Development of silicone polymer-based medical patches containing an analgesic active ingredient

PhD thesis

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2023

1. Introduction, objectives

My work is a joint project of the Institute of Pharmacology and Pharmacotherapy of the University of Pécs, Faculty of Medicine and the Department of Inorganic and Analytical Chemistry of the Budapest University of Technology and Economics. This project combined the long history of both institutions in the medical use of silicones and the development of analgesic drugs.

Researchers at the Institute of Pharmacology and Pharmacotherapy of the University of Pécs have been studying the mechanisms of pain and inflammation for decades, in particular the role of capsaicin-sensitive nerve endings and their ion channels. Pain management is a high priority and transdermal therapy systems (TTS) offer a modern solution for the delivery of active ingredients through the skin.

At the BME Department of Inorganic and Analytical Chemistry, research on silicones has been ongoing since the 1950s. These materials have many applications, especially in the medical field, where they are used to make implants and transdermal patches. The department has many decades of expertise in the development of silicone polymer-based products.

The aim of the present work was to combine the experience of the two research groups to develop and investigate the properties of silicone polymer matrix-based products for transdermal delivery of new types of analgesic drugs.

The objectives of my work were to achieve the followings:

1. Selecting a pharmaceutically and technologically suitable sulfide donor compounds. Developing a silicone polymer matrix system optimized for the properties of the compounds.

2. Testing and qualification of the selected system.

3. Development and qualification of a transdermal system containing the active substance capsaicin.

4. Preclinical testing of the capsaicin-containing transdermal system in in vitro and in vivo systems.

2. Literature review

2.1. Silicone polymers, rubber

Silicones, or organic polysiloxanes, are inorganic polymers that can be found in a wide range of applications. The chemical structure of silicones is composed of organic siloxane chains, similar to building blocks such as silicates and quartz. These polymers have a variety of properties including heat resistance, hydrophobic properties and flexibility.[1]

Silicones are made from different functional monomer units, resulting in products with different structures and properties. These products include silicone elastomers, oils and liquids, whose viscosity varies only slightly with temperature.

One of the outstanding properties of silicones is their water repellency, which allows them to create hydrophobic surfaces. They are also oleo phobic due to their low surface tension, so they do not adhere to organic materials.

The wide range of applications for silicones includes the medical industry, where they are used to make implants and other devices. They are compatible with human tissue, can be sterilized, are water-repellent and do not cause tissue reactions.

Depending on the cross-linking method used, Different types of silicone rubber can be made. HTV (High Temperature Vulcanizing) rubbers are cured at high temperature, while LTV (Low Temperature Vulcanizing) rubbers are cured at low temperature using an addition mechanism. RTV (Room Temperature Vulcanizing) rubbers are cross-linked by various condensation reactions and are used, for example, for the production of dental materials.[2,3]

Fillers are also added to silicone rubbers to increase mechanical strength and affect other properties. Fillers include active and inactive substances and can be used to give different properties to the final products.[4]

Overall, silicones are a widely used material, found in many areas and with a wide range of properties that make them suitable for a variety of applications.

2.2. Transdermal therapy systems

Transdermal therapeutic systems (TTS) offer a convenient, accurate and painless way to administer medication. These procedures were developed in the 1970s, where the drug is delivered to the body through the skin. This allows the drug to be delivered directly into the bloodstream, avoiding liver metabolism. This results in the use of lower doses, reducing the risk of side effects and overdose. TTSs also improve dosing accuracy by absorbing only the active substance through the skin. They also provide a long-lasting, consistent effect, unlike other forms of the drug which require increased monitoring.

However, the physicochemical properties of the active ingredient determine the applicability of TTS and not all drugs are suitable for this method.[5]

Transdermal therapeutic systems can be grouped according to their structure or chemical composition. Based on their chemical composition, they can be divided into: hydrophilic organic copolymers (e.g. polyols, polyethers, etc.) and silicone-based systems (hydrophobic or modified amphiphilic structure), the latter being described in detail in the previous chapter due to their importance for the thesis.

