorders caused by excessive thyroid hormone release—in patients who cannot take medication orally due to gastric ulcers or stool blockages.

2.1.3. INJECTABLE VERSIONS OF ANTI-THYROID MEDICATIONS

Intravenous formulations are an essential alternative for controlling hyperthyroidism, particularly when patients encounter circumstances that inhibit oral or rectal medicine administration. These conditions encompass bowel obstruction, acute vomiting, diarrhea, or the requirement for urgent gastrointestinal surgery[94,95]. In these cases, intravenous methimazole diluted in 0.9% sodium chloride should be employed for efficient treatment.

CONCLUSIONS

At now, LEVO and ATDs are the preferred therapies for hypothyroidism and hyperthyroidism, respectively. These medications are taken orally via injection and rectally. However, maximizing the efficacy of these medications can be difficult due to their pharmacokinetic characteristics and patient adherence.Alternative drug delivery methods presently under investigation exhibit potential as innovative therapies for thyroid disorders. It is anticipated that these treatments would subsequently address issues related to traditional therapies. Alternative medicines emphasize non-oral drug delivery methods to circumvent challenges associated with bioavailability and gastrointestinal side effects. Furthermore, several of these alternatives include methods to enhance patient adherence to medication, an essential component of thyroid illness that generally necessitates long-term management. Improving therapeutic efficacy while minimizing adverse effects and enhancing patient adherence is crucial in the novel medicines being investigated for both hypothyroidism and hyperthyroidism. Nevertheless, prior to the approval of any alternative methods for clinical application, various issues must be resolved. In several instances, these drug delivery methods have solely undergone testing on animals, requiring more clinical studies. Furthermore, certain proposed drug delivery systems necessitate further development to resolve challenges such as scale-up manufacturing and regulatory issues, as they constitute wholly novel dosage forms. Researchers are actively addressing these difficulties to ensure the availability of novel therapy options for individuals with thyroid disease.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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