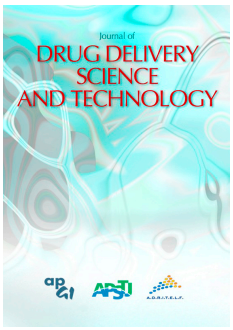

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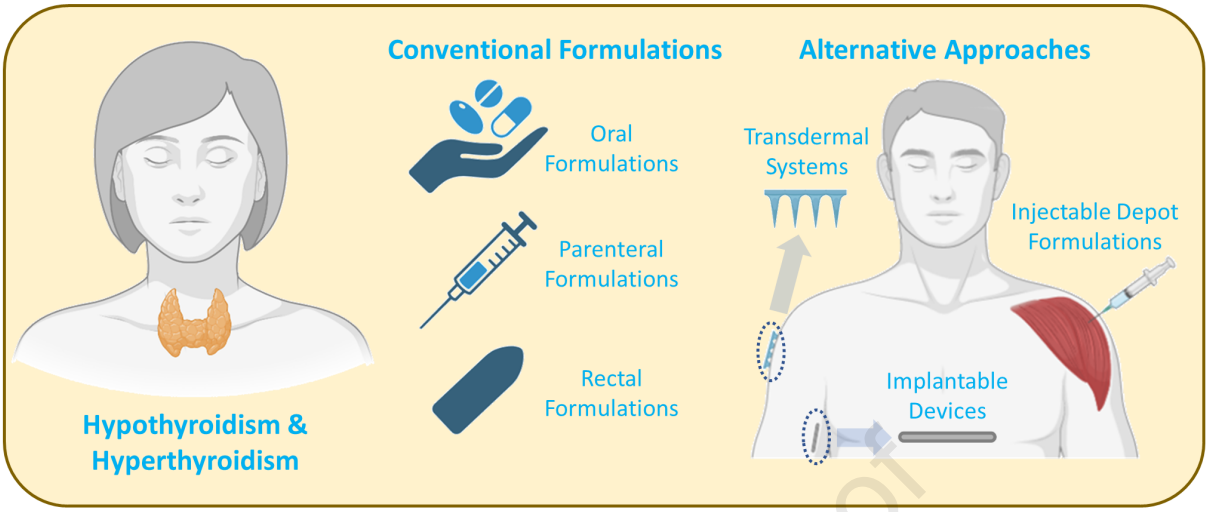

Drug delivery systems for thyroid disease treatment: a mini review on current therapies and alternative approaches.

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Abstract

Thyroid hormones play an important role in many metabolic processes in the human body. However, these processes can often be disrupted by an over or underactivity of the thyroid gland which, if undiagnosed or untreated, can result in serious illness. Currently, therapeutic management of an underactive thyroid gland (hypothyroidism) is typically achieved via replacement therapy with levothyroxine (LEVO), a synthetic form of thyroxine. Conversely, anti-thyroid drugs (ATDs), radioactive iodine or thyroidectomy are established approaches in treating hyperthyroidism. With respect to the route of the administration, drugs to treat hypo and hyperthyroidism can typically be administered through oral (PO) , intravenous (IV), and rectal (PR) routes. Despite the fact that thyroid disorders have been successfully treated for many years, several problems still exist in the conventional treatment approach. Due to issues such as poor patient compliance and concordance, poor gastrointestinal (GI) absorption when taken incorrectly, and interactions with food and other medications, the administration of these drugs often results in sub-optimal dosing with accompanying serious illness if not corrected. Other forms of drug delivery are currently being studied to overcome the dosing complications that frequently occur with LEVO and ATDs with a view to increasing both patient compliance and bioavailability of the drugs in question. This review will examine why there remains a need for novel approaches and discuss studies that have been carried out with regards to this.

1. Introduction

The neuroendocrine and nervous systems play a significant role in regulating and maintaining homeostasis in the human body. The neuroendocrine system facilitates homeostasis by means of secretion and transport of hormones to target sites via the bloodstream, whereas the nervous system allows rapid neuronal communication of information between different regions of the body via the brain, spinal cord and nerves. Both systems are in constant interaction and influence each other with the overall aim of maintaining homeostasis. Neuroendocrine hormones are critical in regulating bodily functions. They have effects on diverse systems such as metabolism, reproduction, electrolyte balance and growth and development [1]. A wide variety of glands distributed throughout the body play a key role in the production and regulation of these hormones (see Figure 1A).

In humans, the thyroid gland is located in the frontal section of the neck [2] and is responsible for the synthesis, storage and release of thyroid hormones [triiodothyronine (T_3) and thyroxine (T_4)] [3] and iodine [4], with T_3 being the active form of thyroid hormone [5]. In normal circumstances the estimated daily production of T_3 and T_4 is estimated to be 30 µg and 100 µg respectively [6]. Both compounds are active, but thyroid receptors typically have a higher affinity for T_3 (approx. 10-fold higher) versus T_4 [4]. Significantly, studies have shown that daily production of T_3 by the thyroid gland is insufficient to meet daily requirements. Therefore, around 80% of daily T_3 comes from the conversion of T_4 into T_3 via-deiodination catalysed by iodothyronine deiodinases [7,8] (Figure 1B), the main difference between T_3 and T_4 being the number of iodine groups.

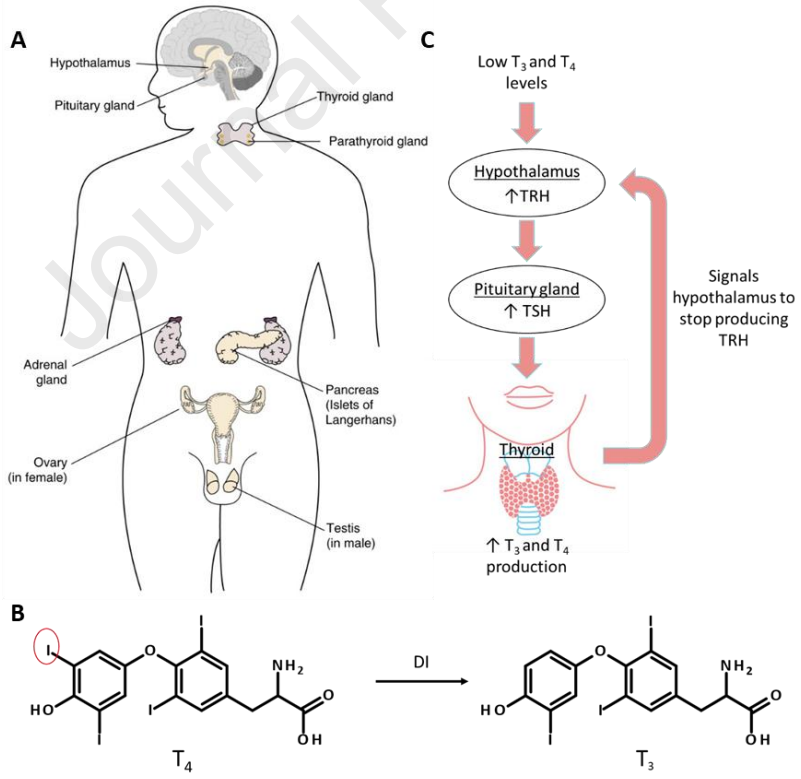

Figure 1. Representation of the endocrine organs in the body, including both male and female organs (A). Reproduced with permission from: [1]. Conversion reaction of T_4 to T_3 catalysed by deiodinase (DI) enzymes in cells (B). Schematic diagram of the HPT feedback loop (C).

