Original Research Article

The Demirci Phenomenon: A Novel Finding of Ivermectin Molecules on Eyelash and Demodex Folliculorum in the Lipid Environment

Abstract

Purpose: This study aimed to investigate the acaricidal mechanism of ivermectin against Demodex folliculorum (DF) and observe its behavior in lipid media, particularly in relation to its movement and selective interaction with the Demodex parasite.

Methods: Eyelash epilation was performed on an ocular rosacea patient, and 8 eyelashes were extracted, 4 from the lower eyelid and 4 from the upper eyelid. Four eyelashes were exposed to 1% ivermectin solution under a coverslip, while the other four served as the control. A high-resolution digital microscope with a noncontact digital thermometer was utilized to monitor the entire process. The behavior of ivermectin molecules and their redistribution towards the Demodex parasite were recorded and analyzed.

Results: Upon exposure to 1% ivermectin solution, intriguing behavior of the drug molecules was observed. The ivermectin molecules moved towards the Demodex parasite, forming distinctive bubbles that effectively covered both the eyelash and the body of the Demodex. Saponification of the oil within the Demodex and eyelashes occurred within 10 minutes. After one hour, the ivermectin bubbles and the empty, shrunken body of the Demodex remained. The acaricidal effect of ivermectin was rapid, predictable, and highly selective.

Conclusion: The study provides valuable insights into the acaricidal mechanism of ivermectin against Demodex folliculorum and demonstrates the unique behavior of ivermectin

molecules in lipid media. The "Demirci Phenomenon" highlights the selective and targeted interaction of ivermectin with Demodex parasites. These findings may have implications for the development of anti-demodex medicine and suggest alternative therapeutic approaches for managing demodicosis.

Key words: chronic blepharitis, demodex, eyelid, ivermectin, parasites.

Introduction

In the last decade, the global scientific community has increasingly acknowledged the remarkable value of ivermectin, an extraordinary drug derived from a single microorganism discovered in the soil of Japan [1].During the late 1970s, Japanese microbiologist Satoshi Ōmura, a researcher at the Kitasato Institute in Japan, and Irish biochemist William C. Campbell played key roles in the discovery and development of ivermectin [2,3].Campbell, who was working in the USA and an expert in parasite biology, obtained Ōmura's Streptomyces cultures and extensively investigated their effectiveness.Campbell's research demonstrated that a specific component from the cultures displayed exceptional efficiency in combating parasites in domestic and farm animals. This bioactive substance was purified and given the name Avermectin. Subsequently, it underwent chemical modifications to create a more potent and effective compound known as Ivermectin.In recognition of their substantial contributions to the development of the drug, Satoshi Ōmura and William C. Campbell were jointly awarded the Nobel Prize in Physiology or Medicine in 2015. Their work on Ivermectin's discovery and advancement had a profound impact on the field of medicine and parasitology [1-4].Despite extensive research conducted since its discovery over 35 years ago, the mode of action of ivermectin in parasitic species remains incompletely understood. While significant strides have been made in uncovering its mechanisms of action, there are still

aspects that require further investigation and elucidation [5]. Intriguingly, the mechanism of action of ivermectin involves its strong affinity for glutamate-gated chloride ion channels present in the peripheral nervous system of invertebrates, specifically targeting parasites like Demodex folliculorum. These ion channels play a crucial role in the neural signaling of these parasites, and ivermectin's binding to them leads to significant consequences for their physiological functions [4,6].