Major organic polymers used in the production of TTS[6]:

cellulose, chitosan, dextran, pullulan, sodium alginate, poly(caprolactam), acrylate copolymers, styrene-ethylene-butylene block copolymers, poly(vinylpyrrolidone).

According to their structure, transdermal therapeutic systems can be Passive TTSs and Active TTSs.

Passive TTSs:

Adhesive polymer dispersion systems are the simplest form of passive transdermal therapy systems. These systems consist of a carrier film, a pressure-sensitive adhesive and a drug carrier. The drug is released by diffusion. These simple patches are easy to manufacture, but the release of the active substance is not always uniform.

The advantages of membrane-controlled transdermal therapeutic systems include efficient application and a technology that has been known and studied for a long time. However, there are also disadvantages to this type of system. For example, the active ingredient is dispersed in a liquid carrier under the control membrane, which carries a risk of overdose or poisoning, as the liquid excipient may be transferred to the skin if the membrane is damaged. In addition, the system cannot be cut or modified, limiting the ability to meet individual dosing needs. The control of drug delivery can also be complex and patients who require variable or individual doses may have difficulty with administration.

In systems based on a non-adhesive polymer matrix, the precise delivery of the drug is achieved by adjusting the composition of the matrix. These mixtures are used to make the formulations, which are then fixed to the skin with a barrier layer.

This prevents the release of too much active substance in case of damage to the regulatory membrane. The system can be used to set the drug release profile, but unfortunately the patches cannot be cut into pieces and the dose cannot be easily adjusted.

The "microreservoir" type patches are thicker, but combine the two characteristics and their drug release is influenced by several physico-chemical parameters. These patches contain the active substance in a hydrophilic polymer solution dispersed in a hydrophobic matrix. The

release of the active substance is complicated because the interfaces act as membranes. Depending on the adjustment of the parameters affecting the release, a zero-order release of the active substance can be achieved. With certain limitations, these patches can also be cut into pieces.[7]

Active TTSs:

Iontophoresis is a technique based on the application of an electric potential, which conducts a constant electric current through the skin, allowing efficient delivery of ionised and non-ionised molecules. Its advantages include avoidance of the liver first pass effect and continuous or pulsatile delivery of the drug depending on the applied current. The procedure is easily controllable, the amount of drug administered can be controlled, and it offers the possibility to deliver polar or high molecular weight compounds. It also reduces the variability of drug levels by allowing the rate of drug delivery to be more strongly influenced by the applied current than by the intrinsic properties of the skin.[8]

Microneedles are very small needle-shaped structures that create pores and allow painless delivery of drugs into the skin or systemic circulation. These needles can improve patient care by minimising pain and helping patients to adhere to medications. They fall into five categories: solid, coated, hollow, hydrogel and dissolvable needles.[9]

2.3. Use of silicone polymers as TTS

Modified silicone polymer-based TTS systems are efficient and economical. They consist of several layers, where the active ingredient is contained in a polymer layer followed by a control layer selected according to the active ingredient. These systems are flexible and the drug release is controlled by the different diffusion properties of the two layers. The basis of silicone polymers has been identified and their cross-linking has been achieved by modifying the system. The addition technique is more practical and applicable for medical purposes, as the catalyst (special platinum compounds) is present in negligible quantity that do not induce biological effects. The addition silicone polymer provides high flexibility for varying drug and excipient compositions. However, it is important to choose the right materials, as amino groups inactivate the catalyst. A support layer is required due to the poor mechanical properties of the thin silicone polymer layer. The polymer mixture is applied to the area by a spreading method. The development and application of this equipment has been the subject of several patents.[10,11]

