Charles University

Faculty of Pharmacy in Hradec Králové

Department of Pharmaceutical Technology

Rheological Properties of Silicone Gels for Scar Treatment

Master's Thesis

Hradec Kralove 2022

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I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing is listed in the bibliography and properly cited.

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First and foremost, I would like to show my sincere gratitude to my supervisor PharmDr. Eva Šnejdrová, Ph.D. Her consistent guidance, encouragement, and patience have been priceless during this project.

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2 ABSTRACT

Charles University, Faculty of Pharmacy in Hradci Králové
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Title thesis: Rheological properties of silicone gels for scar treatment

The thesis is focused on testing of the flow and viscoelastic properties of the scar treatment silicone-based gels, either commercially available or newly formulated gels under development. The theoretical part deals with the scar formation, silicone in scar treatment, and characterization of the gels. In the experimental part, rotational and oscillation tests were performed using a rotational rheometer. The obtained flow curves were fitted by Newton or Power law models. The shear viscosity, coefficient of consistency, and index of flow behaviour were used for gel characterization and comparison. The highest viscosity revealed in the ScarEsthetique cream, followed by RejuvaSil gel. Surprisingly, the Stratamed scar gel and Scar gel Dr. Max showed the lowest viscosity, even lower than the formulations at the development stage. Despite the name "gel", they behave as Newtonian fluids. The elastic modulus G', viscous modulus G", and complex modulus G*, phase angle δ, the gel point, and linear viscoelastic region LVER were selected to describe the viscoelastic behaviour of the tested products. The only viscoelastic solids with a bicoherent 3D gel structure are the RejuvaSil gel and ScarEsthetique cream. Stratamed and Scar gel Dr. Max, and also the formulated gels are viscoelastic fluids. ScarEsthetique cream has the highest stiffness, with the value of complex modulus approximately 5000 Pa. The Rejuvassil gel follows with an order of magnitude lower stiffness. Formulations characterized as viscoelastic fluids have a G* values ranging from approximately 10 Pa to around 70 Pa.

Keywords: silicon; gel; scar treatment; flow behaviour; oscillation test; viscoelasticity.

2 ABSTRAKT

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Katedra farmaceutické technologie
Školitel: PharmDr. Eva Šnejdrová, Ph.D.
Studentka: Ghazal Khorsand
Název práce: Reologické vlastnosti silikonových gelů pro hojení jizev

Diplomová práce je zaměřena na testování tokových a viskoelastických vlastností gelů pro hojení jizev na bázi silikonů, a to komerčně dostupných nebo nově formulovaných. Teoretická část se zabývá vznikem jizev, léčbě jizev a charakterizací gelů. V experimentální části byly provedeny rotační a oscilační testy na rotačním reometru. Získané tokové křivky byly popsány Newtonovým nebo mocninným modelem. Pro charakterizaci a srovnání gelu byly použity dynamická viskozita, nebo koeficient konzistence a index tokového chování. Nejvyšší viskozitu vykazoval krém ScarEsthetique, následoval RejuvaSil gel. Stratamed a Gel na jizvy Dr. Max překvapivě vykazovaly nejnižší viskozitu, dokonce nižší než formulace ve fázi vývoje. I když je v názvu přípravků uvedeno „gel”, jedná se o newtonské tekutiny. K popisu viskoelastického chování testovaných formulací byly vybrány modul pružnosti G', viskózní modul G" a komplexní modul G*, fázový úhel δ, bod gelace a rozsah lineární viskoelastické oblasti LVER. Charakter viskoelastické pevné látky s bikoherentní 3D gelovou strukturou mají pouze RejuvaSil a ScarEsthetique. Stratamed, Gel na jizvy Dr. Max a formulované gely jsou viskoelastické tekutiny. Nejvyšší tuhost má ScarEsthetique krém s hodnotou komplexního modulu přibližně 5000 Pa. Následuje Rejuvassil gel s G* o řád nižší. Formulace ve fázi vývoje, charakterizované jako viskoelastické kapaliny, mají hodnoty G* v rozmezí přibližně 10 Pa až přibližně 70 Pa.

Klíčová slova: silikony; gel; léčba jizev; tokové chování; oscilační test; viskoelasticita.

3 THE AIM OF STUDY

The aim of this diploma thesis was to measure and evaluate the flow and viscoelastic properties of three non-commercial silicone-based scar treatment gels and four commercially available preparations.

The assignment can be expressed in the following steps.

- Study of scientific references to elaborate on the topic's theoretical section.
- Rheological testing of the samples using an absolute rheometer.
- Optimization of the rotational and oscillation testing methods.
- Assessment of the flow curves using appropriate models.
- Selection of characteristics suitable for the description of viscoelastic properties of the tested gels.
- A comparison of tested gels based on selected rheological characteristics.

4 INTRODUCTION

Although the occurrence of traumas and post-surgical scarring is rather high, scar treatment has long been a challenging process for cosmetics and pharmaceuticals developers. Silicone-based products have been one of the most efficient scar treatments since silicone assists the scar healing process through many different mechanisms owing it to its occlusive and moisturizing characteristics. Furthermore, they tend to reduce irritation, redness, and the pain caused by the scar.

Many scar gels have been developed in recent years, but manufacturers are constantly trying to come up with better and more effective formulas by changing the additive ingredients. However, to compare the properties and observe the improvement of the new formulations with the older ones, analysis should be performed based on the rheological characteristics, spreadability, texture profile, etc.

The work follows the diploma thesis of Alena Podzimková,[1] which tested particularly the composition, physio-chemical properties, and also the rheological behaviour of selected gels and compare their attributes to similar commercially available samples.

5 THEORETICAL SECTION

5.1 Wound Healing and Scar Formation

Scar formation is the body's way of responding to injuries caused by an accident, surgery, burns, or skin diseases. The wound healing process is divided into three discrete phases. The inflammatory phase takes place instantly after the injury to protect the tissue from blood loss, possible infections, and to eliminate dead parts by stimulating various signalling mechanisms such as blood coagulation, immune system response, and inflammatory pathways.[2] This process is carried out through the release of various chemical mediators, white blood cells, growth factors, hormones, and other components from platelets and parenchymal cells.[3,4]

After about three days, the wound enters the proliferative phase, during which new capillaries form, keratinocytes create a barrier over the wound surface, and fibroblasts form the scar by generating a collagen network. Keratinocytes are produced as a result of the release of cytokines and growth factors, migrated to the injured tissues and multiplied to adequately enclose the wound. This phase lasts about three to six weeks.[5]

The epithelialisation process begins a few hours after the injury and can last for up to a year. During this phase, most mediators either perform apoptosis or evacuate the wounded area, leaving a scar composed primarily of collagen and other proteins.[2,3] The balance between production and degradation of these particles is the major factor in achieving a firm and consistent scar. The injured tissue continues to remodel over time, and the collagen structure becomes more integrated.[6]

Scars are classified into three types: atrophic, hypertrophic, and keloids. Atrophic scarring occurs below the normal skin level as a result of collagen destruction caused by inflammatory mediators and enzyme release. It is commonly associated with acne scars.[7]

Hypertrophic scars and keloids, on the other hand, form because of excessive collagen production, with hypertrophic scars forming only within the wound boundaries and mostly receding to the natural skin layer, and keloids expanding in size by invading the surrounding tissues and not fading away to the adjacent skin.[8]

Hypertrophic scars typically appear shortly after the trauma, whereas keloids might take months to develop.[9]

According to clinical studies, keloid development is linked with genetic predispositions, and it typically runs in families. The incidence also rises with increasing skin pigmentation, and it is the most common in darker-skinned populations, with whites having the lowest incidence.[8,10]

5.2 Scar Treatment Options

In general, it is preferred to prevent the formation of a scar since its treatment might be challenging, however this process is unavoidable in some cases.[11] As a prophylactic and non-invasive option, we can mention compression therapy, mostly employed for burn scars. It can inhibit scar development by promoting collagen breakdown as a result of decreased blood, oxygen, and nutrient delivery to the tissue. Although, this procedure is inconvenient for the patient since it requires applying pressure to the area 23 hours a day for at least six months.[12,13]

One of the most popular methods of scar prevention is the use of silicone-containing products. Silicone works by hydrating and obstructing the skin barriers, and it has been shown to help with itching and pain, as well as the size and appearance of the scar.[12,13] Some studies have also shown that topical treatments containing flavonoids or onion extract can alter fibroblast production, resulting in less scar formation. Onion extract also has antibacterial and anti-inflammatory properties, which aid in wound healing.[11,14,15]

Intralesional corticosteroid injections is one of the most efficient scar treatments. The mechanism of action is primarily triggering collagen decomposition and glycosaminoglycan formation by reducing inflammation, which inhibits fibroblast synthesis. Triamcinolone acetate is the most often administered medication, however other corticosteroids such as hydrocortisone acetate, methylprednisolone, and dexamethasone are also used.[16,17,18,19]

Even though corticosteroids play a significant role in scar repair, this medication has several drawbacks. Injection of corticosteroids into the lesion is frequently associated with excruciating pain and can result in both hypo- and hyperpigmentation of the skin, atrophy of adipose tissues, rebound phenomena, and development of resistance.[20,21]

Bleomycin, verapamil, and 5-fluorouracil (5-FU) are additional injectable possibilities for scar treatment. Bleomycin is an antineoplastic that suppresses collagen formation in both keloids and hypertrophic scars. Another anticancer drug that can be used with or without corticosteroids is 5-fluorouracil (5-FU). This medicine appears to be an effective and safe alternative and it operates by changing fibroblast proliferation. Verapamil is a calcium channel blocker that works by lowering intracellular calcium levels, causing collagenase overproduction.[11,12,22]

Cryotherapy is an invasive method that involves freezing the affected tissue with liquid nitrogen, inducing vasoconstriction followed by hypoxia, and, eventually, necrosis of excess tissue.[11,23] Surgical techniques are examples of different sorts of invasive therapy. Because surgery has a high recurrence rate, it is strongly recommended to include adjuvant therapies, such as those already discussed or radiation and laser therapy.[23,24]