The Demodex mite, which belongs to the class Arachnida and subclass Acari, is the most commonly found obligate ectoparasite on human skin and eyes [7]. Indeed, these microscopic Demodex mites have a broad distribution among mammals, and their existence is indicative of an ancient parasitic relationship that dates back around 220 million years. This timeline aligns with the evolution of animals that developed hair follicles. Throughout this extensive period, Demodex mites have co-evolved with their mammalian hosts, becoming specialized to inhabit hair follicles and sebaceous glands on the skin [7,8].While they are considered obligate ectoparasites, they generally do not cause harm when their numbers remain in balance. However, under certain conditions, their population can increase, leading to infestations and associated skin and eye conditions [9].Demodex mites can be found on various parts of the human body. They are commonly detected in areas such as the head, outer ear, upper chest, mons pubis (pubic area), and buttocks, and are particularly prominent in specific facial areas. The facial T-zone, which includes the forehead, nose, and chin, is a common site for Demodex mites' presence [10].There are two main subtypes of Demodex mites that are commonly found in humans: Demodex folliculorum (DF) and Demodex brevis (DB). These mites can be distinguished based on their sizes. Demodex brevis (DB) is relatively smaller, typically measuring between 100 and 200 µm. On the other hand, Demodex folliculorum (DF) is larger, with a size range of approximately 200 to 400 µm [11].Addressing Demodex infestations and confirmed demodicosis poses significant

challenges and typically necessitates several months of therapy. Recent studies have indicated that from 42% to 81% of blepharitis patients have concurrent infestations with Demodex mites, and these mites are more commonly found in older patients [12]. The main objectives of therapy are to hinder mite reproduction, eradicate existing mites, and prevent future infestations. In the case of Demodex infestations on the skin and eyelashes, the lipophilic nature of ivermectin is especially significant. The lipid-rich environment of the eyelashes and hair follicles creates an ideal setting for ivermectin to exert its antiparasitic effects.This article provides an overview of the current applications and mechanism of action of ivermectin on DF. Additionally, it introduces the novel "Demirci Phenomenon," a term coined for the first time in the literature, describing the extraordinary behavior of ivermectin molecules that display a targeted curling magnetic action specifically towards the Demodex parasite. The captivating nature of this phenomenon is effectively demonstrated through high-definition in vitro high-resolution microscopy.

Material and Methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Ethical approval for the research has been obtained from the Board of İstanbul Medipol University with document number 02.11.2022-10840098-604.01.01-E.22410. While eyelash epilation and examination for ocular demodicosis under a microscope is a routine procedure at İstanbul Medipol University Ophthalmology clinic, we ensured that proper informed consent was obtained from the ocular rosacea patient.The exclusion criteria are as follows: patients who underwent ocular surgery, Stevens–Johnson syndrome, radiation damage, systemic antineoplastic drug use, contact lens use, trachoma sequel or symblepharon, glaucoma, immunosuppression, and bullous pemphigoid. This patient was randomly selected from the previously known ocular demodicosis patients to examine eyelashes. By modifying the classical Coston method according to Gao's suggestion, we performed eyelash epilation,

extracting a total of 8 eyelashes (4 from the lower eyelid and 4 from the upper eyelid) from this patient [13,14]. Out of these, 4 eyelashes were fixed using classical immersion oil and then covered with a coverslip. Once we observed the Demodex colony at the eyelash root, we placed a drop of 1% ivermectin solution next to the coverslip border, ensuring that the ivermectin and immersion oil under the coverslip came into contact. It is essential to mention that this method is my personal novel approach to administering ivermectin in vitro experiments for my research. (Figure 1) As a control, we fixed the other four eyelashes using classical immersion oil and covered them with a coverslip. To ensure accuracy and detailed analysis, all procedures were meticulously recorded using a digital camera for both analysis and live monitoring purposes. For our observations, we utilized a high-resolution digital microscope (Bresser-Biolux Touch LCD, Bresser GmbH) that we modified by attaching a noncontact digital thermometer (Gaman©, China) to measure the slide's temperature as well (Figure 2). Throughout the entire process, from the beginning of the study to the demise of Demodex, we consistently recorded all procedures using the same digital microscope.