2.4 Background of chronic pain and challenges for analgesic therapy

Acute inflammation is a natural response to tissue injury and involves inflammatory mediators, blood vessels and immune cells. The five cardinal signs of inflammation are redness, warmth,

swelling, pain and loss of function. Acute pain is the nociceptive pain that occurs during inflammation. Inflammatory mediators cause pain by activating receptors on nociceptive nerve cells. Chronic pain, which complicates the lives a lot of people, is caused by nociceptive hypersensitivity to painful stimuli. This is usually the result of peripheral tissue damage or persistent inflammation (inflammatory pain), or due to peripheral or central nervous system adaptation (neuropathic pain). Neuropathic pain can be caused by nerve injuries, diseases, metabolic disorders, tumors, trauma, infections and other factors. Neuropathic pain causes severe suffering and is often chronic. Specific tests are needed to diagnose it and identify the underlying causes.[12]

The treatment of neuropathic pain is challenging because conventional analgesics are often ineffective. Current therapies include drugs such as gabapentin, pregabalin, serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants. Topical treatment options include skin patches containing lidocaine or capsaicin and botulinum toxin injections. Non-steroidal anti-inflammatory drugs (NSAIDs) are generally ineffective in neuropathic pain. Opioids are usually reserved for patients who do not respond to other therapeutic options. However, current therapies may be inadequate because we do not fully understand the mechanisms by which chronic pain develops. The development and persistence of chronic pain involves a number of adaptive changes in the central nervous system.

The nervous system undergoes long-term changes involving adaptations at the cellular and molecular level. [13]

Hydrogen sulfide (H_2S) is a neurotransmitter that plays a key role in several biological processes in the central and peripheral nervous system, including pain modulation and inflammation processes. Hydrogen sulfide has a role in the regulation of energetic dysfunction, apoptosis, inflammatory responses and oxidative stress responses.

However, the role of hydrogen sulfide in chronic pain is controversial. Its slow release plays a protective role, while its rapid release has a pro-inflammatory effect. In addition, exogenous administration of slow-release H_2S donors has been effective in attenuating osteoarthritis and neuropathic pain, making these compounds potential therapeutic tools in the treatment of inflammatory pain. As H_2S needs to be released slowly, proper carrier systems are needed to achieve the analgesic effect. Naturally occurring organic sulfur compounds and synthetic H2S donors include allyl sulfides derived from garlic, such as di-allyl disulfide (DADS). DADS has a number of beneficial properties, such as anti-inflammatory, antioxidant and antinociceptive effects.

However, topical application of DADS may be inconvenient and specific delivery systems may be required to facilitate the controlled release of the active ingredient. Silicone polymer (PDMS) is a possible carrier system for hydrogen sulfide donor molecules such as DADS, as it has apolar and hydrophobic properties that help in better distribution of the drug. This approach allows more efficient and convenient treatment for patients through transdermal application.[14–16]

Capsaicin is a natural component found in hot peppers. It has long been known to have therapeutic effects and several studies have been conducted to understand its use in pain relief. Local application causes a burning sensation, which has been used in pharmacological experiments to induce pain.

Capsaicin has been used for thousands of years to relieve pain, for example in toothache. Over the years it has been used in various forms, such as creams and patches. The concentration and form of capsaicin used were different, but the mechanism of action remained essentially the same.

These products containing capsaicin contained lower doses of the active substance, but their efficacy was not always convincing. They also often required frequent and prolonged use. However, higher concentrations of capsaicin provided more effective pain relief. They were used in various pharmaceutical forms, such as gels, creams, sprays and patches.[17]

Higher concentrations of capsaicin-containing patches (e.g. Qutensa) are effective in relieving neuropathic pain, such as phantom pain. The low systemic concentrations achieved after application do not affect the metabolism of other drugs, so it can be used safely with other analgesics.[18]

A capsaicin transdermal patch may be useful for treating larger areas of skin. In addition, research on capsaicin-induced analgesia may help to understand the peripheral mechanisms underlying neuropathic pain. Products containing capsaicin have minimal side effects, such as transient increases in blood pressure or local reactions such as burning sensations.