Thyroid hormones are produced by the activation of the thyroid gland by thyroid stimulating hormone (TSH) [9]. In addition to their role in regulation of metabolism and growth development {4, 10} thyroid hormones are also essential in maintaining physical, mental and cardiovascular health [10]. Under normal conditions, thyroid hormone production is controlled by the hypothalamic-pituitary-thyroid (HPT) axis via a negative feedback loop [4]. In this loop, the release of thyrotropin-releasing hormone (TRH) from the hypothalamus is stimulated by low plasma levels of T_4 and T_3. Subsequently, the release of TRH stimulates the release of thyroid-stimulating hormone (TSH) from the pituitary which in turn stimulates the thyroid gland to generate T_3 and T_4. Conversely, high levels of T_3 and T_4 feedback and decrease the production of TRH. A low levels of TRH in turn inhibits the production of TSH, completing the feedback loop [11]. The feedback loop can be seen in Figure 1C.

The most common types of thyroid disorders are hyperthyroidism and hypothyroidism. The former is characterised by an excess in thyroid hormone production and secretion while the later is characterised by an insufficient thyroid hormone production. The prevalence of these conditions range between 2 and 6% of population [12]. It is important to note that these conditions and their treatment may have significant chronia health implications for patients. This review provides an overview of conventional therapeutic approaches together with new developments in the field of drug delivery with the aim of successfully treating thyroid conditions described in the literature.

2. Hypothyroidism

Hypothyroidism is a condition characterised by insufficient thyroid hormone production in relation to daily bodily requirements. This condition can be divided into two major categories: primary hypothyroidism and secondary hypothyroidism (NICE, 2019). When diagnosing the patient, T_3, T_4 and TSH levels in the blood are tested.

In primary hypothyroidism (a disorder mainly of the thyroid gland), T_3 and T_4 levels are low while levels of TSH (produced by the pituitary gland to stimulate the thyroid gland) are high. In secondary hypothyroidism which occurs due to inadequate secretion of TSH by the pituitary gland, and tertiary hypothyroidism, which results from inadequate secretion of TRH from the hypothalamus, the levels of T_3, T_4 and TSH are low [10,14]. Worldwide, hypothyroidism is one of the most common diseases with approximately 5% of people diagnosed and a further 5% of the population estimated to been undiagnosed [6,15,16]. Primary hypothyroidism accounts for 95% of cases of hypothyroidism with secondary and tertiary accounting for the remaining 5% of cases [17].

Symptoms such as fatigue, sensitivity to the cold, depression, reduced heart rate and constipation are among the symptoms that can occur with an inadequate amount of T_3 and T_4 in the body. Such symptoms are commonly attributed to other medical conditions, resulting in delayed treatment of the underlying hypothyroidism. This delay can then lead to more severe consequences such as infertility, hypertension, neuromuscular dysfunction, dyslipidaemia and cognitive impairment [18,19]. Hypothyroidism can be attributed to many causes but is most commonly due to deficiency of iodine in the body [6]. This frequently occurs in underdeveloped countries, where iodine intake is low, whereas in developed countries, Hashimoto's thyroiditis is the most common cause of hypothyroidism [6]. Hashimoto's thyroiditis is an autoimmune disorder which over time results in reduced thyroid function and a resultant decrease in production of T_3 and T_4 [20]. Additionally, hypothyroidism can arise from treatments involving radioactive iodine or a thyroidectomy. A thyroidectomy is the surgical removal of part or all of the thyroid gland [21] and is carried out to treat conditions like hyperthyroidism, thyroid cancer and goitres [21]. As an alternative to surgery, radioactive iodine

treatment works by shrinking or completely destroying a typically overactive thyroid gland [22]. Both procedures can result in hypothyroidism, necessitating the need for hormone replacement therapy. The number of treatment options available for patients with hypothyroidism is limited. Table 1 summarises conventional pharmacological approaches for the treatment of hyperthyroidism.

2.1 Conventional Treatment of Hypothyroidism

Conventional treatment for hypothyroidism is based on replacement therapy with levothyroxine sodium (LEVO sodium), a synthetic version of the natural thyroid hormone T_4. This in turn returns TSH concentrations to normal levels [23]. This is normally administered as an oral tablet, however, alternative LEVO sodium formulations have been described in the literature and tested in clinical trials. The following sections will describe these formulations. Table 1 summarises conventional formulations used for treatment of hypothyroidism

2.1.1. Levothyroxine Tablets

The most common treatment for hypothyroidism is by daily intake of LEVO sodium. It is a synthetic sodium salt of the levo isomer of T_4, with identical chemical structure to the endogenous hormone [24]. It is available in various strengths including 25 µg, 50 µg, 75 µg and 100 µg. The starting dose for LEVO sodium is based on the patient's body weight and rounded to the nearest 25 µg [4,13]. Patients are closely monitored with a review occurring three months after initiation of treatment in order to prevent rebound hyperthyroidism that can arise from too high a LEVO sodium dose. The dose of LEVO sodium thereafter depends on the patient's laboratory results and clinical response [13,24]. LEVO sodium is most commonly administered in the form of a tablet, but can also be administered in liquid form or via injection. More recently, a soft gel capsule formulation was approved by the European Medicines Agency and the American Food and Drug Administration [16]. LEVO sodium tablets are taken first thing in the morning, ideally on an empty stomach as it is absorbed in the small intestine [25]. The absorption of LEVO sodium may be reduced if taken with food and other certain medications, leading to a subtherapeutic dose and sub-optimal hormone levels. Problematic foods and medications include dietary fibre, coffee, grapefruit juice, iron, calcium, and proton pump inhibitors [4]. The bioavailability of LEVO sodium can vary from 60% to 80% and its half-life is 6-7 days [10,24].

Patient non-compliance with oral LEVO sodium treatment has been extensively reported [26]. This can be attributed to patients either not adhering to their medication regimen or not following the specific administration instructions provided by healthcare professionals, leading to sub-optimal therapeutic outcome. Numerous studies have studied the effect of supervised once-weekly oral thyroxine dosing in patients that were thought to be non-compliant [26–28], taking into consideration that the half-life of thyroxine is about seven days. This approach was found to be effective and safe as no signs of toxicity were observed when compared with daily therapy [26–28]. Therefore, weekly dosing could be a potential alternative for patients with compliance issues.