Results

Upon adding the 1% ivermectin solution at the border of the coverslip(Figure 1), we made an intriguing observation: the ivermectin molecules started to invade the slide, forming distinctive ivermectin bubbles. As ivermectin interacts with the lipid-rich environment, it initiates a redistribution phase, rapidly moving towards the eyelash and Demodex. Subsequently, the ivermectin molecules effectively covered both the eyelash and the body of the Demodex, presenting a magnet-like attraction or a guided missile effect (Figure 3).

Within a span of 10 minutes, we observed saponification of the oil within the Demodex and eyelashes (Figure 4). After 30 minutes, there was no observed movement of the podosomes (Figure 5). Remarkably, after one hour, only the ivermectin bubbles and the empty, shrunken body of Demodex remained.(Figure 6-7)Based on our careful observations, it became evident

that the acaricidal effect of ivermectin %1 was remarkably rapid, predictable, and appeared to be highly selective.

Discussion

Addressing Demodex infestations and confirmed demodicosis poses considerable challenges and typically demands several months of therapy [1,2]. These minuscule mites are present on various body parts, such as the head, outer ear, upper chest, mons pubis, buttocks, and most notably, in the facial T-zone, meibomian glands, and eyelash follicles.Although Demodex mites are commonly found in many individuals, they do not necessarily cause harm to everyone [10,11]. The relationship between their presence and any resulting harm might be akin to a chicken-and-egg scenario. It's possible that an underlying inflammatory eye condition allows a normal number of mites to proliferate into an abnormal amount. Conversely, the mites could multiply excessively and lead to an inflammatory eye condition. The exact cause-and-effect relationship between Demodex mites and eye conditions is not entirely clear and warrants further investigation [12].Indeed, the sequence of events and the exact cause of Demodex mite-related ocular conditions remain unclear. These microscopic mites primarily reside inside human hair follicles, feeding on dead skin cells and sebum while positioned head-down. During the night, they emerge from the follicles to mate and lay their eggs. Despite their normal presence in many individuals, Demodex mites have been associated with various ocular conditions, such as chronic blepharitis, keratoconjunctivitis, chalazia, keratitis, endophthalmitis, and even periocular basal cell carcinoma. However, the precise relationship between the mites' activities and the development of these eye conditions requires further investigation [10-13].

Systemic demodicosis treatments often include antibiotics, such as tetracycline, doxycycline, metronidazole, and ivermectin. Topical treatments, on the other hand, may involve the application of metronidazole, permethrin, benzyl benzoate, crotamiton, lindane, sulfur, and

various medicinal oils [10,11]. Notably, there is currently only one FDA-approved treatment specifically for demodicosis, although it is not yet available on the market [15].Indeed, the selection of therapy for demodicosis should be tailored to individual patient characteristics and guided by healthcare professionals. Each patient's specific condition, medical history, and potential side effects of the treatments need to be taken into consideration to ensure the most effective and safe course of action.

Ivermectin is an oral semi-synthetic macrocyclic lactone anthelmintic agent that is derived from avermectins, which are isolated from the fermentation products of Streptomyces avermitilis. It has been found that ivermectin exhibits a concentration-dependent inhibitory effect on the motility of a free-living nematode called Caenorhabditis elegans(C. elegans). This property makes ivermectin an effective treatment for various parasitic infections in both animals and humans[16].Ivermectin is considered one of the most essential drugs in both veterinary and human medicine for the control of parasitic infections, which is why it became the joint focus of the 2015 Nobel Prize in Physiology or Medicine. Despite its 30 years of use in human medicine, there is still ongoing research and much to learn about this remarkable compound[17].One of the known properties of ivermectin is its lipophilic nature, which means it has a strong affinity for and can readily dissolve in lipid or fat-based environments. The lipophilic nature of ivermectin allows it to distribute and accumulate effectively in various tissues, cross cell membranes easily, and interact with its target parasites effectively.This characteristic is crucial for its effectiveness against parasites like DF, which are found in lipid-rich environments such as hair follicles and sebaceous glands[18]. Indeed, the lipophilic nature of ivermectin appears to be the key factor behind the unique redistribution pattern of the drug molecules observed in immersion oil, particularly in the vicinity of the eyelash and the DF parasite in our study. This property allows the drug to

interact effectively with the lipid-rich environment, potentially influencing its movement and concentration in these specific areas.