Above all, capsaicin transdermal patches can be a safe and effective method of treating neuropathic pain, especially for those who do not achieve satisfactory results with other analgesics.[17]A number of mainly topical capsaicin-containing medicines and herbal preparations are commercially available, mainly used for the relief of joint and muscle pain (e.g. Dr. Chen, Capsicole, Salonpas Hot, etc., with capsaicin contents ranging from 0.025-0.1%). However, these only deliver capsaicin to the surface layer of the skin and the method and level of administration cannot be controlled.

3. Main methods used for the experiments

<u>Measurement of membrane diffusion</u>

The diffusion properties of DADS across a silicone (PDMS) membrane were investigated using an in vitro membrane permeation system. The membrane thickness and oil content were varied and both the time shift and the steady-state permeation rate were measured. The membrane was placed between two half cells of the membrane permeation system.

A total of 25 mL of phosphate-buffered saline with 25 wt% ethanol (PBS-E25) without active ingredient was placed in the receptor compartment. A total of 10-3 M PBS-E25 containing DADS was added to the donor phase. Samples were taken at each predetermined time point and analyzed by UV/VIS spectrophotometer (Perkin-Elmer Lambda 25) at 207 nm. The DADS content was determined from a pre-recorded calibration curve.

Time shift and steady state permeation rate were determined from concentration vs. t profiles. The diffusion constants were determined from the time shift using the Daynes equation.[19]

<u>Preparation of di-allyl disulfide containing transdermal patches</u>

The TTS samples used in the experiments were prepared by casting on a layer of paper laminated on 0.4 mm thick aluminium foil. DADS was mixed into the silicone rubber. Our starting material was polydimethylsiloxane-(α, ω)-diol R-20. The DADS was dissolved in M350 and added to the silicone base. After weighing the components, Oxam crosslinker was added to the mixture with stirring. The mixtures were homogenized and spread on the carrier film in a thickness of 0.4 mm. The layer was crosslinked at room temperature with a crosslinking time of 30 min. The samples were allowed to rest for 48 hours and then analysed. The development work involved the testing of approximately 20 different matrix compositions to arrive at compositions suitable for in vitro testing.

<u>Preparation of transdermal patches containing capsaicin</u>

The TTS samples used in animal experiments were prepared on 0.04 mm thick paper foil laminated on aluminum foil. Our base polymer was RT-601 A (containing poly(dimethyl-co-methyl-vinyl)-(α,ω)-divinyl-siloxane chains and a cross-linking catalyst). Capsaicin was dissolved in glycerol while heating and then mixed into the silicone base. Crystalline capsaicin diluted with calcium carbonate was also added to the mixture. When it was necessary, additional liquid glycerol was added to the matrix and polysorbate 20 was added as an emulsifier.

RT-601 B cross-linker was added to the mixture while mixing and homogenized, then spread on the carrier film in 0.4 mm thickness. The layer was crosslinked at 70°C.

The operation took 60 minutes. A second control layer was then applied on top of this layer, which did not contain capsaicin, only glycerol and polysorbate. The second layer was then crosslinked at 70°C for 60 minutes. The samples were left for 48 hours and then examined. After testing around 40 different pre-test recipes, we arrived at two possible formulations that were considered suitable for animal testing. Finally, for the animal tests, we prepared patches in two formulations, one with a lower (1 mg/g capsaicin) and one with a higher (2.3 mg/g capsaicin) active ingredient content.

Measurement of in vitro release of transdermal patches

In vitro tests were performed in two different ways. Firstly, an indicative measurement was performed in a Franz cell, which models static and vertical subcutaneous drug release. In the second method, patches were tested in a flow-through cell device that mimics the drug concentration dissolved in blood.

Measurement in the Franz cell

In vitro drug release tests (In Vitro Release Test, IVRT) were performed using a modified, in-house manufactured Franz-type diffusion cell to model drug release from patches in IVRT.