2.1.2. Levothyroxine and Liothyronine

Recent studies have investigated the potential of combining liothyronine and LEVO for patients who experience ongoing symptoms when taking LEVO alone, even when TSH levels are reported as normal [29]. A review by Escobar-Morreale. H. et al. evaluated whether LEVO sodium therapy alone or in

combination with liothyronine resulted in euthyroidism in both animal models and humans [30]. In animal models, subcutaneous infusions of LEVO or synthetic T_3 (liothyronine) or combination of liothyronine plus LEVO were given to thyroidectomised rats. Neither liothyronine nor LEVO alone restored euthyroidism whereas a combination therapy of liothyronine plus LEVO was effective in restoring euthyroidism in the rats. Obviously, with regards to secretion, transport and metabolism of thyroid hormone, there is considerable biochemical difference between human and rat models. In humans, the principal serum transport protein is thyroid binding globulin (TBG), whereas in rats, the principal thyroid hormone-binding protein is transthyretin. This suggests that mechanisms involved in the regulation of tissue thyroid hormone concentrations by deiodination and non-deiodination pathways of T_3 and T_4 metabolism may be both tissue and species specific. Other factors such as the regulation of uptake and subsequent exit of iodothyronines into and out of organs and tissues may be affected by this also. Results from this review found that in humans the combined therapy of LEVO plus liothyronine treatment did not appear to be more effective than the standard treatment of LEVO alone. Until further studies are carried out, LEVO will likely remain the drug of choice in the treatment of hypothyroidism in humans [13,30].

2.1.3. Levothyroxine Soft Gel and Liquid

Since the mid-nineteenth century, LEVO has been the drug of choice for hypothyroidism and remains so to this day [4]. Whilst it has undoubtedly been successful in maintaining optimal levels of T_3 and T_4 within a therapeutic range, its optimal use can be challenging. Principally, this is due to its pharmacokinetic profile and factors that influence its optimal dosing [4]. Patient compliance may be reduced when taking LEVO due to its specific daily dosing regimen which in turn can lead to a subtherapeutic serum concentration resulting in potentially serious adverse effects associated with sub-optimally treated hypothyroidism. A 2021 review was carried out by Nagy. Endre V. et al. with the aim of establishing if soft gel and liquid formulations, containing pre-dissolved thyroxine, provide greater bioavailability over conventional tablets [16]. Significantly, the main difference between tablet, soft gel and liquid formulations is the physiochemical processes that occur before absorption in the GI tract. Tablet formulations undergo disintegration and dissolution before absorption, whilst soft gel capsules undergo melting before absorption and liquid formulations simply undergo absorption. Patients may indeed benefit from the liquid or soft gel capsule formulations if they require frequent dose adjustments of their tablet formulation due to fluctuations that can occur with GI disorders. Patients who find it difficult taking the tablet formulation at least 30 minutes before food in the morning may also benefit from the liquid or the soft gel formulation as these formulations do not interact with food [31,32]. These liquid and soft-gel formulations have been claimed to improve bioavailability, but, to date, there is insufficient evidence to demonstrate this conclusively due to the small scale of the studies involved [16]. Undoubtedly there is a need for additional routes of delivery in the treatment of hypothyroidism in order to overcome the complications that can arise when taking LEVO orally. This paper will review some of the studies that have been undertaken to determine other routes of drug delivery.

2.1.4. Levothyroxine injections

A potential solution for extreme cases of non-compliance is the administration of weekly injections of LEVO sodium intramuscularly (IM). This approach has proven to be successful in restoring thyroid levels in hypothyroid patients [33], highlighting the potential of IM injections in the delivery of LEVO

sodium. This approach has been reported to be successful in a wide range of studies suggesting that IM injections may be a promising alternative to address patient non-compliance [34,35]. As mentioned previously, LEVO sodium oral absorption can be erratic leading to abnormal thyroid levels even in compliant patients. LEVO injections could be a suitable approach for this group of patients. Groener et al. also reported the use of once-weekly subcutaneous LEVO injections administered to patients with a history of difficulty achieving desired thyroid levels following oral LEVO sodium treatment [36]. This study emphasized the challenges associated with oral administration of LEVO sodium while highlights the benefits of subcutaneous administration.

2.1.5. Rectal formulations

Rectal administration using suppositories has been a successful alternative to oral delivery for many drugs in patients who are unable to take medicines orally, especially the young and elderly. Kashiwagura *et al.* carried out a study to evaluate the clinical efficacy of LEVO suppository in thyroidectomized rats [37]. The bioavailability of LEVO suppository was lower when compared to oral LEVO and this could be related to the formulation of the suppository. The suppository prepared in this study did not need any special equipment and therefore it can theoretically be prepared in a hospital or community pharmacy. This formulation was prepared by melting the excipients (a 1:1 mixture of Witepsol H-15 and Witepsol E-75) with the drug, giving a final drug content of 75 µg per 1.35 g of suppository. To increase bioavailability further development is needed to optimise the formulation and preparation of the suppositories. Whilst rectal administration avoids first pass metabolism, which can be beneficial in the treatment of hypothyroidism, it may not necessarily increase patient compliance due to the nature of the delivery. For some patients, they may be opposed to inserting a suppository rectally over taking a tablet orally and some may find it difficult to insert the suppository [37].

2.2. Alternative drug delivery systems for hypothyroidism

2.2.1. Transdermal drug delivery systems

Table 2 summarises transdermal drug delivery systems used for the delivery of drugs used in the treatment of hypothyroidism. Whilst topical drug delivery is normally aimed at delivering a drug to a specific area rather than systemically, a study was carried out by Azarbayjani *et al.* to investigate whether the topical delivery of LEVO through smart polymeric nanofibers can result in systemic effects [38]. Using the electrospinning technique to develop a sustained topical delivery of LEVO, nanofibrous membranes were electropsun into blends of poly-N-isopropylacrylamide (PNIPAM) and poly vinyl alcohol (PVA) (Figure 2A-B). After analysing the interactions between the polymers and drug, the permeation of LEVO sodium from the polymeric nanofibers was studied by confocal microscopy and excised human skin. While the polymeric nanofibers were able to sustain and prolong the penetration of LEVO, the amount of LEVO that penetrated the skin would not be sufficient enough to cause a systemic effect *in vivo* [38].

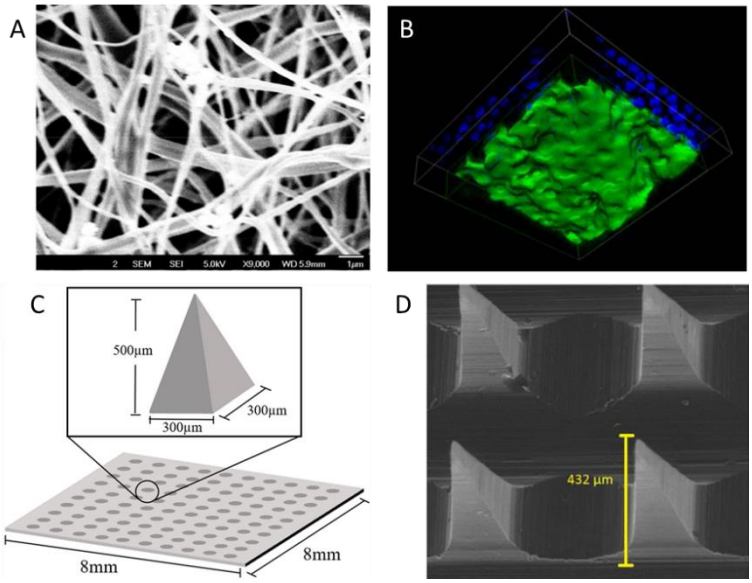

Figure 2. Field Emission Scanning Electron Microscopy (FESEM) image of the polyvinyl alcohol (PVA)/poly-N-isopropylacrylamide (PNIPAM) nanofiber-based mat containing 2 mg/mL of levothyroxine (T_4) (A). Picture of the epidermis and localization of green fluorescence contained in the polymeric nanofibers. Binary image of the skin after the flow through diffusion studies. Staining of cell nuclei with DAPI is shown as blue signal (B). Reproduced with permission from [38]. Design and dimensions (C) and SEM image of the microneedle (MN) array (D). Reproduced with permission from [39,40].