Radiotherapy is believed to be the most beneficial adjuvant treatment to surgery. Despite being an effective therapy, it is contraindicated for pregnant women, children, or scars in radio-sensitive areas.[20,23] There are also several laser techniques, and they are chosen based on the type of the scar and the patient's preferences. The mechanisms of action differ in ablative and non-ablative methods. Ablative approaches include 2940-nm erbium-doped yttrium aluminum garnet (Er:YAG) laser and the 10 600-nm carbon dioxide (CO2) laser. The laser beam emitted by them is captured by water molecules in the skin, resulting in tissue damage.[17,22]

Non-ablative methods, such as 585-nm or 595-nm pulsed dye laser, and 1064-nm neo-dymium-doped:yttrium-aluminium-garnet (Nd:YAG) laser cause thermal damage to the skin, which results in ischemia. Thus, it is necessary to cool down the skin when doing laser therapy in order to minimize superficial damage to the skin.[17,22,25]

5.3 Silicone in Scar Treatment

As previously stated, silicone-based products are commonly used in the treatment and prophylaxis of scars. Available forms of silicone in the market are silicone gel sheets, creams containing silicone oil, and silicone gels. Silicone gel dressings are semi-permeable sheets that, while efficient, they are inconvenient for the patients due to their difficult application, the skin's reaction to the adhesive tape, and excessive perspiration.[12,23,26]

Another type of topical dosage form is silicone-oil-containing cream, which has been demonstrated in studies to reduce scar manifestation; however, it is more effective when used in combination with an occlusive water-resistant dressing. On the other hand, topical silicone gel has been reported to be equally effective as silicone gel sheets. When the gel is applied to the skin, it dries out to form a fine, water-impermeable, transparent layer of silicone over the scar, which facilitates the healing process.[12,17,26]

5.3.1 Characteristics

Silicones are polymers consist of dimethylsiloxane monomers. They have a repeating silicone-oxygen backbone with organic groups connecting straight to the silicone atom. Its physio-chemical properties make the rotation around the bonds and certain deformations possible. The structural correlation with the physical characteristics of the polymer is a great benefit for its pharmaceutical preparation and manufacture. The silicone-oxygen bonds have greater angles than those of carbon-oxygen bonds. Carbon-silicone bonds are also longer than carbon-oxygen and carbon-carbon bonds. Because of these structural differences, molecules are modified to achieve the optimal physical properties.[27,28,29]

Three kinds of silicones are used for scar treatment:

1. Silicone fluids: they are polydimethylsiloxane (PDMS) chains that are short, unbound, and straight.
2. Silicone gels: these are PDSM chains that have been cross-linked, generally explained by the presence of a catalyst.

3. Elastomers: these are long, severely cross-linked PDMS chains that are also formed in the presence of a catalyst.[9]

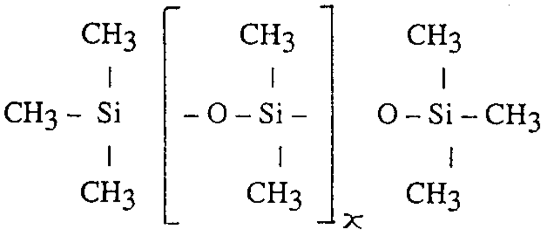


Figure 1. A silicone polymer's chemical structure

5.3.2 *Mechanism of Action*

Many clinical studies have shown that silicone has a significant impact on the treatment and prevention of scar. It is highly advised to apply the silicone-containing product to the scarred tissue for 12 to 24 hours each day for at least two to three months. Different mechanisms imply the action.[30]

Increased skin surface temperature by 1.7 °C might be one factor, since this slight temperature rise can stimulate collagenase activity, resulting in the breakdown of excess collagen.[26]

The occlusive and hydrating properties of silicone are two further mechanisms by which it influences scar formation. When the outermost layer of epidermis, also known as stratum corneum, becomes dehydrated, it initiates a signaling pathway to retain water by directing keratinocytes to generate cytokines.[30] Cytokines then stimulate fibroblasts to produce collagen.[26] Because of its semi-permeable qualities, silicone dressing and gel prevent water evaporation and keep the area moist. Silicone provides the same amount of hydration as unwounded normal skin since extreme occlusion caused by other form of dressings such as plastic dressing can be ineffective.[31,32]

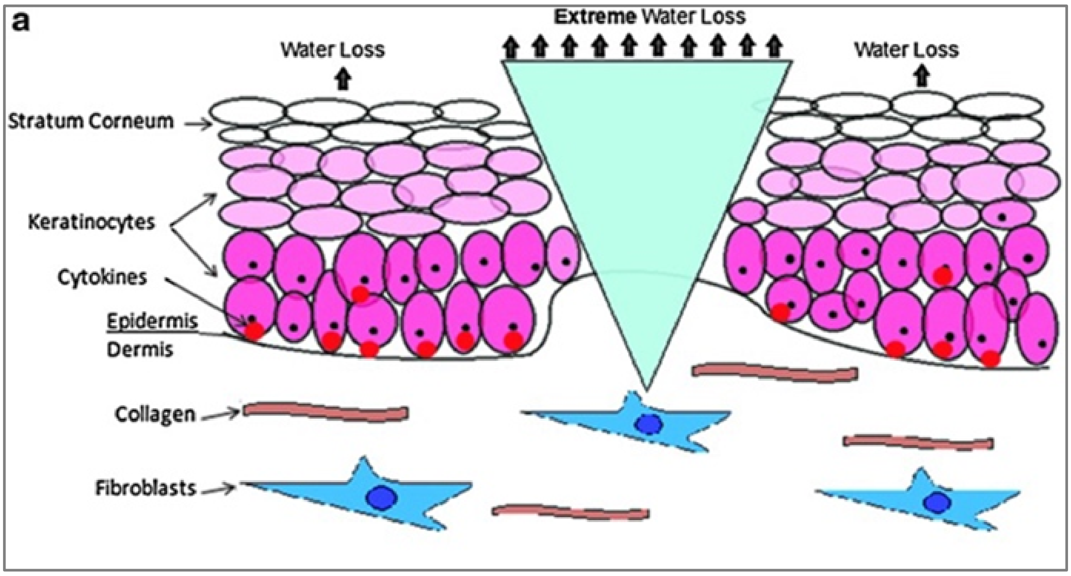


Figure 2a. Water evaporation under extreme conditions.[31]

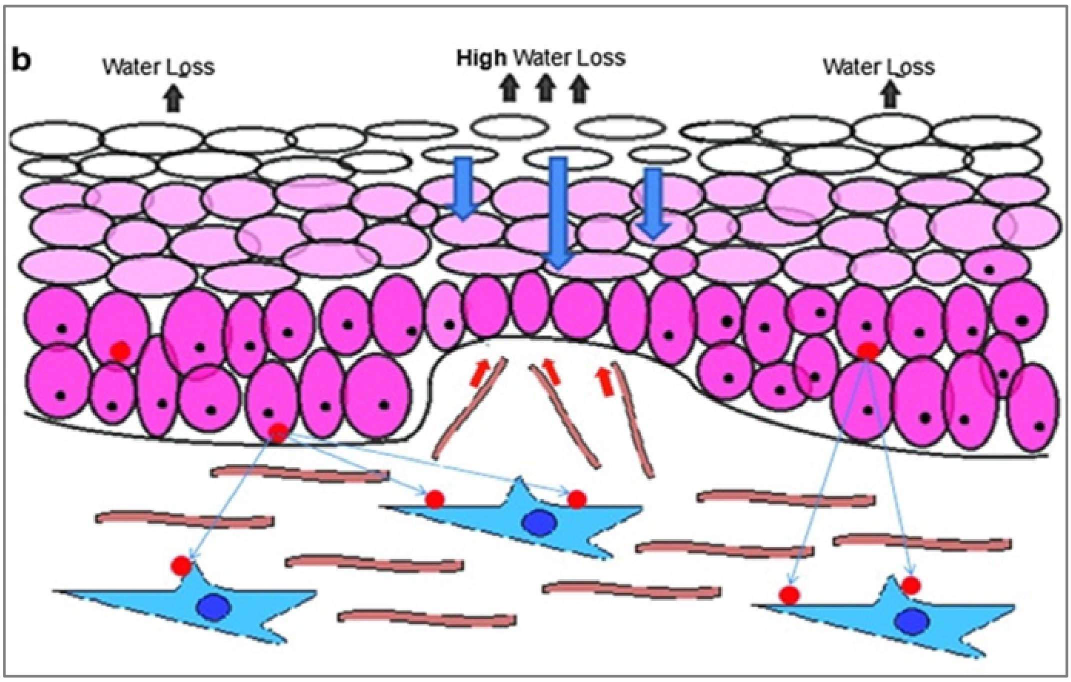


Figure 2b. Water evaporation under high conditions.[31]

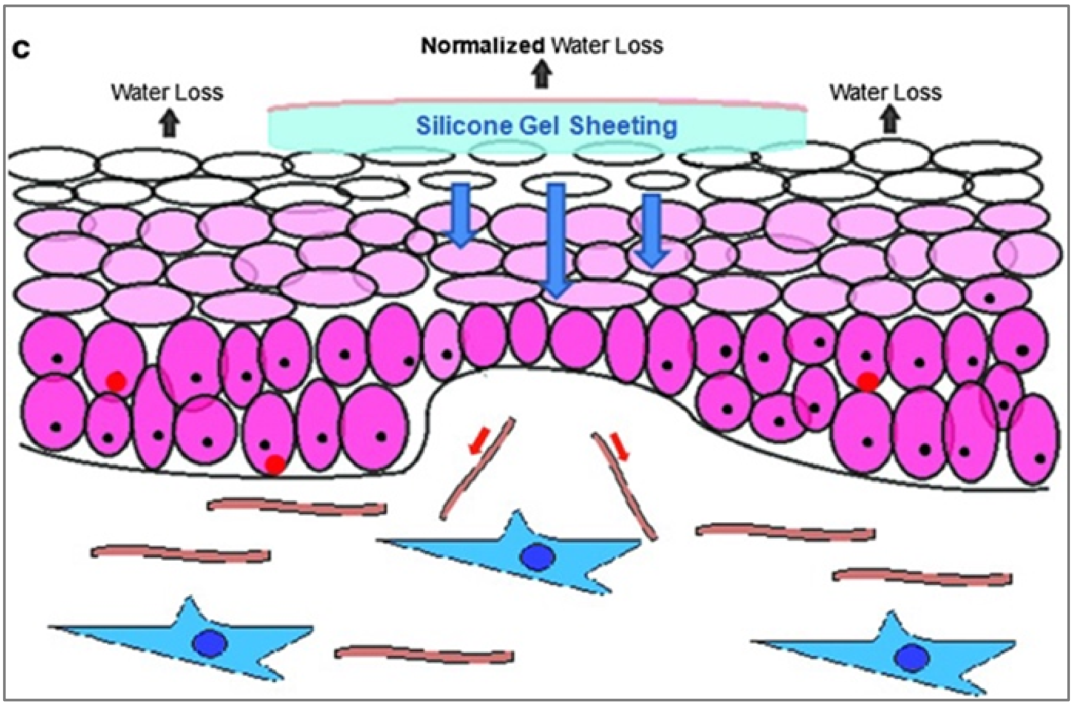


Figure 2c. Water evaporation under normalized conditions.[31]