The receptor phase was in phosphate buffer (PBS pH 7.4 ± 0.15) containing 25% m/m ethanol at room temperature. The test took 3 hour and the mixing speed was 450 rpm. The concentration of the active substance was measured by spectrophotometer (Perkin-Elmer Lambda 25) at 207 nm.

Measurement in the flow-trough cell

Samples of patches ($12.56\ cm2$ each) were tested at $37\ °C \pm 0.5\ °C$ in a flow-through cell to determine the release of the active substance. The flow rate (PBS, 25% ethanol) was 25 ml/h and the drug content was determined hourly using a spectrophotometer (Perkin-Elmer Lambda 25); the test lasted 6 hours.

Animal experiments:

Male Wistar rats, weighing 200-250 g, were used as experimental animals for the studies and were kept at the Institute of Pharmacology and Pharmacotherapy, University of PTE. The experiments were conducted in accordance with animal welfare regulations and approvals.

During hind foot incision, the plantar surface was treated with povidone-iodine and the wound was closed with sutures. Transdermal patches containing capsaicin were applied to the animals. The patches were applied in two ways: immediate application and delayed application. In both cases, the patches were applied to the animals with a wound dressing.

After application of the patches, the heat-induced pain threshold of the hind feet was measured using an elevated temperature water bath. The heating was controlled by a pedal and the animals

were accustomed to the test by three trial measurements. The onset of thermal allodynia, which appears as postoperative pain, was confirmed by a decrease in the pain threshold before application of the transdermal patch. Experiments were performed in 10 animals.

4. Results

4.1. Testing of sulfide-containing patches

In order to find the most suitable excipient, the solubility of DADS in different materials was investigated. For this study, PG, PEG 400 and M-350 were selected on the basis of preliminary studies, as they do not interact with the chosen active substance and are well established for medical use. The best solubility (0.4 g DADS/g silicone oil) was measured in dimethylsilicone oil, lower in PEG-400 (0.3 g DADS/g PEG400) and very low in PG (0.05 g DADS/g PG). These results clearly indicate that silicone oil is the best choice as a liquid excipient.

After selection of the appropriate excipient, membranes were prepared and the diffusion of DADS was investigated. When testing the R-5 linear polymer based membranes, a rather large variation in the results was observed, leading to the conclusion that the cross-linking density of the polymer is probably too high for a properly controlled diffusion of DADS.

We then moved on to the investigation of R-20 based matrices. Here we found much more transparent correlations. A careful examination of the relationship between the liquid excipient content and the diffusion constant (in addition to the four reported compositions, additional measurements were made during the preliminary experiments to establish the extreme values) showed that the diffusion constant of the active ingredient increases with increasing amounts of silicone oil.

Based on the measured data, a silicone oil content of 3% is the threshold value; up to this amount of excipient, the diffusion property of the active substance in the matrix hardly changes. Above this amount, however, the change in the diffusion constant is proportional to the increase in the amount of oil

Two patches with different lifetimes (4 and 8 days) were tested by an in vitro drug release test (IVRT). The cross-linked structure of the sample is stabilized in at least 3 days under storage conditions (room temperature, normal humidity), based on previous results. Therefore, the drug release properties of the sample were tested on the fourth day. After the same period, the stability of the drug release was determined, as the change in the drug release properties is not related to the change in the matrix structure.

In the IVRT measurement, a significantly larger amount of DADS was released from the 4-day patches within 3 hours than from the 8-day patches.

The 8-day patches had significantly lower drug release values. The release rate (IVRT) itself provides relevant information for comparison on a lifetime basis.[20]

Two patches with different silicone oil contents (5 and 10 wt%) were tested with modified IVRT. In the measurement, a significantly larger amount of DADS was re-released from the 4-day patches within 6 hours than from the 8-day patches.

The regulation of the release of the patches in the flow-through cell was monitored. The older DADS patch showed better controlled drug release over time, but the amount released was lower.