The accepted theory of ivermectin's anthelmintic and insecticidal mode of action proposes that it acts as a selective positive allosteric modulator of glutamate-gated chloride channels present in nematodes and insects[18,19]. When ivermectin is administered to an affected individual, it specifically binds to and opens inhibitory glutamate-gated chloride ion channels in various locations, such as the membranes of pharyngeal muscles, motor nerves, female reproductive tracts, and the excretory/secretory pores of invertebrates like Demodex mites.Indeed, upon binding to the glutamate-gated chloride ion channels, ivermectin induces an influx of chloride ions through these channels. This influx leads to hyperpolarization of the nerve or muscle cells in the parasite, resulting in its paralysis. Consequently, the immobilized parasite becomes unable to function and eventually succumbs to its death[18-20]. At higher concentrations, ivermectin acts as an allosteric modulator of ion channels found in the host's central nervous system. Fortunately, it does not easily cross the mammalian blood-brain barrier, where ligand-gated chloride ion channels are located in mammals. As a result, humans are spared from experiencing adverse effects on their central nervous system when ivermectin is administered within recommended doses.

Although ivermectin is generally well-tolerated and relatively safe in most mammals, caution should be exercised when administering large overdoses of the drug[17,18]. In such cases, ivermectin may cross the blood-brain barrier, leading to depressant effects on the central nervous system. This potential risk should not be overlooked[2].Furthermore, at concentrations higher than those used as anthelmintics, ivermectin exhibits a range of additional effects in tissue culture, including antiviral, antimalarial, antimetabolic, and anticancer properties[4]. While ivermectin's primary target is glutamate-gated chloride channels, it also shows activity against various other invertebrate neurotransmitter receptors,

such as gamma-aminobutyric acid(GABA), histamine-, and pH-sensitive chloride channels. Parasitic nematodes have diverse molecular glutamate-gated chloride ion channels in different tissues, leading to varying sensitivities to ivermectin[18,19].As a result, the most ivermectin-sensitive tissues and the phenotypic effects of the drug vary depending on the parasite species.Researchers conducted competition experiments to gain insights into the ivermectin binding site by inhibiting ivermectin binding using various avermectin derivatives and the neurotransmitter GABA. Surprisingly, GABA did not compete with ivermectin binding, despite previous suggestions that ivermectin acts on the GABA-gated chloride channel in certain invertebrate systems[18].

In the realm of scientific discovery, ivermectin continues to amaze and captivate researchers, as it shows increasing promise in improving global public health by treating a diverse array of diseases. Particularly extraordinary is its unexpected potential as an antibacterial, antiviral, and anti-cancer agent[5].However, it is important to note that the use of oral ivermectin may entail certain side effects, including diarrhea, dizziness, nausea, allergic reactions, skin swelling, fainting, fast heartbeat, fever, joint pain, vision changes, yellowing of the eyes or skin. Proper caution and medical supervision are essential when administering the drug[21]. The in vitro finding, which I have termed the "Demirci Phenomenon," is a fascinating observation of the redistribution and curving movement of ivermectin molecules. This intriguing behavior resembles the patterns seen in sandscapes, and it occurs directly toward the Demodex parasite and eyelash in the lipid-rich environment. This remarkable discovery has the potential to pave the way for innovative approaches in the development of anti-demodex medicine and cutting-edge technologies. By understanding and harnessing this unique phenomenon, new strategies may be unlocked to combat Demodex infestations effectively.Indeed, the redistribution behavior and movement of ivermectin through the Demodex parasite, particularly in lipid-rich regions of the eye, hold significant importance