The generation of a negative static electric field when the skin is in constant contact with a silicone cushion (a silicone occlusive sheet containing silicone oil) might affect collagen alignment and result in scar regression. The cushion provides greater friction than other types of silicone, and the unique dynamic movement between the silicone oil leaking from the cover and the skin makes this effect exclusive to the silicone cushion.[26,30,33]

As previously stated, the stratum corneum maintains water by hydration with the assistance of silicone. This permits oxygen to flow more easily through the skin, and the oxygen tension in the region rises as a result of the gas-permeability of silicone applied to the wound. Angiogenesis is inhibited by higher oxygen pressure. Hypoxia is caused by a decrease in blood, oxygen, and nutrient supply, as well as a drop in mast cell concentration. Histamine synthesis decreases, resulting in scar improvement.[34] Histamine is a mast cell mediator that stimulates migration, proliferation, and differentiation of fibroblasts.[35]

Aside from its preventive and therapeutic properties, silicone also plays an essential role in the decrease of wound pain and pruritus. Clinical investigations show that this effect is caused by a reduction in mast cell concentration and an increase in fibroblast Fas antigen expression.[30]

5.4 Gels

Gels are semi-solid preparations that are generally composed of two constituents. A solid gelling agent and a liquid medium. Due to the three-dimensional structure of the gel, the liquid medium is trapped and enable to move. Based on the liquid nature, gel can be either hydrophilic or hydrophobic. Different approaches are used to classify gels. They are classified based on the nature of their colloid phase, solvent, and rheological properties.[36,37]

The gelling agent should be easily affordable, inert, safe, and incapable of reacting with other formulation components. While stored, the gelling agent is meant to obtain a solid-like structure that will easily break when exposed to shear. These forces can be exerted by shaking or squeezing the container, as well as spreading the gel on the skin. Gels should have anti-microbial property and have a non-sticky consistency. It is also important to note that the apparent viscosity of the gel may increase or decrease as the temperature rises, depending on the interactions between the polymer and the solvent at molecular level.[36,37,38]

5.4.1 Types of Gels

In (Table 10), you can find a summary of the different kinds of gel based on the nature of their liquid medium, basic properties, advantages, disadvantages, and their uses.[36,39]

Table 1. Polymeric gels and their characteristics, advantages, disadvantages, and major use in the field of pharmacy.[36,39]

	Characteristics	Advantages	Disadvantages	Uses
HYDROGELS	hydrophilic gelling agent can swell by absorbing a large amount of liquid	low cost, biocompatible, harmless, and flexible; can interact with a wide range of substances, the fundamental part of many other gels, high sensitivity to external factors, good spreadability and cooling effect	low mechanical strength, not suitable for lipophilic substances, possible microbial contamination due to the polysaccharide nature	treatment of atopic dermatitis, eczema, anti-inflammatory products, wound treatment, anti-scar activity, skin regeneration; dressing materials, dental materials, super-absorbents, medical implant components
ORGANOGELS	the gel network can reverse its properties by heating, non-polar gelling agent is captured in the three-dimensional structure	easy formulation, inexpensive, biocompatible, thermodynamically stable, higher mechanical strength, proper carrying agent for lipophilic compounds, higher resistance to microbial contamination	better function with lipophilic particles, heat has a strong influence on their stability, greasy texture, and not readily washed	skin care, base in wound healing products, drug carriers in transdermal systems, parenteral agents, bioadhesive agents, vaccine preparations, rectal products

Table 1. continuation[36,39]

	Characteristics	**Advantages**	**Disadvantages**	**Uses**
EMULGELS	gels based on emulsions that can be o/w or w/o by adding a surfactant	simple and affordable preparation, biocompatible, long durability, ideal carrier option for controlled release delivery system, thixotropic, quickly spreads, and leaves no stains	air bubbles can form during the formulation process, and the surfactant in them might lead to undesired skin irritation	analgesic, anti-inflammatory preparations skin softening, moisturising effect treatment of various kinds of skin disorders
BIGELS	a combination of hydrogel and organogel without addition of surfactants	basic formation, no additional emulsifier, diversified activity owing to the presence of both lipophilic and hydrophilic parts, cooling effect, washability, and good spreadability	phase separation due to lack of emulsifier unstable at higher temperatures	analgesic, anti-inflammatory preparations, carrier for antibiotics, moisturising and care products

5.4.2 Nature of the Gel

Gels are composed of structural network formed by polymers. These polymers can be natural polymers, such as proteins or polysaccharides, semisynthetic cellulose derivatives, such as methylcellulose, or the synthetic ones, like carbomer. They can also contain inorganic substances such as bentonite or aluminium hydroxide, as well as surfactants.[36] The presence of the network accounts for the gel’s rigid structure. The nature of the polymeric particles and the type of bonding between these particles determine the properties of gel.[38]

Swelling: If a gelling agent is consistently in touch with a sufficient amount of its solvent, it begins to absorb the liquid and expand in volume. This is referred to as swelling. The swelling rate is determined by the quantity and strength of bonds formed between the molecules and the gelling agent.

Syneresis: The evacuation of some discharged liquid, appears in different gels. With increasing the concentration of gelling agent, the incidence of syneresis decreases. This phenomenon reflects the thermodynamic instability of the original gel.

Ageing: The process of agglomeration generally happens slowly and spontaneously. This is referred to as ageing, and it results in the gradual condensation of the gelling agent’s structure.

Structure: The presence of a network generated by the intermolecular interactions of the gelling agent, gives gels their rigid structure. The particles’ nature and the pressure applied straighten them out and improve their flowability.

Rheology: The nature of gelling agent solution and flocculated dispersion is pseudoplastic, which means that their viscosity decreases with increasing shear rate.[37,38]

5.5 Rheological Behaviour of Gels

Gels are viscoelastic materials possessing both viscous and elastic properties. Depending on the applied pressure, they have both solid-like and liquid-like qualities.[40] Under small stresses, these materials deform elastically and begin to flow when the stress reaches a particular threshold known as yield stress.[41]

The true value of yield stress is exceedingly difficult to determine since the value varies frequently as the materials are affected by the testing and measuring methods, as well as the testing conditions.[42] While yield stress can be apparent in everyday activities such as squeezing a toothpaste out of the tube, a glassy liquid can behave like a solid under sudden pressure and flow like a liquid when the duration of the pressure is prolonged and yet display no true yield stress. Which is why the apparent yield stress is introduced, and it indicates the specific stress at which a noticeable reduction in viscosity occurs.[43]

5.5.1 Rotational Testing

A rheometer determines the viscosity by generating a definite shear stress/rate. The rotational speed is translated to shear rate using a conversion factor, and the torque is converted to shear stress using a conversion factor, which is generally done by the instrument. Shear rate is typically preset when doing a rotational test, which means that the equipment transforms the given shear rate into speed to detect the torque and convert it to shear stress. A flow curve is how this sort of measurements are called.[44]

The flow curve is a graph of the correlation between shear stress and shear rate.[45] It can provide viscosity at zero shear rate, the rate at which viscosity starts to drop, commonly known as the critical shear rate, and how fast the viscosity reduces when subjected to significant stress.[46]

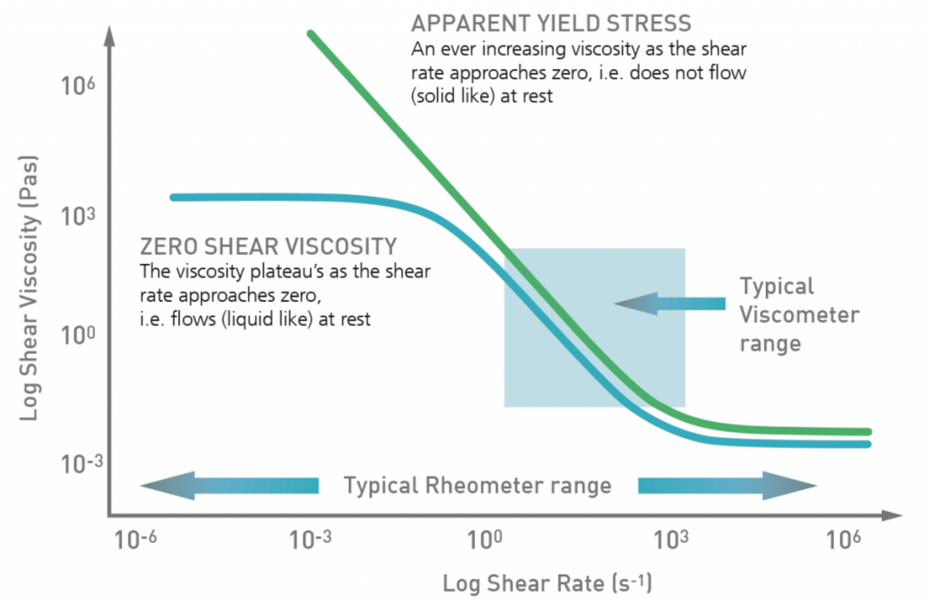


Figure 3. since various processes require different shear rate ranges, a rotational rheometer can detect viscosity over a broader range.[47]

5.5.2 Model Fitting

The aim of rheology science is to develop models for describing the behaviours of substances under specified stress. In the form of mathematical models, the relationship between rheological parameters such as stress, strain rate, and stress growth rate has been defined.[46]

The constant shear stress over a variety of shear rate is assessed to determine which models are best suited for the sample, and the correlation coefficient is used to demonstrate the proper fit.[43]

Rheological models are commonly used to describe the flow behaviour of pharmaceutical excipients and preparations. They can be categorised as Newtonian or non-Newtonian. The Newtonian model describes the most basic fluid flow behaviour; a linear constant that shows a proportionate relationship between shear stress and shear rate under constant temperature and pressure is the fluid viscosity. Newtonian fluids begin flow rapidly as the force is applied, and the shear stress rises as shear rate increases. The graph of shear stress versus shear rate for

Newtonian fluids creates a straight line that goes through the origin of the plot parameters, and the Newtonian, or dynamic, viscosity of the fluid is the slope of the line (Figure 4).