Transdermal drug delivery systems have been recognised as successful and are widely used in the delivery of medicines. They avoid the first-pass effect of metabolism that is associated with the oral route, therefore improving bioavailability, and reducing interactions. They can also prolong the release of medicines which can improve patient adherence. The transdermal route of delivery could also be beneficial in the treatment of hypothyroidism as it overcomes the recognised complications associated with taking LEVO orally [41]. A study was carried out by Padula *et al.* to evaluate the transdermal administration of LEVO sodium by investigating the characteristics and *in vitro* permeation of the drug [42]. Various solutions containing cyclodextrins or organic solvents as solubilizing agents were examined, using Somatoline® as a reference formulation. As a barrier for the *in vitro* permeation of LEVO, the skin of a rabbit's ear was used due to its similarity to human skin in passive conditions. In this study, it was concluded that the transdermal administration of LEVO shows promise for achieving a localised effect. However, for systemic drug delivery, it showed less promising results as the permeated amount was significantly lower than the required dose for reaching therapeutic drug levels [42].

Microneedle (MN) arrays represent a minimally invasive approach that can be used to bypass the *stratum corneum* barrier and thus improve transdermal drug delivery efficacy [43–45]. Accordingly, Ghazi and Al-Mayahy manufactured LEVO-loaded hyaluronic acid (HA) dissolving MNs for transdermal delivery [40] (Figure 2C-D) [40]. The HA-based MN arrays developed in this study showed an outstanding insertion ability in both models, Parafilm M® and human skin, after applying a force of 32 N per array. *In vitro* LEVO release studies showed that 96% to 98% of loaded drug was gradually released after 60 minutes. The authors also demonstrated that the MN array started to dissolve after 5 minutes of the insertion, and it was completely dissolved at 60 minutes. Moreover, the *ex vivo* permeation study revealed that the use of the MN array enhanced the transdermal delivery of LEVO compared to control samples, an aqueous drug solution and a polymeric needle-free film.

2.2.2. Implantable drug delivery systems

Implantable drug delivery have demonstrated significant success in the sustained and prolonged delivery of drugs in the body [46–49]. These devices can be prepared using a wide variety of shapes, geometries, materials and drugs for various applications such as contraception and the treatment of a range of chronic conditions [49–56]. Advantages of implants over oral drug delivery include the prolonged release of drug, bypassing first pass metabolism and increased patient compliance [46,48,57]. This type of drug delivery systems has also been used for the delivery of drugs in the treatment of hypothyroidism (Table 2). A study by Bianco *et al.* showed that the use of pellet systems or osmotic pumps that are subcutaneously implanted in rodents are an excellent way for T_3 to be released at fixed amounts for a predefined number of days [58]. The operation of the ALZET® osmotic mini pump is due to the difference in osmotic pressure between the subcutaneous area and where the pump is implanted (Figure 3A) [58]. Due to higher osmolality of the pump influx, water builds up in the reservoir which causes T_3 to be displaced at a known rate into the subcutaneous area. The pellet system by the Innovative Research of America contains a biodegradable matrix allowing for continuous release of T_3 in animals over a predefined period. The osmotic pump and the pellet system have been shown to exhibit stable amounts of T_3 in rodents that have no thyroid gland [5,58]. Similarly, subcutaneous biodegradable implants, made of poly(caprolactone), for sustained LEVO release have been developed [59–61] (Figure 3B-C). These implants were capable of providing *in vitro* sustained LEVO release over at least 100 days [59], during which the drug release was influenced by the composition of the polymeric matrix. A combination of poly(caprolactone) polymers with two different molecular weights yielded a linear release profile over 100 days. This formulation was tested in rat models and LEVO plasma levels were detected for at least 28 days after implantation. Modifying the formulation or size of the implants had a direct influence on the release profile [61]. Other pharmaceutical companies have developed technology that could provide a stable release of T_3 to patients for treating hypothyroidism. ProNeura®, which is a solid rod consisting of ethylene-vinyl acetate and T_3, was developed by Titan Pharmaceutics to deliver T_3 subcutaneously. This preliminary study demonstrated that T_3 was continuously released in intact beagle dogs and thyroidectomized rats over 6 months. When implanted, it also showed a short-term serum peak of T_3 followed by stable circulating levels of T_3 [5]. ProNeura® is undergoing preclinical trials at present.

Following with the subcutaneous route, Kashanian *et al.* developed a LEVO-loaded (through hydrogen bonding) porous silicon membrane with a height of ~2 µm (Figure 3D) [62]. *In vitro* drug release results revealed that 87% of the total amount of loaded drug (21 µg) was released during the first two weeks, showing a first-order release profile. Moreover, the authors suggested that the membrane size required to reach the therapeutic dose is viable for further consideration as an implantable drug delivery system. Another subcutaneous implant containing a nanochannel membrane for the sustained release of different hormones, including LEVO was design and developed by Geninatti *et al.* [39,63]. Figures 3E and 3F show an illustration of the nanochannel membrane and the abovementioned subcutaneous implant with the membrane. The drug reservoir of the implant was loaded with 900 µL of a LEVO solution (20 mg/mL) and the *in vitro* release revealed a linear release profile for more than 15 days. Although the author presented valuable and promising findings, further concerns such as the properties of the dissolution media and the size of the implant should be considered. Moreover, moving forward, preclinical studies using suitable animal models are needed to confirm the safety and efficacy of these implants.