when the drug is used topically or orally. For ophthalmologists, examining the eyelashes, especially for Demodex Folliculorum, becomes a crucial aspect of diagnosing and monitoring demodicosis. Understanding how ivermectin interacts with the lipid environment and targets the parasites can help improve the effectiveness of topical treatments for ocular demodicosis, leading to better patient outcomes and management of this condition.Indeed, there have been numerous research studies that demonstrate the increased treatment success of ivermectin against demodicosis. Over the years, ivermectin has been extensively researched and proven to be highly effective in treating Demodex mite infestations, particularly in conditions like rosacea and other skin and ocular disorders associated with these parasites[22].In a previous study, Martin Schaller et al. discovered that ivermectin 1% cream exhibits a dual mode of action, acting as both an anti-inflammatory and acaricidal agent in papulopustular rosacea. Additionally, they observed a higher rate of treatment success in patients with a higher baseline density of Demodex infestation [19]. The results of the recently published ANSWER trial (oraceA soolaNtra aSsociation in patients With severE Rosacea) demonstrated that topical treatment with Ivermectin, either alone or in combination with doxycycline 40 mg, efficiently reduced not only papules and pustules but also erythema in rosacea patients, as evaluated by CEA score [23,24].As clinicians, we have long been aware of the high effectiveness of ivermectin and have gained knowledge about its mechanism of action. However, this study presents the first high-definition demonstration of molecules in lipid media, showcasing the fascinating redistribution movement towards the eyelash and Demodex folliculorum. Figures 2 to 6 provide a detailed insight into the acaricidal mechanism of ivermectin, ultimately leading to the observation of the empty cytoskeleton. These groundbreaking findings shed new light on the precise interactions and effects of ivermectin on Demodex parasites, contributing to a deeper understanding of its therapeutic potential in combating demodicosis.A similar observation was reported in the research conducted by

Paichitrojjana A. et al, where they compared the in vitro killing effect of Thai herbal essential oils with ivermectin. Mites exposed to sweet basil oil demonstrated rapid changes, such as shrinking, distortion, and deformation, leading to their demise within a few minutes. On the other hand, mites exposed to ivermectin showed a different pattern, becoming smaller and translucent after two hours before their ultimate death [25].This is an observational research and is a limited study due to the number of cases, but the research is intended to demonstrate an observation.

Conclusion: to the best of our knowledge, there has been no demonstration of ivermectin molecule movement behavior, nor any observation of selective ivermectin bubble covering of Demodex mites in the existing literature. Based on our results, as observed, ivermectin interacts with the lipid-rich environment, triggering a redistribution phase, swiftly advancing towards the eyelash and live Demodex. Subsequently, the ivermectin bubbles encased both the eyelash and the body of the Demodex, akin to a swarm of bees latching onto a target.These findings highlight the distinct effects of different treatments on Demodex mites and provide valuable insights into alternative therapeutic approaches for managing demodicosis.