Pharmaceutical systems are mostly non-Newtonian. There is no corresponding connection between shear stress and shear rate for these materials; their viscosity varies as their shear rate changes. The most interesting models in pharmaceutical technology are the Bingham plastic, power-law and Herschel-Bulkley models. Majority of the substances do not comply to a single model precisely, but rather to a variety of models.

The power-law model is based on the assumption of a non-linear correlation between the shear stress and the shear rate. The shear stress grows as a function of the shear rate raised to a constant exponent in power-law models. At low shear rate measurements, this model is a well fit. Compounds with Bingham plastic behaviour do not flow until the shear stress reaches above a threshold value known as the yield point. Changes in shear stress and shear rate are proportional once the yield point is achieved. The plastic viscosity is defined as the proportionality constant or the slope of the curve.

The Herschel-Bulkley model is a combination of the effects of Bingham and power-law behaviour in a substance; the model is applicable to those materials with a yield stress and a nonlinear connection between the shear stress and the shear rate. The power-law and Herschel-Bulkley curves are determined by a coefficient of consistency K ($Pa \cdot s^n$) and an index of flow behaviour (or power-law exponent) n (dimensionless).

Many of non-Newtonian fluids are affected by shear rate. Some non- Newtonian fluids are useful in the pharmaceutical technology because their viscosities fall as the shear rate increases but subsequently rise, or gel, when shear ends. Thixotropy is indicated by the continuous increase in gel strength, which relies on how long the material has been at rest.[48]

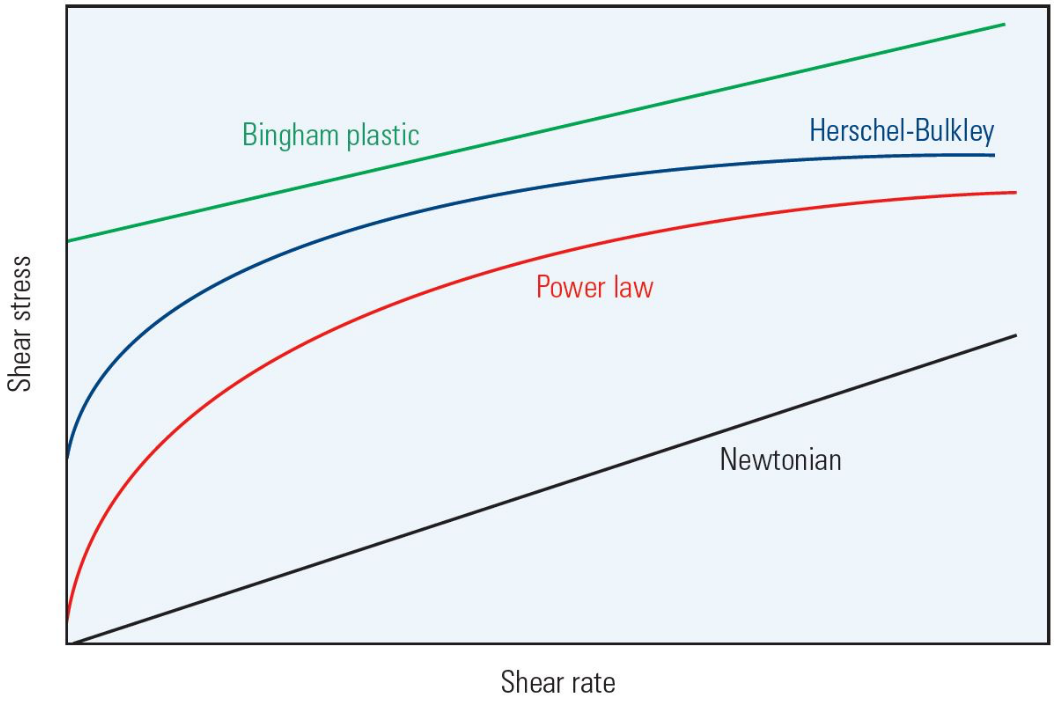


Figure 4. Rheological models.[48]

5.5.3 Oscillation Testing

A small amplitude oscillatory stress or strain is applied to the gel to gather information on its viscoelastic behaviour under minor deformations.[49] The test can be done using an absolute rheometer and it is recommended to use cone and plate or parallel plate geometry.[50] The variations in elastic modulus (G') or elastic stress (σ') with increasing amplitude are observed as the oscillatory stress/strain increases.[43]

Because oscillatory motion is so like a circular motion, a whole oscillation cycle is equal to a 360° or 2π radian rotation. The amplitude of the oscillation determines the maximum stress/strain imposed, and the frequency indicates the number of oscillations per second. To operate the test with a parallel plate, the sample is applied between the plates with an indicated gap. The top geometry oscillates constantly at a given stress or strain amplitude and frequency.[40]

Essential information on the sample's stiffness, elasticity, structural strength, and deformation cab be presented with this test. The Complex Modulus G* measures sample rigidity; the higher it goes, the more rigid the structure. The phase angle δ demonstrates the degree of elasticity and therefore springiness of the formation; the closer it is to 90°, the more fluid-like the sample behaves. A simple G* vs. phase angle δ graph can display relative stiffness and elasticity (Figure 5).[50]

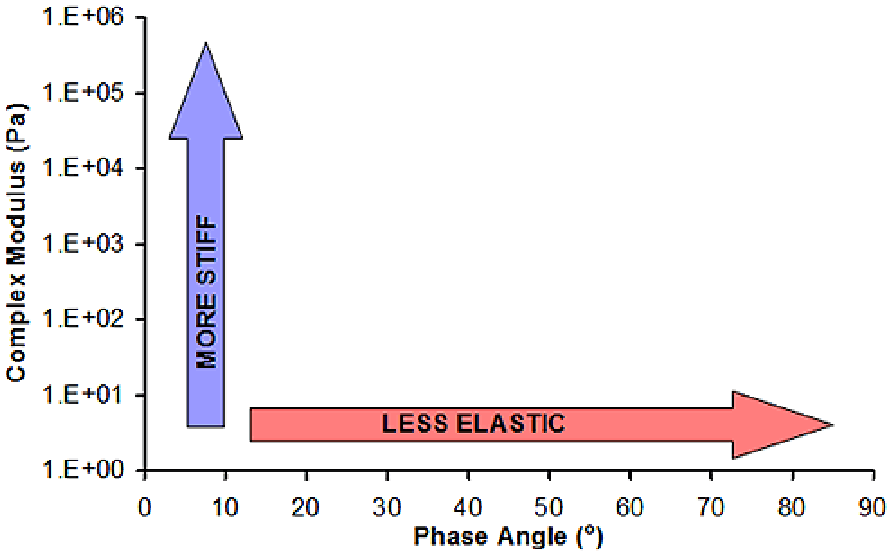


Figure 5. Phase angle verses complex modulus graph.[50]

This test can also provide additional information such as yield stress and yield strain, which reflects structural strength and the extent of structural deformation. The yield point is indicated, and the measured values of stress and strain at this point are yield stress and yield strain, respectively. This data can be helpful for benchmarking products.[50]

The maximum stress happens at maximum strain in an entirely elastic sample where the stress is proportional to the strain. Deformation is the highest at this point, and stress and strain are considered to be in phase. In the case of a purely viscous substance, where stress is proportional to strain rate, the maximum stress arises when the strain rate is the greatest. In this time, flow achieves its maximum, and stress and strain are out of phase by 90°. For viscoelastic materials, the phase difference between stress and strain is between the two extremes (Figure 6).[40]

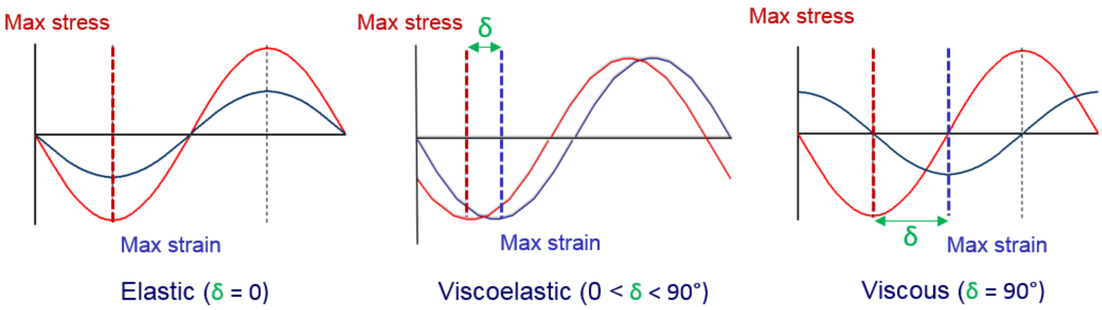


Figure 6. The relationships between stress and strain wave for a purely elastic (ideal solid), purely viscous (ideal liquid) and a viscoelastic substance.[40]

This phase difference permits the viscous and elastic components to facilitate the total material stiffness G* determination; phase angle δ is a relative measure of the material's viscous and elastic properties. Purely elastic materials have a δ value of 0°, whereas pure viscous substances have a δ value of 90°. Because viscoelastic materials have both properties, their phase angle δ will be between 0° and 90°, while 45° indicates the borderline between solid-like and liquid-like behaviour.

The storage modulus G' provides the elastic contribution to G* since G' shows energy storage, whereas the viscous contribution is referred to as the loss modulus G" because it represents energy loss.