4.2. Testing of capsaicin-containing patches

As a result of membrane diffusion studies, it was revealed that the Wacker RT-601 polymer, selected for health considerations, is difficult to mix with glycerin, with a maximum solubility of only 4-5 m/m% glycerin in the matrix. With the use of more glycerin, over time (depending on quantity, 3-7 days), the matrix and liquid excipient separate, and some of the glycerin diffuses out of the polymer matrix.

Even at 5 m/m% glycerin content, the diffusion constant of capsaicin is relatively low, and the solubility of capsaicin in glycerin is also low (0.01g capsaicin/g glycerin). Therefore, it was necessary to increase the capsaicin content in the matrix, and this could not be achieved by simply increasing the amount of glycerin.

The solution was found by using polysorbate-20 alongside glycerin, a well-known emulsifier in pharmaceutical technology. In further investigations, samples containing small amounts of solid capsaicin and two different excipients were prepared. For low capsaicin content samples, the matrix could not achieve controlled drug release, and even with higher capsaicin content, issues arose with drug release.

This problem was resolved by introducing the required amount of capsaicin in solid form, using an inert carrier (calcium carbonate) into the matrix. Since capsaicin is solid at room temperature, has a relatively high melting point, and is of low volatility, it did not pose problems during aging studies.

In additional composition experiments, they reached compositions suitable for more demanding measurements, correlating with IVRT and IVPT results. The differences between capsaicin-containing patches regarding permeability and drug release were similar to those observed in IVRT and IVPT experiments.

Carrageenan reduced the mechanical pain threshold post-treatment, and capsaicin treatment resulted in an elevated pain threshold, but it was still lower than the pre-application value.

Control patches did not alter threshold values. The sensitivity of carrageenan-injected paws increased, but contralateral paws did not show increased sensitivity.

The overall findings from these studies indicate that the drug release and effects of capsaicin-containing patches can vary through the skin, and different compositions may yield diverse results.

5. Discussion

5.1 Conclusions on the development of DADS patches

The main objective of this research was to develop a transdermal therapeutic system (TTS) that allows the controlled and slow release of DADS (di-allyl disulfide) and similar sulfide donor molecules. In this case, DADS is a compound of natural origin extracted from garlic and has a number of beneficial effects, such as analgesic and anti-inflammatory effects.

In the first step, we modified the recipe for the production of DADS to obtain a higher purity and potency of the substance. This high purity allowed for a better interpretation of subsequent experiments and more reliable results.

Then, different silicone oils suitable for the development of TTS systems were investigated. Silicone oils were used as storage and diffusion media for DADS and the effects of their different concentrations were analysed.

The results showed that the amount of silicone oils has a significant effect on the rate and amount of drug release. In particular, systems containing 5% and 10% silicone oil were effective in increasing the release of DADS.

Transdermal therapeutic systems offer advantages such as long-term applicability, maintenance of continuous and stable drug levels, and ease of administration and dose adjustment. The results suggest that DADS and similar sulfide donor compounds may hold promise for the treatment of pain and inflammation, and transdermal patches may provide an effective means for the controlled and slow release of these compounds. As a next step in research, further studies of DADS and similar compounds are needed to further develop TTS systems.

5.2 Conclusions on the development of capsaicin-containing patches

During our research, we developed and tested transdermal patches for the controlled release of the active substance capsaicin. Our technology employed a diffusion gradient based on a modified silicone polymer to control drug release. Using a cross-linked silicone polymer method, two types of patches with different concentrations of capsaicin were prepared and tested under in vitro and in vivo conditions.

The silicone rubber used as a matrix is apolar, while capsaicin is relatively polar. To compensate for this, we used glycerol as a solvent, which is soluble in capsaicin and skin-friendly.

An emulsifier was used to aid the dispersion of glycerol in the silicone matrix. It was found that the capsaicin-saturated glycerol was not effective enough for the desired drug delivery, so solid capsaicin was dispersed in the matrix.