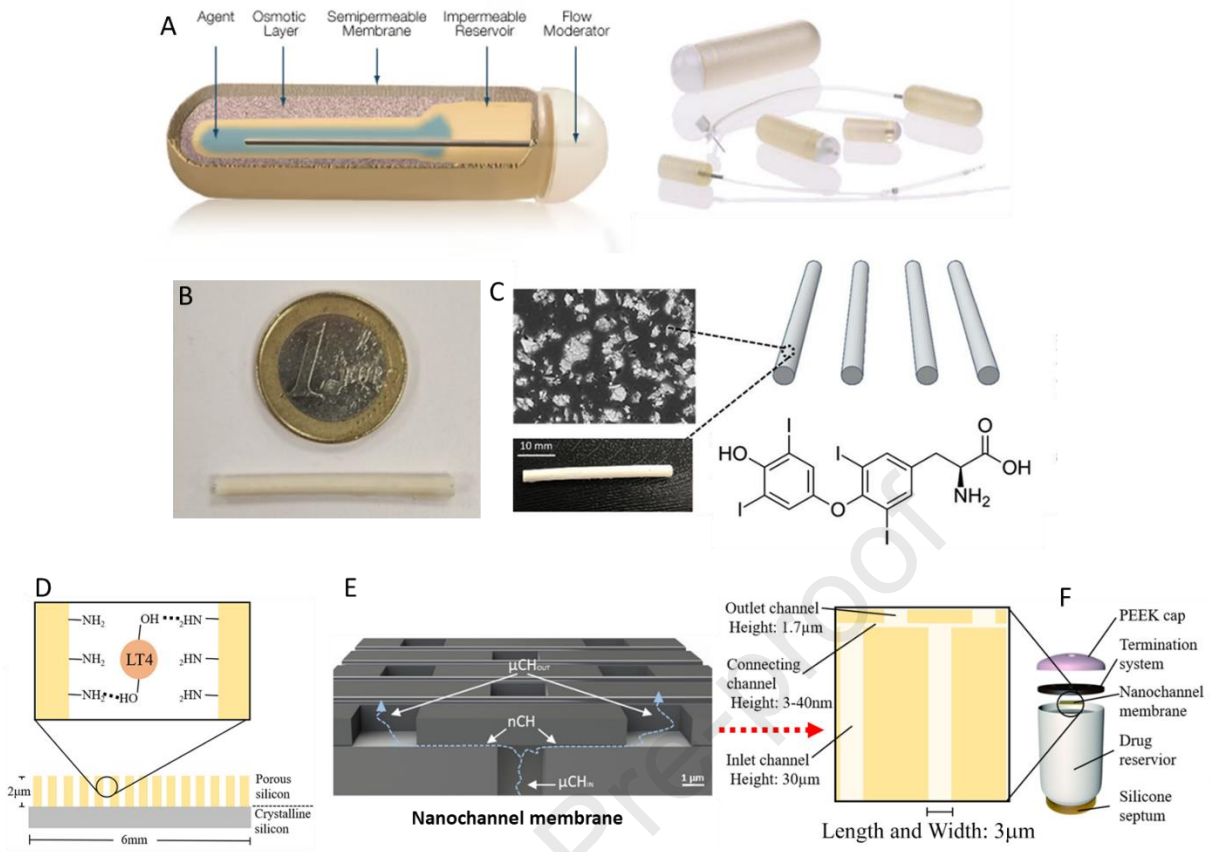

Figure 3. Diagram showing the ALZET® osmotic pump design and different pump sizes. Reproduced with permission from ALZET® Osmotic Pumps (A). Picture of the poly(caprolactone)-based implant next to a 1€ coin (B). SEM image of the implant showing that LEVO was homogenously dispersed throughout all the formulation; and an illustration and a digital image (scale bar of 10 mm) of the rod-shaped implants with dimensions of 2.5 mm × 40 mm prepared using solvent moulding. The chemical structure of LEVO is also represented (C). Reproduced with permission of [59,60]. An illustration of the porous silicon membrane, where the LEVO molecules are bonded through hydrogen bonding (D). Reproduced with permission from [39]. A representation of the cross section of the nanochannel membrane (E) and an illustration of all the components of the subcutaneous implant including the nanochannel membrane (F). The nanochannel membrane are 6 mm × 6 mm wide and 730 µm in height, while the size of the implant is around 2.5 cm in length. Reproduced with permission from [39,63].

2.2.3. Injectable formulations

Subcutaneous delivery of LEVO has shown to be a reliable way of rapidly delivering exact amounts of LEVO due to its fast absorption. However, using an aqueous solution, the half-life of the drug is approximately only 2 hours [5]. This route would therefore only be suitable if a patient needed emergency treatment but would not be suitable for daily dosing due to the need for repetitive injections to maintain therapeutic T_3 levels. *In situ* forming gels or depot forming injectable formulations have been extensively described in the literature to address this limitation [64–68]. The use of these types of formulation for LEVO delivery could improve hypothyroidism treatment as they could potentially reduce the absorption rate of LEVO in the body and increase half-life in patients with hypothyroidism [5]. A study was carried out by Kamali *et al.* to evaluate the use of a triblock copolymer

called PLGA-PEG-PLGA to prepare in-situ forming gels (ISFG) for minimizing burst release of LEVO [10] (Figures 4A and 4B). PLGA-PEG-PLGA was used instead of PLGA to prevent the initial burst release that occurs with other ISIGs. Rapid diffusion of N-methyl-pyridone (NMP) was prevented by the hydrogen bonding between NMP and PEG molecules. Another way that the initial burst release could be decreased was due to the thermosensitive properties of PLGA-PEG-PLGA. There was no need for a surgical placement of this triblock formulation as it was liquid at room temperature and when injected into the body it converted into a gel. As this triblock was not stable in water, NMP was used to dissolve it. When injected, thermosensitive response of the triblock and phase inversion occurs resulting in formation of the gel. To avoid a burst release, different weight ratios of the triblock were investigated. The use of PLGA-PEG-PLGA instead of PLGA prevented rapid diffusion of NMP into the release medium and showed a lower initial release of LEVO. It also showed that the solvent NMP and copolymer are biocompatible, biodegradable and able to deliver the drug for 21 days [10].