When viscoelastic properties are being measured, it is necessary to perform the measurements in the material's linear viscoelastic region (LVER), where stress and strain are proportionate. The imposed stresses in that area are insufficient to breakdown the structure. When the applied stress is increased above the yield stress, the curve exhibits non-linearity, indicating the point at which G' becomes a stress or a strained dependent (Figure 7).[40]

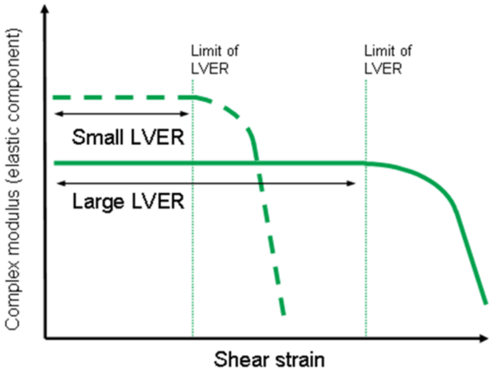


Figure 7. Graph showing the LVER for different materials as a function of applied strain.[40]

Because G' and G'' are not material constants, which clastic materials exhibit time dependency. The time dependence can be examined in an oscillatory test by altering the frequency of the applied stress or strain, with high frequencies relating to short time scales and low frequencies referring to longer time scales. At high frequencies, G' is greater than G'' and thus solid-like behaviour dominates ($\delta < 45°$), but at low frequencies G'' is more than G' and solid-like behaviour predominates ($\delta > 45°$).

G' and G'' are parallel in a gel-like substance, and phase angle δ is has constant value between 0° and 45°. Both viscoelastic solid and gel-like materials exhibit yield stress behaviour because macroscopic flow requires the breaking of any related structures.[40]

5.6 Commercially Available Silicone-Based Scar Gels

Stratamed, manufactured by Stratpharma AG in Switzerland, is a popular scar gel made of polysiloxanes, and siloxane resin. When it is applied to the skin, it dries and produces a silicone gel sheet with semi-occlusive qualities. It softens and flattens the scar while also lowering the redness, itching, and discomfort. This gel can also be applied to open wounds facilitating the epithelialisation process.[51]

Dr. Max scar gel is used to treat scars and also stretch marks. Because it cannot be used on open wounds, it should be applied two to three weeks following the injury or surgery. It is made up of PDMS, PDMS cross polymer, and trimethylsiloxane silicate. Like every other scar gel, it needs to be applied 24 hours a day for a minimum of three months.[52]

Rejuvasil is a scar gel produced by the American company Rejuvaskin. Aside from liquid silicone, it also includes vitamin C, which helps the product penetrate the skin easier, a plant-derived component, squalene, and Emu oil, all of which have moisturizing and antioxidant effects.[53]

ScarEsthetique is another product from the Rejuvaskin manufacturer. It is a silicone-based cream containing numerous botanicals, polypeptides, and antioxidants that primarily target scar hyperpigmentation rather than scar size and height. It is indicted for those with minor surgical scars and those who are not allergic to natural substances.[54] This cream contains anti-inflammatory ingredients such as onion bulk extract, Calendula flower, and Arnica Montana flower.[55]

6 EXPERIMENTAL SECTION

6.1 Tested samples

Stratamed, Stratpharma AG (Switzerland)

Scar Gel Dr. Max, Dr. Max (Czech Republic)

RejuvaSil, Scar Heal Inc (USA)

Scar Esthetique Scar cream, Scar Heal Inc (USA)

Scare treatment gel marked F1, F2, F3 (preparations at the formulation stage)

6.2 Measuring Methods

6.2.1 Initiation of the Rheometer

Testing of the rheological properties of the scar treatment gels was performed using an Absolute Rheometer Kinexus Pro+ (Malvern, UK) equipped with SW r-Space for Kinexus version 1.76

At first, the compressed air and pressure supply had to be monitored and all the covers had to be removed. The software was started after the rheometer had been stabilised for 5 minutes and a green light on the Kinexus device would light up to show that the computer and the machine were linked. Then, according to the properties of the material and type of the test, the upper geometry was then selected and placed into the instrument. The last step in following the software was to set the zero gap. That means, the upper geometry was lowered and meet the lower geometry. Once the zero gap was set, the machine was ready for use and the sample could be loaded.

First, the suitable sequence for the test was selected from the software and the shear rate range was input. After placing the sample on the lower geometry, it was compressed by the upper geometry and the excess sample outside the upper plate was scraped using a plastic spatula as a step known as “trimming”. The measurement was initiated with the sample being covered with a thermostable lid, followed by the temperature and number of samples per decade being chosen.

After removing the sample from the machine, the lower and upper geometries were cleaned with ethanol and water, and the equipment was ready for the next measurement. Three measurements were performed for each sample. Finally, the results were collected, and the flow properties of the samples was analyzed using r-Space software when the experiment was completed.

6.2.2 Rotational Testing

The flow behaviour of the samples was evaluated by using the Toolkit_V005 Shear Rate Ramp – Alternative Flow Curve sequence accessible in the "rFinder" toolbar of the software. The test parameters are in the (Table 2). The flow curves were then mathematically described in either Power law model or Newton model based on the course of the curves. The suitability of the model was determined according to the value of the correlation coefficient demonstrating how well the model fits the data. The closer it gets to one, the better the correlation is between the measurements and the predictions. The coefficients of the Power law model, the index of consistency K ($Pa\cdot s^n$) and index of flow behaviour n (dimensionless), or the shear viscosity η ($Pa\cdot s$) of the Newton model were evaluated using the SW r-Space for Kinexus. The Power law index varies from zero for extremely shear thinning materials to one for Newtonian materials with the constant viscosity. The index of consistency is numerically equivalent to viscosity measured at 1 s^{-1}. The average and standard deviation of the three measurements of newly loaded samples were obtained for the evaluation of the flow behaviour of the tested products as well as for their comparison.

Table 2. Parameters for rotational measurement

Sequence	Toolkit_V005 Shear Rate Ramp – Alternative Flow Curve
Geometry	CP 2/20
Temperature	25 °C
Shear Rate Range	0.1 – 100 s^{-1}
Sample Per Decade	10

6.2.3 Oscillation Testing

The oscillation amplitude sweep test was performed to measure the viscoelastic characteristics of the samples, with the sequence being rSolution_0017 Evaluating product texture using oscillatory testing. After choosing the PU 20 geometry, the sample was loaded, and the measurement began immediately after trimming and placing the thermostable covers on the geometry and the sample.

The relative stiffness of the products given by G*, as well as the phase angle δ of the product indicating its degree of elasticity, are all measured at frequency of 1 Hz and then used to assay the sample texture deformations under increasing amplitude. The average and standard deviation of the three measurements of newly loaded samples were obtained for the evaluation of the viscoelastic behaviour of the tested products as well as for their comparison.

Table 3. Parameters for Oscillation Measurement

Sequence	rSolution_0017 Evaluating product texture using oscillatory testing
Geometry	PU20
Gap	0.5 mm
Temperature	25 °C
Shear Rate Range	0.1 – 100 %
Frequency	1 Hz
Sample Per Decade	10

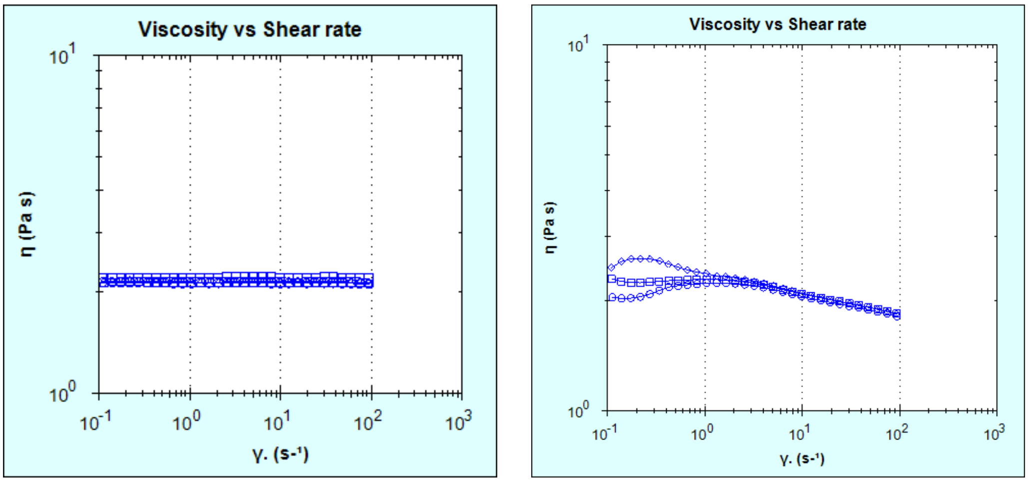
7 RESULTS AND DISCUSSION

An absolute rotatory rheometer Kinexus Pro + Malvern Instruments equipped with SW r-Space for Kinexus 1.76 was used to test the flow and viscoelastic properties of scar treatment semi-solid products that were either commercially available, or formulations under development. The tests Toolkit_V005 Shear Rate Ramp – Alternative Flow Curve and Measure_0036 Single frequency strain controlled temperature ramp were selected from a large number of rotatory and oscillating tests and results analysis methods included in SW r-Space.

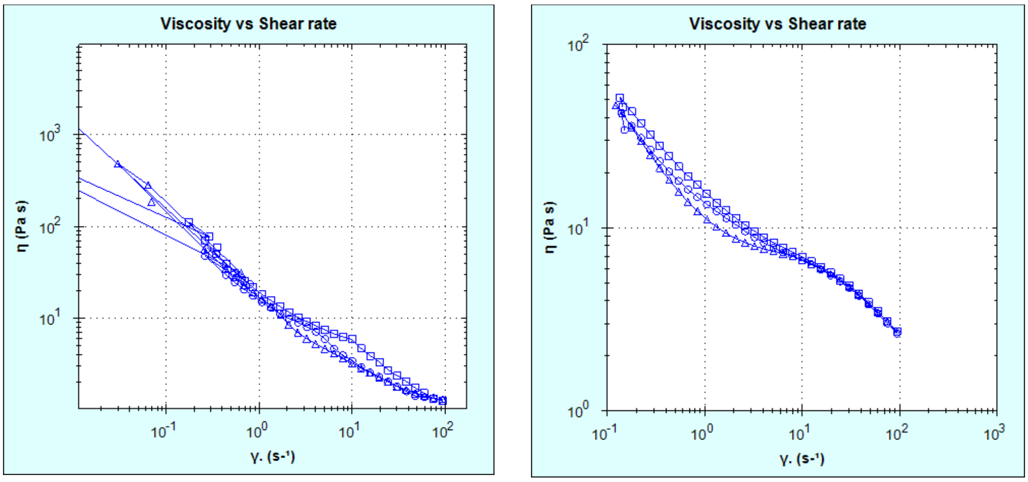
7.1 Flow Behaviour of Silicon-Based Formulations for Scar Treatment

Non-equilibrium (alternative) flow and viscosity curves were obtained from the course of which the type of flow was deduced. By applying a suitable model (see Figure 4), coefficients were obtained to compare the tested gels. The suitability of the model was determined according to the course of the flow curve and the correlation coefficient approaching one.