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FIGURE LEGENDS

Figure 1 Drop of 1% ivermectin solution next to the coverslip border

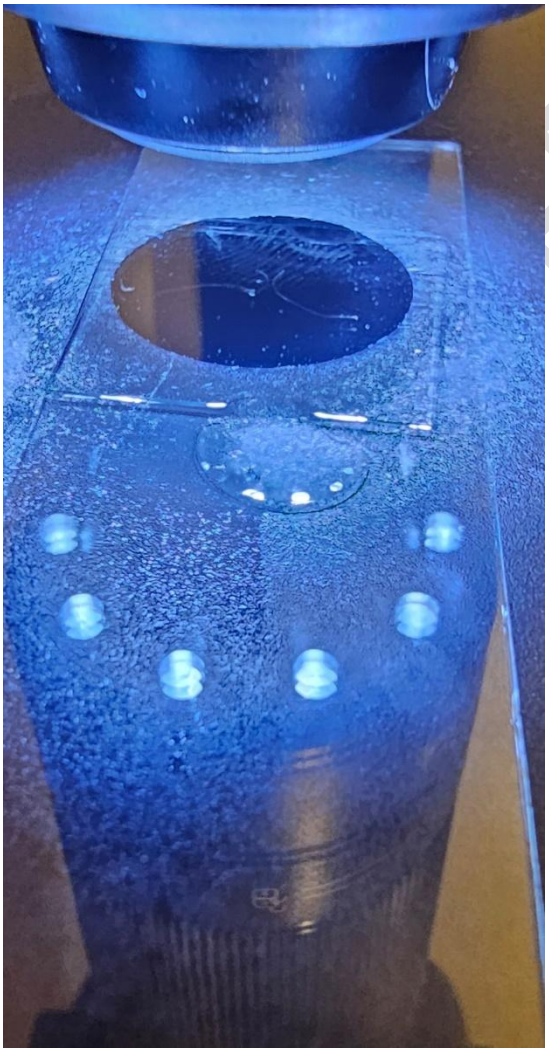

Figure 2 High-resolution digital microscope (Bresser-Biolux Touch LCD, Bresser GmbH) that we modified by attaching a noncontact digital thermometer (Gaman©, China) to measure the slide's temperature

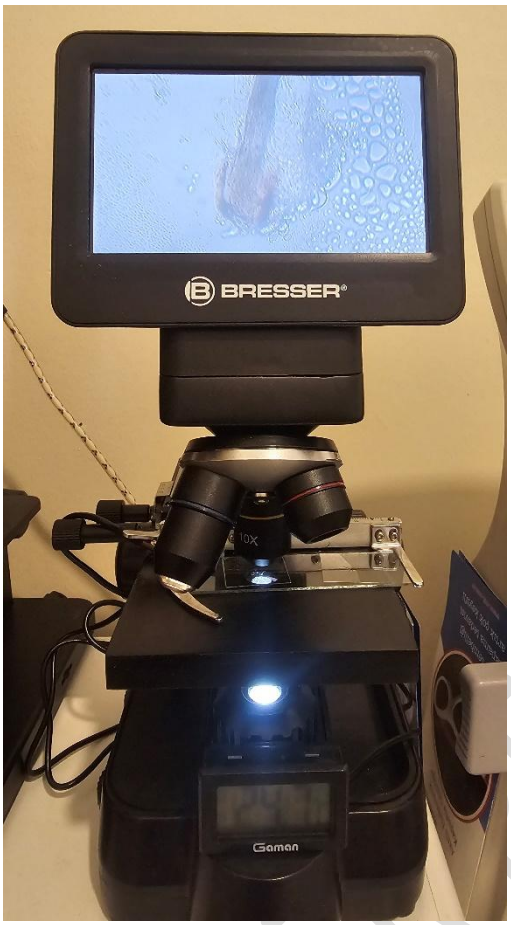

Figure 3 Before a drop of 1% ivermectin, demodex and eyelash

Figure 4 After 2 minutes of a drop of 1% ivermectin at the border of the coverslip