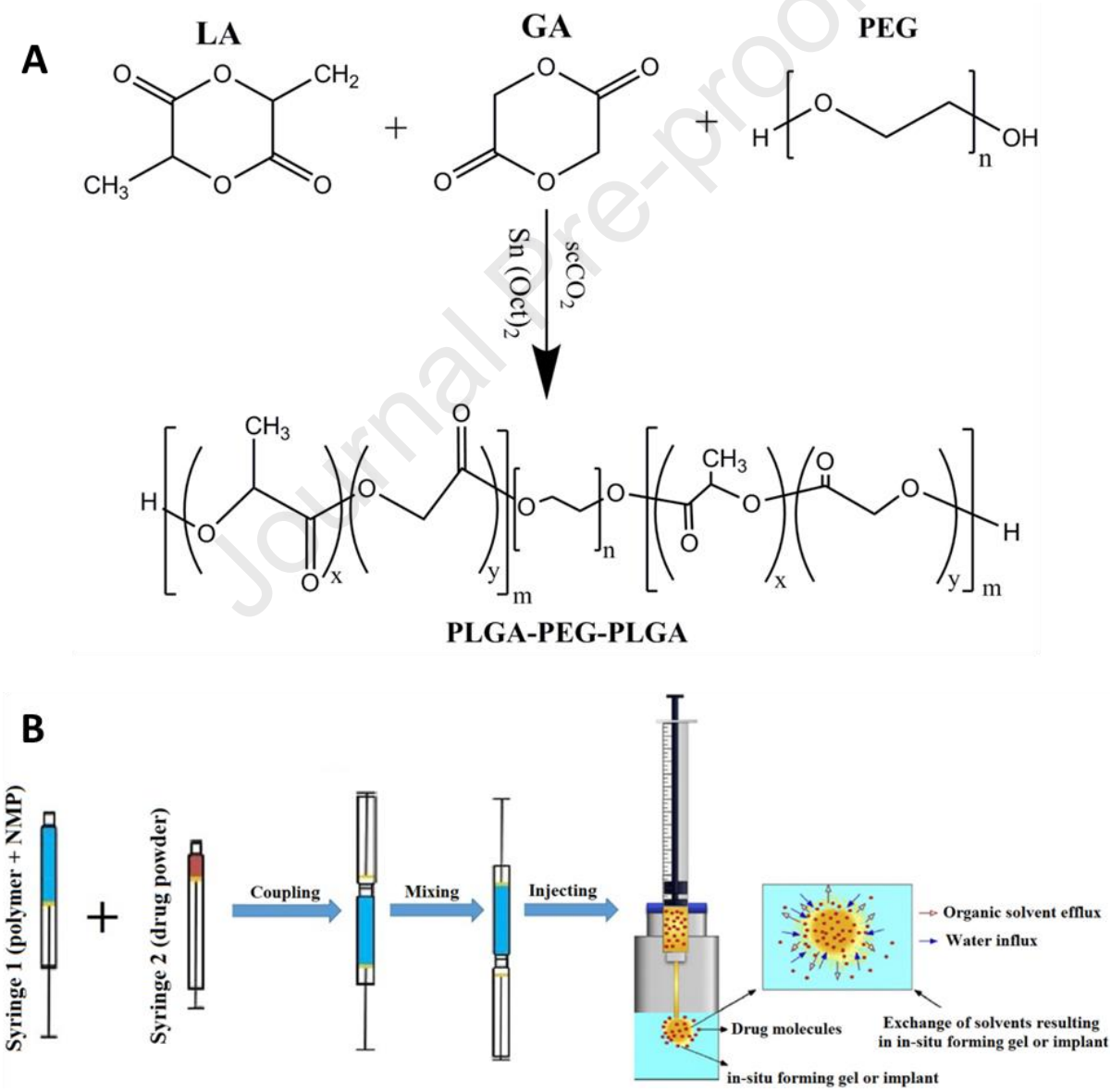

Figure 4. Ring-Opening Polymerization of PLGA-PEG-PLGA was catalysed by stannous octoate (Sn $(Oct)_2$) using supercritical carbon dioxide ($SCCO_2$) (A). Preparation of *in-situ* forming gel (ISFG) or implant (ISFI) using two coupled syringes (B). Reproduced with permission from [69].

Despite being the mainstay of hypothyroid treatment for many years, the desired therapeutic outcome of LEVO can be impaired by several factors such as variable bioavailability, malabsorption, food-drug interactions and patient non-compliance.

To address these issues, initial attempts have been made to improve drug bioavailability and patient adherence by developing liquid solutions, soft gel capsules, injections and rectal formulations. However, robust clinical evidence is yet to show their efficacy. Alternatively, transdermal and implantable delivery systems for sustained drug release have been developed and tested both *in vitro* and *in vivo*. Although these studies demonatrate significant potential with meaningful outcome, it is noteworthy that no clinical (human) studies have been conducted thus far (Table 2).

Table 1. An overview of existing technologies for the treatment of hypothyroidism.

Formulation	Advantages	Disadvantages/Limitations	References
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.	[26–28]
Levothyroxine and Liothyronine	• Euthyroidism restoration in rats.	• In patients, no clear advantage was observed over the standard treatment with LEVO alone.	[29,30]
Levothyroxine Soft Gel and Liquid	• No food-drug interactions. • Improved bioavailability and patient adherence.	• Insufficient evidence due to limited number of studies. • Lack of data on long-term TSH variability.	[16,31,32]
Levothyroxine injections (IM and SC)	• Enhanced patient compliance. • Sustained drug release. • Avoiding drug malabsorption.	• Limited data (case reports).	[34–36]
Rectal formulations	• Simple and does not require any special equipment. • For the treatment of patients in whom oral administration is not possible. • To improve bioavailability, T_4 levels can be maintained in patients by administering suppositories at a dose	• Limited data (6 patients). • Lower bioavailability compared to oral route.	[37]

	1.8 times higher than that of the tablet.		

Table 2. An overview of novel technologies for the treatment of hypothyroidism.

Formulation	Advantages	Disadvantages/Limitations	References
Transdermal 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 transdermal delivery of LEVO using microneedles was only demonstrated *ex vivo*.	[38,40,42]
Osmotic pumps or subcutaneously implanted pellets	• Prolonged drug release. • Bypassing first pass metabolism. • Increased patient compliance. • Continuous release of T_3 in rodents over a predefined period.	*In vitro* and *in vivo* data only. No clinical (human) studies have been completed yet.	[5,58]
Subcutaneous poly(caprolactone) implants	• Prolonged drug release. • Bypassing first pass metabolism. • Increased patient compliance.Sustained LEVO release over at least 100 days.		[59–61]
ProNeura®	• Prolonged drug release. • Bypassing first pass metabolism. • Increased patient compliance. • Continuous T_3 release in beagle dogs and thyroidectomized rats over 6 months.		[5]
LEVO-loaded porous silicon membrane	• Prolonged drug release. • Bypassing first pass metabolism. • Increased patient compliance. • Sustained drug release for 14 days.		[62]

Subcutaneous implant containing a nanochannel membrane	• Linear release profile for more than 15 days.		[63]
Injectable formulations	• Prolonged drug release. • Bypassing first pass metabolism. • Increased patient compliance. • *In situ*-forming gel (PLGA-PEG-PLGA) with a minimum burst release.		[10]

3. Hyperthyroidism

Hyperthyroidism is disease characterised by an excessive production and secretion of thyroid hormones [70]. Grave's disease is the most common cause of hyperthyroidism and is due to an autoimmune response that leads to an overproduction of thyroid hormone and glandular hyperplasia [71]. In addition to Grave's disease, toxic multinodular goitre and solidary toxic adenoma can cause hyperthyroidism [70]. The production of an excess of thyroid hormone has a direct influence on many organs. Patients with hyperthyroidism often experience symptoms such as tachycardia, weight loss and tremors of the extremities [70]. In addition to these symptoms, patients often experience other physical manifestation of hyperthyroidism such as palpitations, altered sleep, heat intolerance problems, polydipsia, hyperdefecation, nausea/vomiting, shortness of breath and increased perspiration [70].

Untreated hyperthyroidism can lead to serious cardiovascular complications including atrial fibrillation, embolic stroke and congestive heart failure [70,72,73], with patients above 60 years of age having a higher risk of experiencing these complications [70,72]. As a result of these complications, it has been reported that patients suffering from hyperthyroidism present a higher risk of all-cause mortality [74]. In addition to cardiovascular complications, hyperthyroidism can lead to thyrotoxic periodic paralysis [75], a condition characterised by an increase of intracellular potassium sequestration [75] leading to muscular paralysis, thyrotoxicosis and acute hypokalaemia [70]. Additionally, high levels of thyroid hormones can lead to osteoporosis [76] and abnormalities within the reproductive system for male (gynaecomastia) and female patients (menstruation irregularities and reduced fertility) [77,78].

3.1 Conventional Treatment of Hyperthyroidism

Conventional therapeutic modalities for hyperthyroidism include the use of anti-thyroid drugs (ATDs), radioactive iodine or thyroidectomy. The later is the oldest approach and the preferred form of treatment for Grave's disease [79]. It is important to note that patients undergoing a total thyroidectomy will require LEVO treatment [80]. Therefore, LEVO drug delivery systems described in previous sections can be applied to patients with complete thyroid gland resection. Alternatively, radioactive iodine therapy (RIT) is another form of treatment for hyperthyroidism. This therapeutic approach consists of ablation of the thyroid gland using ^{131}I at doses ranging between 150 and 200 mcCi/g over periods of up to 18 weeks [79]. ^{131}I is administered as sodium iodide orally as a capsule or liquid [81]. The thyroid uptake of ^{131}I in patients treated with capsules or liquids is around 60% [82]. This therapeutic option is not recommended for patients that are pregnant, breastfeeding or planning

to be pregnant [70]. This review is focused on the different drug delivery approaches for thyroid disease treatment. The surgical alternatives or radioactive ablation of the thyroid gland will not be discussed in the following sections. Table 3 summarises conventional pharmacological approaches for the treatment of hyperthyroidism.