To achieve this, a powder dilution with calcium carbonate was used. Results showed that this method was able to achieve adequate drug release kinetics. Control layers were experimented with and during sample preparation, capsaicin diffused out of the patch undisturbed but only in the desired amount.

We tested several formulations and arrived at patches suitable for animal studies. In vivo experiments were carried out to narrow down the range of ideal formulations, and patches containing 1 mg/g and 2.3 mg/g capsaicin were prepared and tested.

Flow-through cell assays showed that higher concentrations of capsaicin were released from patches with higher drug content, and then kinetics were formed at a rate of 2 $\mu g/cm^2$/hour in the equilibrium state. In patches with lower capsaicin content, the release of the drug gradually decreased due to an increase in the diffusion path.

In both formulations, the regulatory layer adequately controlled the drug release. The kinetics of capsaicin release decreased slowly during drug release.

Clinical studies have shown that patches with low capsaicin content can be effective in treating neuropathic pain. Clinical trials of low capsaicin patches have shown significant pain relief in patients. This is because the local capsaicin action acts directly on the nerve endings involved in pain sensation, without reaching high systemic concentrations. The results suggest that somatostatin may also play an important role in the mechanism of action of capsaicin. The research conducted suggests that transdermal capsaicin-containing patches may be effective in the treatment of neuropathic pain.

The patches developed in this work can also be applied to other agents. The patches show good drug release kinetics and the technology is suitable for small-scale production.

6. Summary of the novel results

One of the objectives of my work was to develop TTSs that exert their analgesic effect by transdermal delivery of TRPA1 activating agent (sulfide donor molecules) and TRPV1 activating agent (capsaicin). My further objectives were to test and qualify these systems under both in vitro and in vivo conditions. During my PhD research I have achieved the following new results:

1. Based on the results of membrane and matrix diffusion experiments, we developed a silicone polymer-based TTS optimized for carrying a sulfide donor molecule using di-allyl disulfide as a model drug. During the development of the system, we have developed a suitable polymer-surfactant combination capable of carrying and properly delivering sulfide-containing compounds, and have gained experience with the use of this type of volatile active substance.

2. In vitro studies of DADS drug-containing TTS models have shown that it is possible to develop systems with near-zero order drug release kinetics for volatile sulfide donor molecules.

3. Through extensive development work, membrane and matrix diffusion studies, single and multilayer samples, and testing of several possible combinations, we have developed a silicone polymer-based TTS containing the active ingredient capsaicin, which is a fully biocompatible system, with homogeneous drug distribution and long-term stability.

4. In our in vitro studies, we found that the developed capsaicin-containing TTSs release their active ingredient over the long term, according to zero-order kinetics, uniformly and reliably. We have found that the capsaicin released from the developed system penetrates effectively through the skin and is released in sufficient amounts to exert a systemic effect.

5. In our in vivo studies, we found that the prepared capsaicin TTSs were effective in reducing acute pain in several animal models (rat, surgical wound pain model and carrageenan-induced inflammation pain model) in a well-detectable manner.

These experiments have been performed under conditions that will serve as preclinical results for a later phase in which we aim to use the results in the drug development process.

7. Practical applicability of scientific results

The innovative structure of the TTS was developed by our research group and the patent is pending. The silicone polymer matrix provides a suitable carrier for small molecule organic active ingredients (e.g. capsaicinoids, allyl sulfides) with significant therapeutic potential in the development of new types of analgesic and anti-inflammatory agents. Due to this structural design, TTS containing low doses of capsaicin ensure a long-lasting and uniform rate of penetration of the active ingredient into the skin.

Advantages of TTS containing low doses of capsaicin :

(1) effective pain relief without loss of sensory nerve function or initial analgesia;

(2) provide a uniform rate of sustained release of the active ingredient;

(3) the active ingredient can be delivered to the deeper layers of the skin;

(4) the therapeutic effect can be terminated at any time by removing the patch;

 (5 the dose to be applied can be easily adjusted by cutting the patch to size;

(6) contamination of hands and clothing can be easily avoided.

The combination of topically administered low-dose capsaicin with non-steroidal anti-inflammatory drugs (NSAIDs) is an empirically based therapeutic option for the treatment of chronic degenerative polyarthritis in both neurological and rheumatological clinical practice, but the exact mechanism of this combination therapy is not yet clear.

8. Future plans

In the TTS we have developed, the carrier material for low-dose capsaicin is a silicone polymer matrix with a cross-linked structure that distributes the drug evenly throughout the patch, ensuring a uniform and sustained release. The innovative carrier material and the new type of analgesic mechanism of action offer a number of advantages over commercially available high-dose patches or creams. It should be stressed that these advantages are also maintained when low-dose capsaicin is combined with other active ingredients.

Since low-dose capsaicin causes a sustained, low-intensity activation of the TRPV1 receptor and triggers the release of a local vasodilator, it logically follows that the increased blood supply to the inflamed area could potentially facilitate the absorption of other analgesic agents (e.g. NSAIDs).

Our research group therefore aims to further develop low-dose capsaicin TTS, in which we plan to combine capsaicin with an NSAID whose solubility in a silicone matrix can be well controlled by apolar or polar solvents. The novel combination of low-dose capsaicin and NSAIDs in a single patch is a unique niche product in the analgesic market, which is in great demand in neurological and rheumatologically patient care. The tools and methods used to produce the TTS are modelled on industrial production, so the technologies used can be applied to small-scale production with minor modifications.

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10. Publications list

10.1. Publications related to the thesis

László, S.; Hajna, Z.; Egyed, A.; Pintér, E.; Wagner, Ö. Development of a Silicone-Based Polymer Matrix as a Suitable Transdermal Therapeutic System for Diallyl Disulfide. Pharmaceuticals 2022, 15, 1182. https://doi.org/10.3390/ph15101182

IF: 5.215

László, S.; Bátai, I.Z.; Berkó, S.; Csányi, E.; Dombi, Á.; Pozsgai, G.; Bölcskei, K.; Botz, L.; Wagner, Ö.; Pintér, E. Development of Capsaicin-Containing Analgesic Silicone-Based Transdermal Patches. Pharmaceuticals 2022, 15, 1279. https://doi.org/10.3390/ph15101279

IF: 5.215

10.2. Publications not related to the thesis

Weisz E, Szűcs ZP, Farkas J, Grimm A, Rácz G, **László S** Ruttkay T (2022) Innovative artificial lesions to mimic difficult airway pathology in cadavers, supporting airway management training. Trends in Anaesthesia and Critical Care 44, pp. 43-48 https://doi.org/10.1016/j.tacc.2022.04.009

IF: 0.870

Nemes B, **László S**, Zsidó BZ, Hetényi C, Feher A, Papp F, Varga Z, Szőke É, Sándor Z and Pintér E (2023) Elucidation of the binding mode of organic polysulfides on the human TRPA1 receptor. Front. Physiol. 14:1180896. doi: 10.3389/fphys.2023.1180896

IF: 4.755

Cumulative impact factor of publications related to the thesis: 10.43

Cumulative impact factor of all publications: 16.055

10.3. Poster presentations

László Sz., Bátai I. Z. , Pozsgai G. , Wagner Ö. , Pintér E. Silicone based transdermal delivery system for diallyl disulfide X. Jubileumi Interdiszciplináris Doktorandusz Konferencia (IDK2021) Pécs, Magyarország 2021

László Sz., Bátai I. Z. , Pozsgai G. , Wagner Ö. , Pintér E. Silicone based transdermal delivery system for diallyl disulfide 6th World Congress on Hydrogen Sulfide in Biology & Medicine Budapest, Magyarország 2022

László Sz., Pozsgai G. , Wagner Ö. , Pintér E. Development of analgesic silicone-based transdermal patches, 3rd Regional Congress of Physiological Societies and the 5th Congress of Croatian Physiological Society Plitvice, Horvátország 2022

11. Acknowledgements