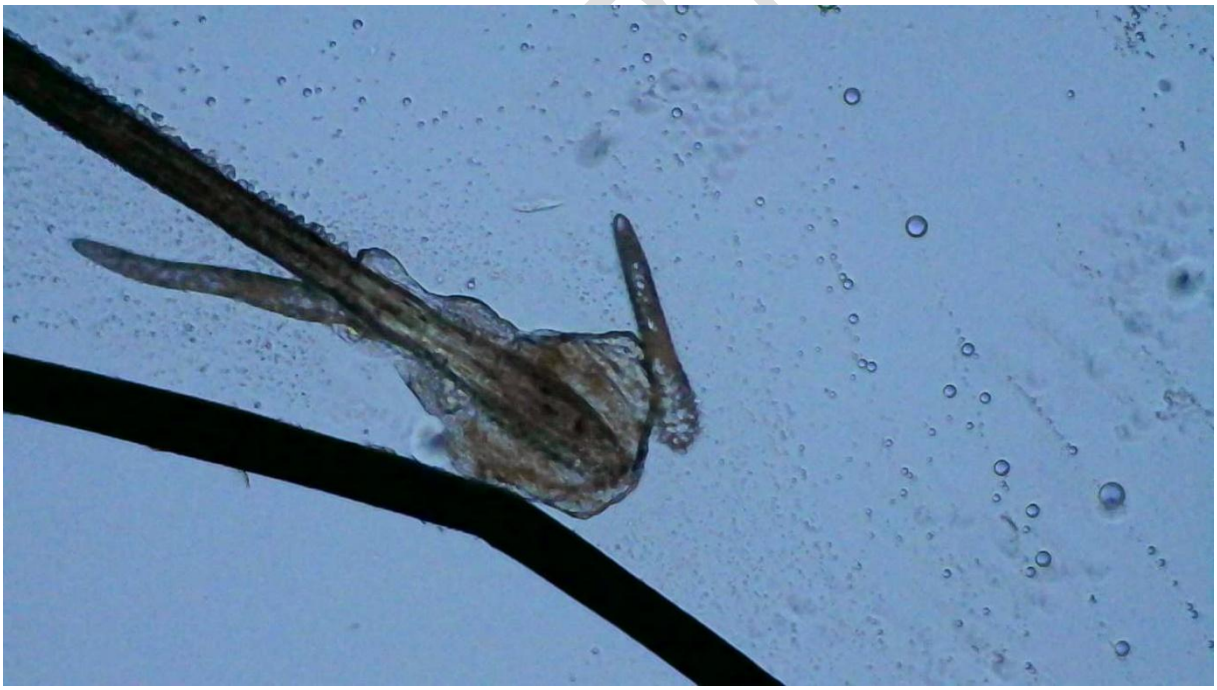

Figure 5 Thirty minutes later, completely covered with ivermectin bubbles, no podosome movement is seen

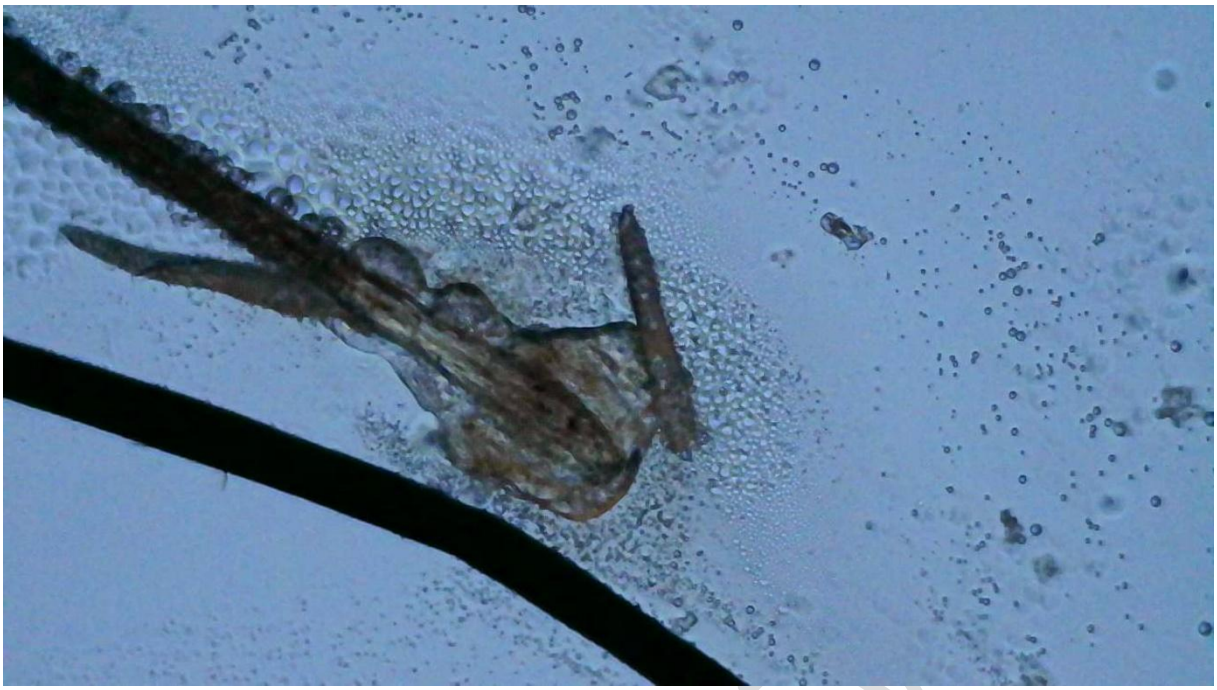

Figure 6 Remarkably, after one hour, only the ivermectin bubbles and the empty, shrunken body of Demodex remained.

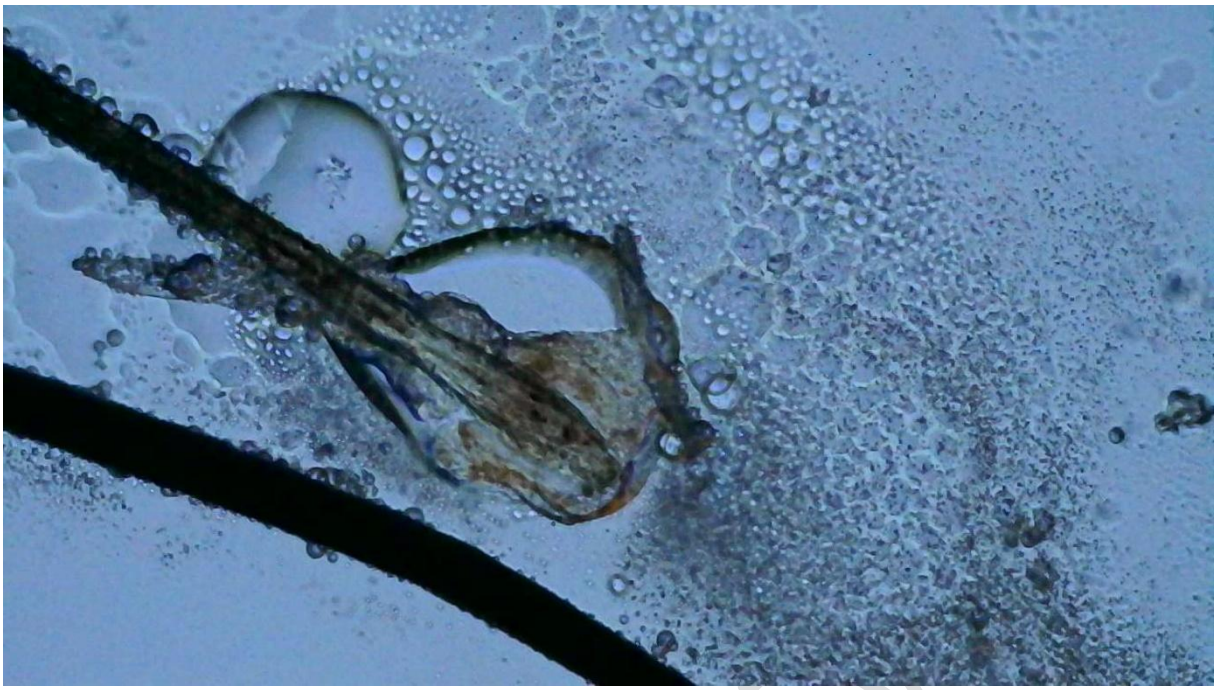

Figure 7 Disposed cytoskeleton of Demodex.