3.1.1. Oral administration of anti-thyroid drugs

ATDs have been extensively used for hyperthyroidism treatment. This family of drugs include thiamazole (also known as methimazole), propylthiouracil and carbimazole [70]. ATDs are actively transported into the thyroid to inhibit the organification and oxidation of iodide, as well as the synthesis of T_4 and T_3 [83]. Normally, thiamazole (with an oral bioavailability of 93%) is the preferred drug to treat Graves' disease [70] as this compound shows a better efficacy and a prolonged duration/half-life when compared to propylthiouracil [70][84]. Therefore, thiamazole can be administered once-daily instead of, like propylthiouracil, multiple doses per day. Moreover, propylthiouracil shows lower oral bioavailability (ca. 80%) [85]. In addition, thiamazole displays less severe side effects. A further compound, carbimazole (oral bioavailability ca. 90%) [86] is activated by conversion into thiamazole [70].

There are two approaches to treat hyperthyroidism using ATDs: titration or "block and replace". The former requires adjustment of the ATD dose over time to achieve and maintain normal thyroid gland function [87]. On the other hand, the "block and replace" approach requires higher doses of ATDs in combination with LEVO [70]. Both approaches have been demonstrated to be effective in treating hyperthyroidism. However, the "block and replace" strategy has been associated with a higher incidence of side effects compared to the titration method [88]. Therefore, titration strategy is the preferrred [89].

The initial dosage of thiamazole varies depending on the size of the thyroid gland and the severity of the condition. Patients with a mild form of the disease and/or smaller thyroid glands typically receive daily doses of 10-15 mg of thiamazole [70]. On the other hand, patients suffering from severe forms of the disease or presenting with large thyroid glands require 20-40 mg of the drug per day [70]. Carbimazole requires higher doses, approximately 140% of the thiamazole dose [70] while propylthiouracil requires between 50 and 150 mg, administered three times per day. After the start of the treatment, thyroid function is tested after 4-6 weeks, and then monitored every 2-3 months until normal thyroid function is attained [89]. Upon achieving normal thyroid function, patients receive a maintenance daily dose of 5-10 mg of thiamazole for up to 18 months [90] or longer [91]. The equivalent doses for propylthiouracil are 50 mg two or even three times per day [70]. One of the main limitations of ATD-based treatment is high hyperthyroidism relapse rates after discontinuation of treatment [70].

3.1.2. Rectal administration of anti-thyroid drugs

Similarly to LEVO, rectal delivery of methimazole and propylthiouracil has also been evaluated [92–94]. Nabil et al. prepared methimazole suppositories containing 60 mg of the drug by mixing it with Span 80 and cocoa butter. The pharmacokinetic parameters observed for the suppositories were similar to those obtained with oral administration [94]. These findings suggested that the rectal route may be an effective route of administration for ATDs. In addition, the rectal route can also be used for propylthiouracil. Bartle et al. demonstrated that suppositories prepared using glycerol esters

(Whitepsol® H-15) and loaded with propylthiouracil could induce similar T_3 serum levels to oral drug administration [93]. These results are somewhat intriguing considering that rectal propylthiouracil showed lower bioavailability when compared to oral [93]. Rectal administration of propylthiouracil is not limited to suppositories and enemas have also been successfully used [95,96]. This method reported reduced T_4 levels after the administration of a propylthiouracil enema [95]. Suppositories and enemas have also been shown to be highly effective in controlling serious cases of thyrotoxicosis and thyroid storm (life threatening conditions produced by an excessive release of thyroid hormones) in patients with gastric ulcers or bowel obstruction who are unable to take the drug orally [96,97].

3.1.3. Anti-thyroid drug injectable formulations

Intravenous formulations provide a further alternative for the management of hyperthyroidism, especially when patients with hyperthyroidism have certain conditions that prohibit the administration of drugs orally or rectally [98]. These conditions include bowel obstruction, severe vomiting and diarrhea or the need to perform emergency gastrointestinal surgery [98]. Patients such as these can be treated with intravenous methimazole dissolved in 0.9% sodium chloride.

2.2. Alternative drug delivery systems for hyperthyroidism

2.2.1. Transdermal delivery of anti-thyroid drugs

Transdermal delivery of ATDs has been extensively studied for veterinary applications [99]. However, the application of ATD-based transdermal drug delivery systems has not yet been investigated for human use. Table 4 summarises transdermal delivery approaches for ATD.

The first approach explored the use of gels and organogels for ATD administration through the skin as alternative to oral delivery [100]. For this purpose, Pluronic F-127-based gel and Pluronic Lecitin organogel for the delivery of methimazole were investigated. This work demonstrated that the prepared gels were stable over periods of up to 3 months. Pluronic formulations showed higher methimazole permeation during *in vitro* Franz cells permeation studies than organogels containing lecithin (ca. 100% vs 77% of the initial drug content) [100]. However, none of these formulations were tested *in vivo* so more work is needed to ascertain the clinical efficacy of these transdermal formulations.

An alternative to oleogels is the development of a methimazole prodrug to improve transdermal drug delivery of this compound [101]. For this purpose, an esterification reaction was used to transform methimazole into the 2-sulfonyl-1- methylimidazole prodrug [101] (Figure 5). To achieve this, the drug was attached to long chain fatty alcohol (hydrophobic carrier) using propiolic acid (Figure 5). This compound displayed enhanced permeability through the skin (37-times faster than parent drug) [101], due to its higher lipophilicity. Dai et al. also demonstrated that the drug undergoes hydrolysis after permeation, resulting in the release of the parent drug and this process can be stimulated by the presence of glutathione [101]. The safety of the methimazole prodrug was evaluated in a rat skin model, showing that the application of this compound for 7 days did not alter the skin structure. Despite these promising results, the study did not present any pharmacokinetic data in animal models. Therefore, more work is required to ascertain the efficacy of this promising prodrug *in vivo*.

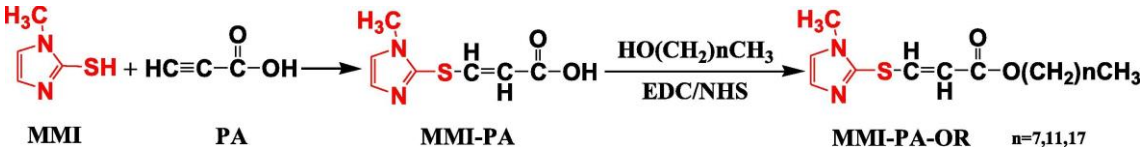

Figure 5. Diagram showing the synthesis route of amphipathic GSH responsive 2-sulfonyl -1-methylimidazole prodrug (MMI-PA-OR). MMI means methimazole and PA means propiolic acid. On the other hand, EDC means N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and NHS means N-Hydroxysuccinimide. Reproduced with permission from [101].