The viscosity curves for commercial formulations are shown in (Figure 8). Based on the course, Stratamed is a Newtonian fluid with constant viscosity, and without obvious yield point (Figure 8a). The Scar gel viscosity curves show a slight viscosity decrease (Figure 8b), and therefore the power law model was used for fitting. But the index of flow behaviour is close to one, so it is a Newtonian type of flow (Table 5). The significant decrease in viscosity with shear rate is evident on the curves of ScarEsthetique cream (Figure 8c) and RejuvaSil gel (Figure 8d). The Formulation 1, 2 and 3 are viscous Newtonian fluids with just a slight difference in viscosity. Shear viscosity values η (P·s) resp. coefficients of consistency K (P·s^n) are given in (Table 8).



a) Stratamed scar gel b) Dr. Max Scar gel



c) ScarEsthetique cream d) RejuvaSil gel

Figure 8. Viscosity curves for commercial scar treatment product

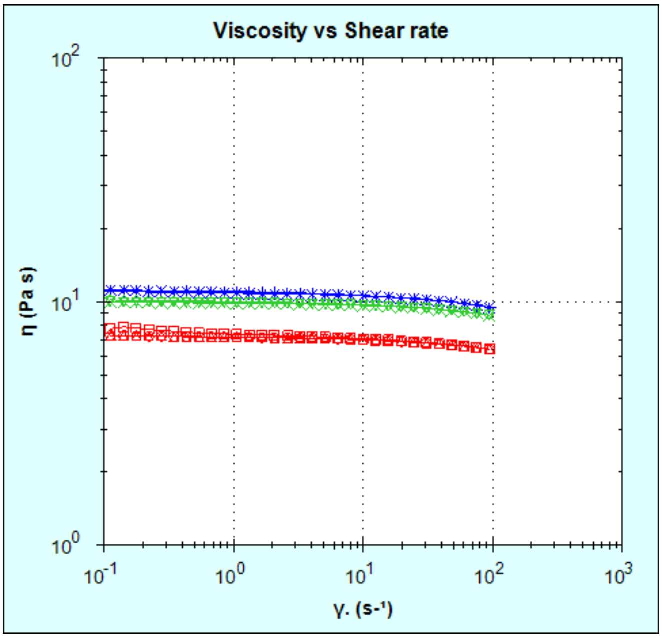


Figure 9. Viscosity curves for non-commercial scar treatment gels: Formulation 1 (red lines), Formulation 2 (green lines), Formulation 3 (blue lines)

Table 4. Shear viscosity of Stratamed scar gel

Stratamed	Newton model	
	Shear viscosity (Pa s)	Correlation coefficient
1	2.197	1.0000
2	2.136	1.0000
3	2.120	1.0000
average	2.151	
SD	0.041	

Table 5. Power law coefficients for Dr. Max Scar gel

Scar gel	Power law model		
	K1 (Pa s^n)	n (-)	Correlation coefficient
1	2.371	0.9468	1.0000
2	2.222	0.9684	0.9999
3	2.121	0.9799	0.9997
average	2.238	0.9650	
SD	0.126	0.0168	

Table 6. Power law coefficients for ScarEsthetique cream

ScarEsthetique cream	Power law model		
	K1 (Pa s^n)	n (-)	Correlation coefficient
1	22.520	0.3318	0.9748
2	18.330	0.3046	0.9151
3	16.230	0.3724	0.9859
average	19.027	0.3363	
SD	3.202	0.0341	

Table 7. Power law coefficients for RejuvaSil gel

RejuvaSil	Power law model		
	K1 (Pa s^n)	n (-)	Correlation coefficient
1	17.800	0.5872	0.9959
2	15.480	0.6206	0.9966
3	14.530	0.6335	0.9905
average	15.937	0.6138	
SD	1.682	0.0239	

Table 8. The values of shear viscosity for F1, F2, F3

	Formulation 1		Formulation 2		Formulation 3	
	η (Pa s)	Corr.	η (Pa s)	Corr.	η (Pa s)	Corr.
1	6.680	0.9997	9.204	0.9997	9.971	0.9995
2	6.650	0.9997	9.201	0.9997	9.967	0.9995
3	6.642	0.9997	9.225	0.9996	9.971	0.9995
average	6.657		9.210		9.970	
SD	0.020		0.013		0.002	

(Figure 10) shows a comparison of the commercial products and formulations under development. The highest viscosity revealed in the ScarEsthetique cream followed with RejuvaSil gel. Surprisingly, the Stratamed scar gel and Dr. Max Scar gel showed the lowest viscosity, even lower than the formulations at the development stage. Although they have "gel" in their name, they behave as Newtonian fluids. Formulation F1 has the lowest viscosity of the formulations developed, Formulations F2 and F3 have approximately the same viscosity.

The gel structure will eventually be demonstrated by oscillation tests.

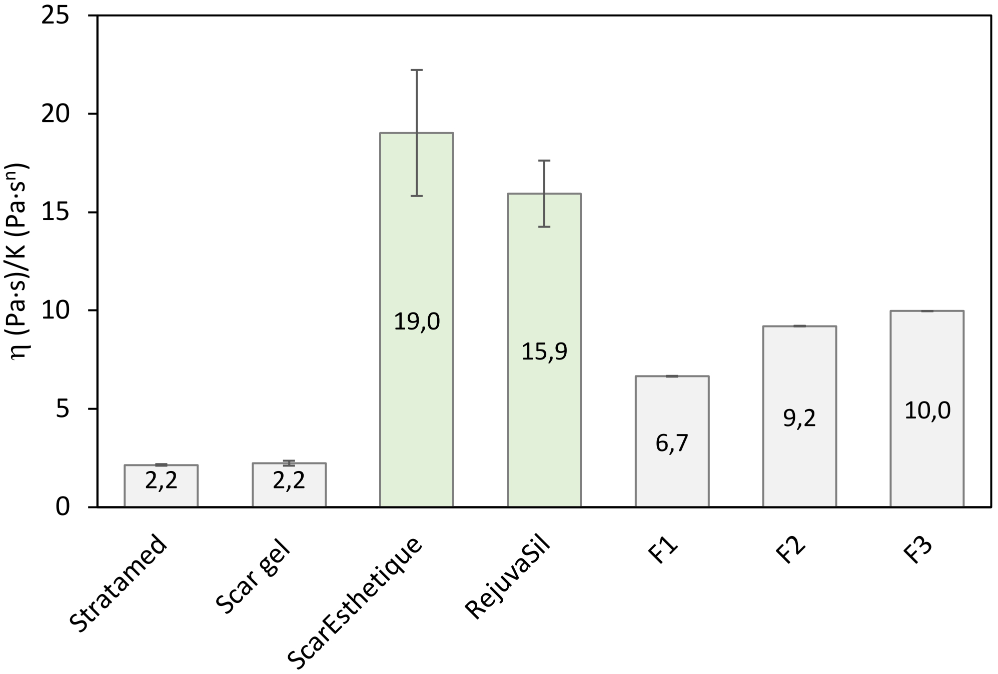


Figure 10. Comparison of shear viscosity η (grey columns), resp. coefficient of consistency (green columns) of commercial and non-commercial formulations.

7.2 Viscoelastic Behaviour of Silicon-Based Formulations for Scar Treatment

The structure of the scar treatment semi-solid formulations was evaluated comprehensively using the rSolution_0017 evaluating product texture in oscillatory testing. The test includes sample loading, oscillating measurements at a constant frequency of 1 Hz in the range of shear stress ν % 0.1 to 100, evaluation of rheological characteristics, data storage and sample unloading. The measurement conditions are given in (Table 3).

The following rheological characteristics were selected to describe the viscoelastic behaviour of the tested products: elastic modulus G', viscous modulus G", and complex modulus G*, phase angle δ (°), the gel point, and linear viscoelastic region LVER. These parameters provide important information regarding gel stiffness, flexibility, and structural strength. The stiffness of the gel is characterized by a complex modulus G*, with higher values indicating a stiffer structure. The elasticity of the gel is related to the phase angle δ, while lower values indicate greater elasticity, i.e., greater flexibility.

(Figure 11-17) show a course of the elastic modules G', the viscous modules G" and the phase angles δ for all tested formulations. Only the elastic modules of RejuvaSil gel (Figure 11) and ScarEsthetique cream (Figure 12) are higher than the viscous modules, which means that these formulations are the viscoelastic solids having a bicoherent 3D gel structure. This is also confirmed by the phase angle values, which are significantly lower than 45°.

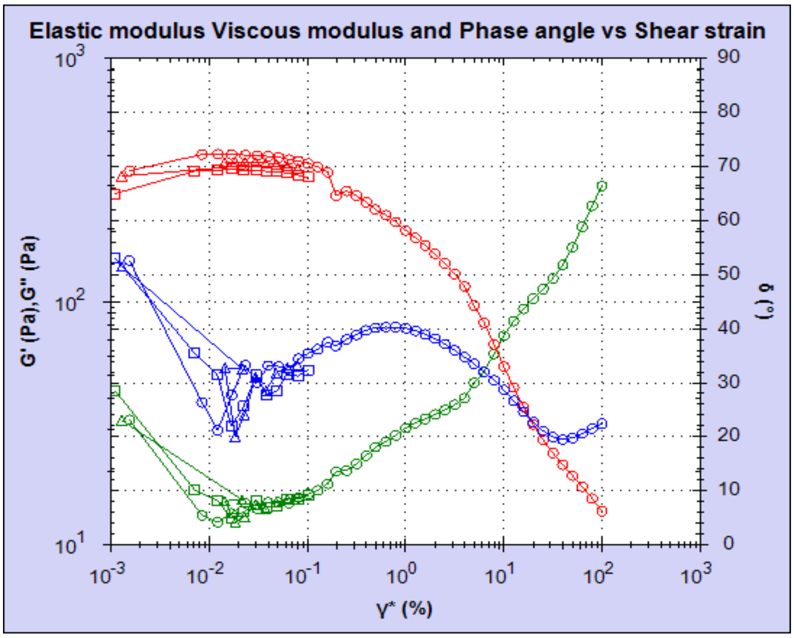


Figure 11. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of RejuvaSil gel

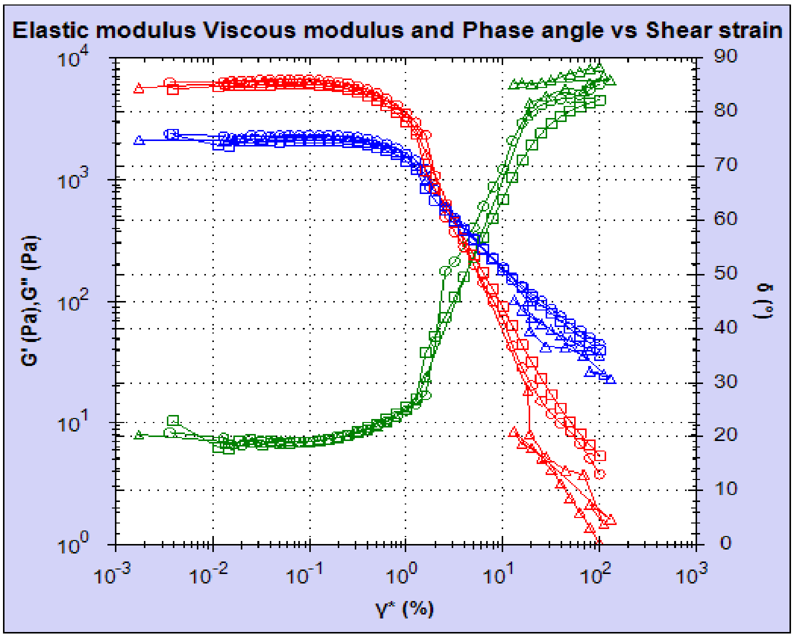


Figure 12. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of ScarEsthetique cream

At the point of intersection of the curves of the elastic modulus G' and the viscous modulus G", i.e., when the values of the elastic modulus and the viscous modulus are equal (G' = G"), the gel structure is destroyed, and the gel-sol transformation takes place. The value is also referred to as a gel point. For RejuvaSil gel, gel point is indicated at about 30 Pa compared to the about 500 Pa for ScarEsthetique cream. It can be stated that the structure of ScarEsthetique cream is significantly stronger than the structure of RejuvaSil gel. The stronger gel structure of ScarEsthetique cream is also verified by the higher extend of LVER (Figure 11 and 12, Table 9).

Table 9. Linear viscoelastic region (LVER) and values of gel point for RejuvaSil gel and ScarEsthetique cream: complex shear strain n (%) and complex shear stress s* (Pa)

Formulation	RejuvaSil gel			ScarEsthetic cream		
	ν %	G* (Pa)	Gel point (Pa)	ν %	G* (Pa)	Gel point (Pa)
1	0.1014	0.3336	31.33*	100.30	40.18	462.6
2	0.0791	0.2829		113.66	36.68	491.7
3	0.1000	0.3442		100.35	44.86	537.9
avrg	0.0935	0.3202		104.77	40.57	497.4
SD	0.0125	0.0328		7.70	4.10	38.0

* Only measurement No. 1 detected the gel point, the measurements No. 2 and 3 were skipped due to slippage

As can be seen in the (Figure 13 and 14), two more commercial scar healing preparations, Stratamed and Dr. Max Scar gel, are viscoelastic fluids as they have a higher viscous modulus G" than the elastic modulus G', and what is more the values of phase angle δ are approaching 90 °.

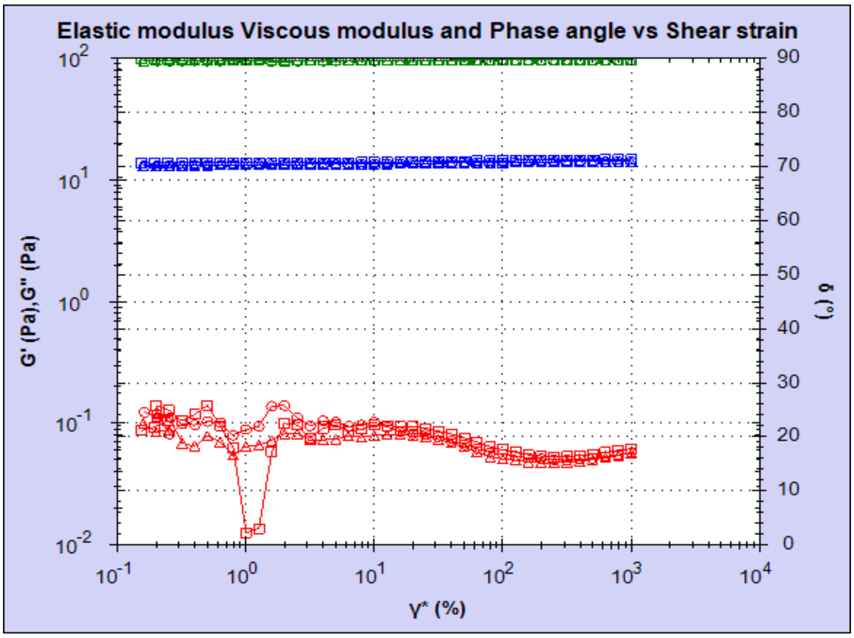


Figure 13. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of Stratamed

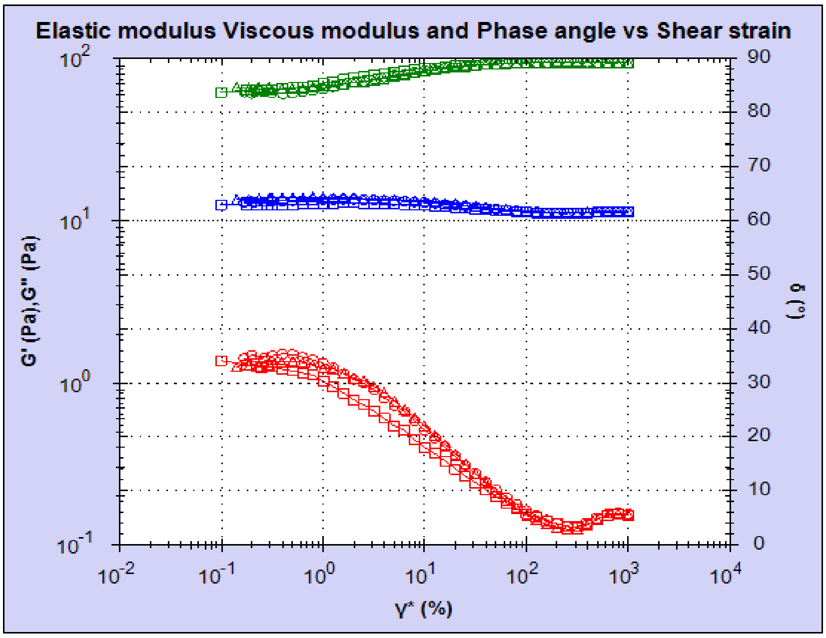


Figure 14. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of Dr. Max Scar gel

The methodology of testing viscoelastic properties, implemented on commercial preparations, was used to test the newly formulated scar healing gels during equivalence studies.

Based on the courses of G", G' and δ of the Formulations 1-3 in the (Figures 15 – 17) can be stated that the formulations are viscoelastic liquids with G" > G' and δ approaching 90°.

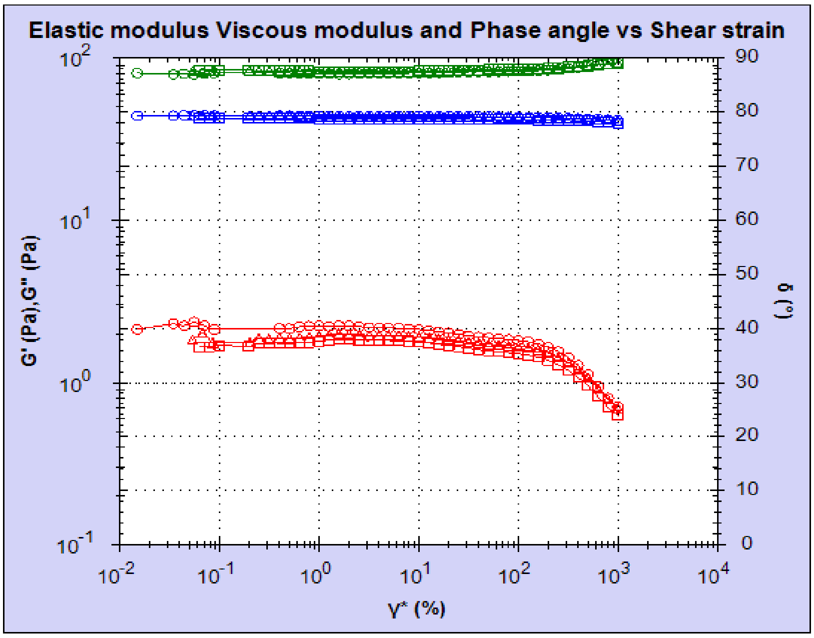


Figure 15. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of F1 Formulation

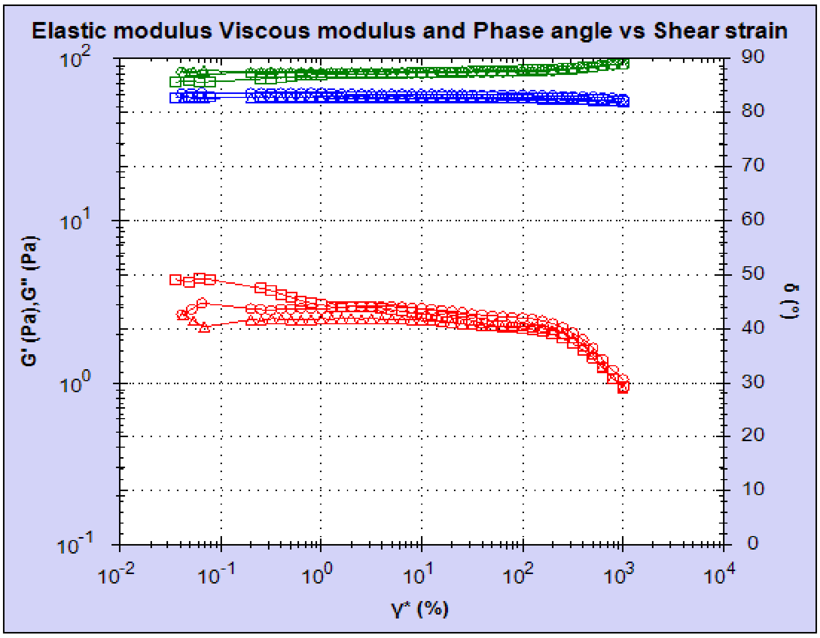


Figure 16. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of F2 Formulation

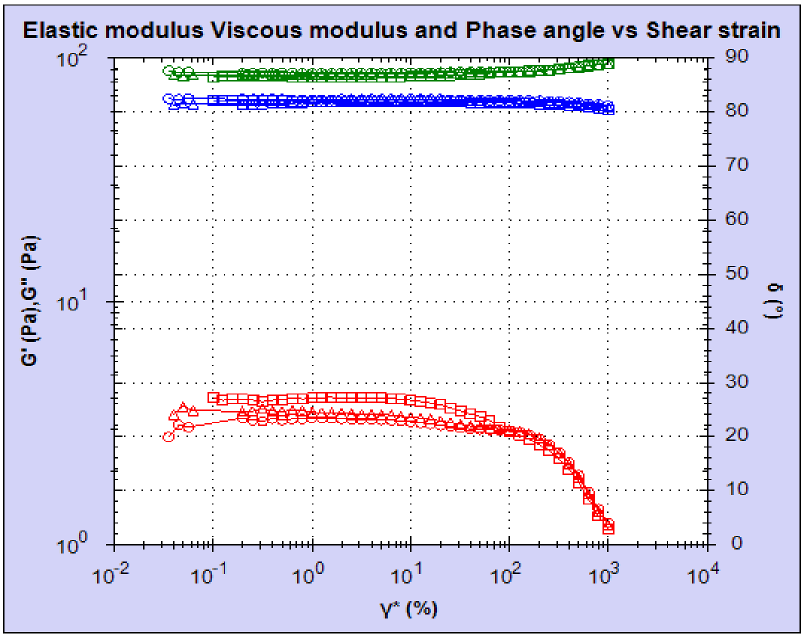


Figure 17. Elastic modulus G' (red), viscous modulus G" (blue), and phase angle δ (green) of F3 Formulation

The values of the complex modulus G* and phase angle δ for all tested formulations were evaluated and presented in (Table 10 and 11). The G* reflecting a stiffness of the gel formulations whereas the δ shows gel elasticity.

Table 10. Value of Complex Modulus G* (Pa) and the phase angle δ (°) of commercial silicone scar semisolid formulations

	Stratamed		Scar gel Dr. Max		ScarEsthetique		Rejuvasil gel	
	G* (Pa)	δ (°)	G* (Pa)	δ (°)	G* (Pa)	δ (°)	G* (Pa)	δ (°)
1	14.69	89.79	12.51	84.14	4100	22.49	358.5	12.24
2	14.20	89.80	11.85	89.01	5279	21.51	346.8	9.46
3	14.19	89.80	11.62	89.04	5746	20.09	358.9	10.08
avrg	14.36	89.80	11.99	87.40	5042	21.36	354.7	10.59
SD	0.29	0.01	0.46	2.82	848	1.21	6.9	1.46

Table 11. Value of Complex Modulus G* (Pa) and the phase angle δ (°) of F1, F2, and F3 Formulations

	F1		F2		F3	
	G* (Pa)	δ (°)	G* (Pa)	δ (°)	G* (Pa)	δ (°)
1	43.50	87.52	61.33	87.31	67.42	87.46
2	43.16	87.74	56.92	87.71	66.72	87.38
3	41.90	87.83	57.69	87.77	65.77	87.06
avrg	42.85	87.70	58.65	87.60	66.64	87.30
SD	0.84	0.16	2.36	0.25	0.83	0.21

Comparison of gel stiffness expressed as a complex modulus G*, and gel elasticity expressed as a phase angle δ is presented in (Figures 18) and (Figure 19). The ScarEsthetique cream has the highest stiffness with the value of complex modulus approximately 5000 Pa. The RejuvaSil gel follows with an order of magnitude lower stiffness. Formulations characterized as viscoelastic fluids have a G* in the range of approximately 10 Pa to approximately 70 Pa. The elasticity of the gel is fully correlated with the stiffness of the gel because the gels with the high value of G* have the lowest values of δ.

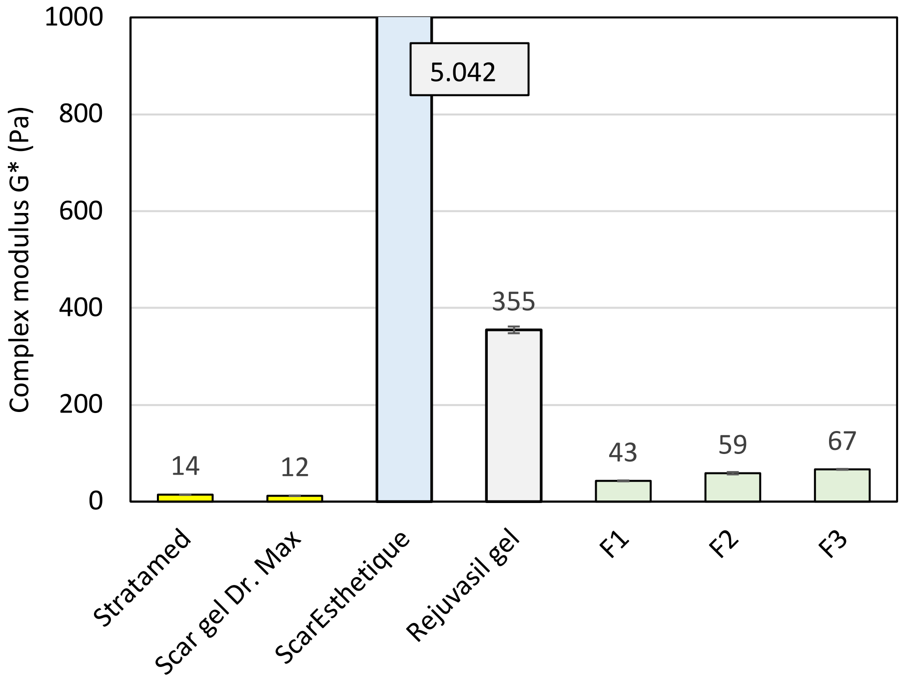


Figure 18. Comparison of gel stiffness expressed as a complex modulus G*

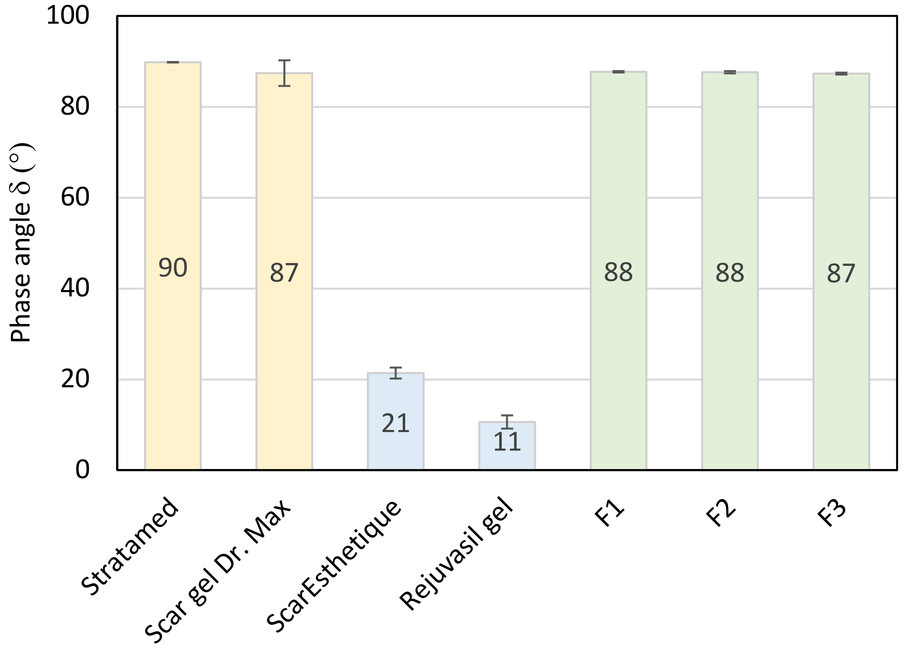


Figure 19. Comparison of gel elasticity expressed as a phase angle δ

8 CONCLUTIONS

Based on the conducted studies in this diploma thesis, the following conclusions cam be drawn:

- Flow curve analysis revealed that Stratamed is a Newtonian fluid with constant viscosity and no obvious yield point. Dr. Max Scar gel shows a minor viscosity decrease, however ScarEsthetique cream and RejuvaSil gel display significant decrease in their curves. Formulations 1, 2, and 3 are viscous Newtonian fluids with just a minor viscosity change.
- ScarEsthetique cream was the most viscous, followed by RejuvaSil gel. Unexpectedly, the viscosity of Stratamed gel and Dr. Max Scar gel was the lowest, even lower than the under-development formulations. Although they are called "gel", they behave like Newtonian fluids. Formulation F1 has the lowest viscosity among the formulations developed, whereas formulations F2 and F3 are almost the same.
- Only the elastic modules of RejuvaSil gel and ScarEsthetique cream are greater than the viscous modules, indicating that both formulations are viscoelastic solids with a bicoherent 3D gel structure.
- The gel point values and LVER show that the structure of ScarEsthetique cream is substantially stronger than the structure of RejuvaSil gel.
- Stratamed and Dr. Max Scar gel, and two more commercial scar healing preparations, as well as formulations F1, F2, and F3 are viscoelastic fluids with larger viscous modulus than elastic modulus, and their phase angle values nearing 90°.
- ScarEstehtique cream has the highest stiffness. RejuvaSil gel follows with an order of magnitude lower stiffness. Formulations characterized as viscoelastic fluids showing quite low stiffness.

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