2.2.2. Oral and buccal drug delivery systems

As previously discussed, conventional ATD-based treatment is typically by means of oral tablets. This route of administration is usually convenient for the patient and ATDs demonstrate high oral bioavailability values. However, oral administration of some of ATD is nontheless challenging. Propylthiouracil is the best example of this as it requires multiple daily doses and rapid release/absorption of this drug is associated with hepatotoxicity [70,102]. Therefore, the development of sustained release formulations for propylthiouracil could be highly beneficial for patients. Xiao et al. developed co-crystals of propylthiouracil with nutritional conformers (gentistic acid, cinnamic acid, kaempferol and ellagic acid) [102]. The co-crystal systems were formed by hydrogen bonding interactions between the conformers and the drug [102]. These novel crystalline forms showed slower release rates than pure propylthiouracil, decreasing the overall solubility of the drug by up to 77% in simulated gastric conditions, and up to 85% under simulated intestinal conditions [102]. Moreover, the resulting co-crystals showed excellent stability over 3 months under accelerated storage conditions (75% RH and 40°C) [102]. These results suggest that the crystals can slow down the release/dissolution of propylthiouracil while yielding stable crystalline systems. Further work is required to study the incorporation of these co-crystals into solid oral dosage forms and to evaluate their performance in an *in vivo* model.

Buccal drug delivery is a further alternative to oral drug delivery. This route can be used for systemic drug delivery, avoiding drug instability in the GI tract and associated first-pass metabolism [103]. Considering these advantages, De Caro et al. developed buccal tablets for methimazole delivery [104]. This was a novel study as the permeability of methimazole across buccal mucosa had not previously been determined. Therefore, the first step of this study was to evaluate permeability using an *in vitro* Franz cell setup using porcine buccal mucosa and obtaining linear permeation profiles over periods up to 5.5 hours [104]. The results suggested that in order to achieve sustained drug release, methimazole should be incorporated into a suitable drug delivery system. Eudragit® RS100 was combined with methimazole to prepare mucoadhesive tablets and the *in vitro* drug release was subsequently evaluated. The resulting formulation did not exhibit a sustained drug release profile and after 2 hours, the entire drug cargo had been released [104]. Subsequently, glycerol tristearate was used as a hydrophobic coating to control drug release [104]. Two coating thicknesses (0.05 and 0.1 mm) were successfully prepared achieving a significant drug release reduction. Thinner coatings (0.05 mm) yielded around 20% of the initial drug cargo after 4 hours while the thicker coating (0.1 mm) provided a release of between 5 and 10% of the initial drug cargo after 4 hours. Methimazole permeation across excised porcine buccal mucosa from coated tablets was measured and the results followed the same trend observed in the drug release experiments.

At present, the antithyroid thionamide drugs, methimazole, propylthiouracil and carbimazole, are the cornerstones in the treatment of hyperthyroidism. Methimazole shows higher oral bioavailability,

longer half-life and better efficiency than propylthiouracil [105]. The later requires higher doses and normally administered two or three times a day. Therefore, propylthiouracil is used only when methimazole is not appropriate, such as pregnant and lactating women [106,107]. On the other hand, carbimazole is a prodrug and is converted to methimazole after administration. It has been demonstrated that after administration carbimazole experiences a quick enzymatic process producing methimazole. Methimazole plasma levels are lower when carbimazole is administered than after the administration of equal amounts of methimazole (10 mg of carbimazole equates to 6-7 mg of methimazole) [108]. Carbimazole is preferred in some patients due to lower gastrointestinal tract side effects [109]. Rectal and injectable formulations were developed as alternatives to oral delivery in certain conditions showing promising findings but require further clinical evaluation. Moreover, buccal delivery of methimazole was investigated to explore its potential for systemic administration and oral sustained-release system via co-crystallization of propylthiouracil with nutraceuticals was developed. Other transdermal formulations were also investigated as substitutes for oral formulations of methimazole. However, these interesting administration routes were not evaluated in vivo or in the clinical practice (Table 4).

Table 3. An overview of existing technologies for the treatment of hyperthyroidism.

Formulation	Advantages	Disadvantages/Limitations	References
Oral methimazole	• High oral bioavailability (ca. 93%). • Prolonged duration of action. • Can be administered once-daily. • Less severe side effects.	• Risk of first trimester methimazole-induced embryopathy.	[70,84]
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.	[70,85]
Oral carbimazole	• Prodrug of methimazole. • Oral bioavailability of ca. 90%.	• Requires higher doses compared to methimazole.	[70]
Rectal formulations	• Similar pharmacokinetic parameters to oral administration of methimazole and propylthiouracil. • Highly effective to control serious cases of thyrotoxicosis and thyroid storm.	• Insufficient evidence due to limited data and number of case studies.	[92–97]

	• For the treatment of patients who are unable to take the drug orally.		
Injectable formulations	• Alternative parenteral route of administration (intravenous) of methimazole in certain rare cases.	• Limited data (case reports).	[98]

Table 4. An overview of novel technologies for the treatment of hyperthyroidism.

Formulation	Advantages	Disadvantages/Limitations	References
Transdermal drug delivery systems	• Gels and organogels of methimazole showed high drug permeation through the skin using *in vitro* Franz cells. • Methimazole prodrug displayed enhanced skin permeability compared to parent drug.	• No *in vivo* or clinical studies have been completed yet.	[100,101]
Oral and buccal drug delivery systems	• Co-crystals of propylthiouracil with nutritional conformers exhibited sustained drug release and excellent stability over 3 months. • Coated buccal tablets for systemic methimazole delivery showed controlled release profile.		[102,104]

5. Conclusions

Currently, LEVO and ATDs remain the treatments of choice for hypothyroidism and hyperthyroidism, respectively. Clinically, these drugs are administered orally, via injection, and rectally. Nevertheless, achieving optimal use of these agents can be challenging due to their pharmacokinetic profiles and patient compliance. Other drug delivery routes currently under study show promise as novel therapeutic treatments for thyroid disease. It is hoped that these treatments will, in turn, help overcome complications associated with conventional therapies. Alternative therapies focus on non-oral drug delivery strategies to avoid issues related to bioavailability and gastrointestinal tract-related

side effects. Moreover, some of these alternatives offer mechanisms to improve patients' adherence to treatment, a critical aspect for thyroid disease, which typically requires long-term management. Enhancing therapeutic outcomes while reducing side effects and improving patient compliance is essential in the new treatments being studied for both hypothyroidism and hyperthyroidism. However, before any of these alternative methods can be approved for clinical use, several points need to be addressed. In some cases, these drug delivery systems have only been tested on animals, necessitating further clinical trials. Additionally, some of the proposed drug delivery systems will require more development to address issues like scale-up manufacturing or regulatory concerns, as they represent entirely new dosage forms. Researchers are currently working to resolve these issues, ensuring that new therapeutic alternatives are available for patients suffering from thyroid disease.

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7. Conflict of interest

No potential conflict of interest was reported by the author(s).

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Declaration of interests

☒ 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 paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: