Current role of tribological tests: striving for full characterization of medicinal and cosmetic products

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Abstract

Tribology investigates the events that happen on the surfaces of two substances/objects that are in direct or indirect contact through assessing friction, lubrication and/or wear. In particular, friction measurements could provide the information on the textural characteristics of (per)oral pharmaceutical preparations and contribute to the understanding of palatability. On the other hand, tribological tests have been more intensively used to characterize topical preparations (pharmaceutical, cosmetic), giving a thorough insight into the tactile and texture properties of these preparations. However, these tests are often combined with rheological, textural, and certain biophysical approaches. Additionally, the materials used for constructing artificial joints and articular cartilages are true tribological systems, developed and optimized in order to have properties that resemble the natural ones. Since tribological studies can be used to assess a wide range of drug dosage forms and products in general, the equipment used may be quite diverse. Accordingly, a special section of this work is committed to the description of the testing equipment's specifications and the applied protocols. The investigation of recently regulatory discovered phenomena, such as transformation/metamorphosis of the vehicle/base of topical preparations, have brought tribology back into focus as a potential assessment method.

Key words: friction, oral dosage forms, topical drugs, cosmetic products, artificial joint/cartilage

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Introduction

The investigation of phenomena and processes occurring on interacting surfaces, whether in direct or indirect contact, or in relative movement, is a part of the scientific field of tribology (1). Numerous scientific disciplines apply tribological tests to describe the behaviour of a material both on the macro- and (sub)micro-level. So far, tribological studies are most commonly used in mechanical engineering (2-4), electronic science (5), organic and inorganic chemistry (6, 7) and in the food industry (8), but they are gradually entering the field of biomedicine as well (9-11). A review of the applicability of tribological parameters for in-depth characterization of medicinal (both drugs and medical devices) and cosmetic products will be the main scope of this article.

Friction, lubrication and wear

Tribology is described by three fundamental terms: friction, lubrication and wear (12), which require a more detailed explanation.

Friction is a force that resists sliding. Among the different types of friction, static and kinetic, as well as external and internal ones, are more frequently assessed. Each of them can be perceived in everyday life. For example, while walking, friction occurs between our feet and the ground (i.e., kinetic friction), and opening a bottle requires us to overcome a degree of friction in order to separate it from the cap (i.e., static friction). On the other hand, atoms and molecules sliding across each other in their relative motion are a typical example of internal friction, while the surfaces of two bodies cause external friction in near contact (13). Friction is a unitless parameter commonly determined as the coefficient of friction (COF) or friction value (12).

Lubrication is directly correlated to friction. When a lubricant is loaded between two surfaces, it fills all the micropores and microrough areas, leaving them smooth and supple. The result of this effect is a reduction of the COF. Lubrication properties of materials are typically represented in the form of a Stribeck curve (Figure 1), where the COF (μ) is given as a function of entrainment velocity (U) or film thickness (14). There are three regimes that describe what happens on a lubricated surface: *i*. the boundary regime, *ii*. the mixed regime, and *iii*. the hydrodynamic regime of lubrication. Figure 1 shows the Stribeck curve of a tribological system. At lower (maintenance) speeds, a small peak occurs (stage II), indicating that a small portion of the lubricant particles is entrained between the two surfaces, resulting in a minor increase in COF – i.e., the boundary regime. At higher speeds, there is a plateau region (stage III to IV) representing the mixed regime of lubrication. In this phase, the rearrangement of the entrained particles provides an increase of the gap, further separating the two sliding surfaces. At the end of the curve, a more prominent peak occurs on the Stribeck curve (stage IV). The lubricant layer between the two surfaces becomes thinner as the speed increases. Two tribo-surfaces come into near contact with each other, and at this stage there are only small particles keeping the two surfaces separated. However, if the rotation speed continues to rise, the COF tends to decrease again. The explanation lies in the fact that, at this point, there are more lubricant particles between the two surfaces, forming a multi-layered lubricant film.

As a result, the gap between the surfaces becomes larger and friction decreases. This last region of the Stribeck curve (V) represents the hydrodynamic region of lubrication (14, 15).

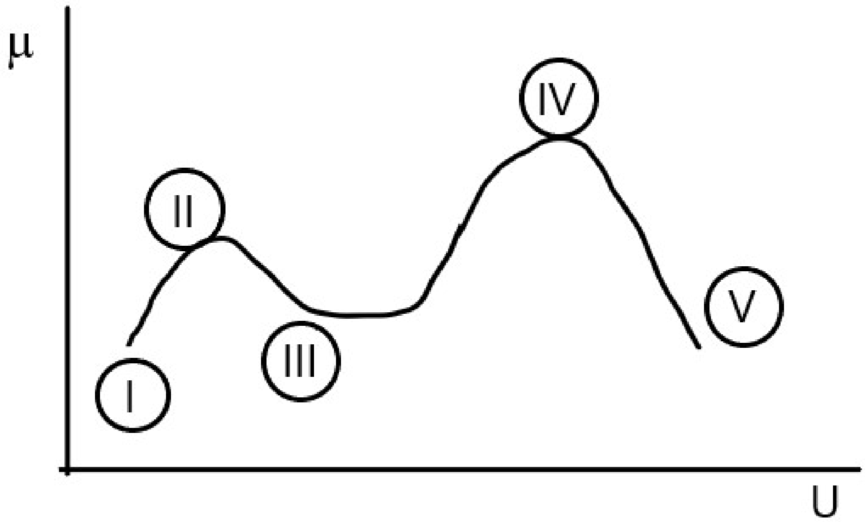


Figure 1. **A typical tribological Stribek curve: stages I-II represent the boundary regime; stages III-IV represent the mixed regime, while stage V represents the hydrodynamic regime of lubrication**

Slika 1. **Tipičan prikaz tribološke krive po Stribeku: deo I-II predstavlja granični režim; deo III-IV mešani režim, dok deo krive obeležen brojem V predstavlja hidrodinamički režim lubrikacije**

Wear is the final parameter of the tribology triad. It is explained by a sequence of events in which, e.g., atoms, chemical transformation products, fragments or constituents of a formulation are caused to leave the system by themselves or under the influence of an external force (12).

So far, wear testing has found its main application in the characterization of artificial cartilages and total hip replacement (16, 17). Like natural joints, artificial ones suffer a similarly great load, since extensive friction occurs between these surfaces. In order to minimize the friction between two surfaces, there is a need to create a material with sufficient lubricating qualities, but also one that is resistant to wear (18). Finding a balance between firmness and lubrication becomes a challenge in this situation. Tribology is a comprehensive tool that enables the design of systems with the desired characteristics and performance.

Despite their merits, tribological tests are still insufficiently utilized for the development of medicinal products. Only a few studies have implemented measurements of friction and lubrication for the purpose of deeper understanding of the characteristics of pharmaceutical products that are taken orally (9, 19, 20), while a slightly broader application of tribology is observed in the characterization of topical products (15, 21).

Biotribology

Tribology is a multidisciplinary science, contributing to a number of scientific areas, biotribology being one of them (3). The subject of biotribology is an improved understanding of specific physiological processes inside the human body and various anatomical modalities that enable specific movements in the animal and plant world. This research has identified some natural materials/systems as surfaces/objects with optimal tribology parameters, thus directing the trends in the mechanical, pharmaceutical and food industry towards the development of materials with mirroring properties (22). The human (and animal) musculoskeletal system is a perfect example of a tribo-system, responsible for locomotion (23). Joints consist of two or more bones whose heads are in direct contact with each other. The only thing that separates them is a thin cartilage surrounded by the synovial fluid, aiming to lubricate the bone surface and prevent the emergence of high friction values during movement (24). With age, the cartilage becomes thinner and the bone heads begin to rub against each other, causing wear (25). This simple example clarifies how all three tribological properties – lubrication, friction and wear – are mutually dependent.

Following the joints, the skin is the tissue that shows the most perceptible tribological behaviour (24). The skin is the largest human organ with numerous functions. It is not only a physiological barrier, but also a part of the thermoregulatory system and the application site for drugs and cosmetics (26). While rubbing the product in, the finger exerts some pressure on the skin surface, and in response, the skin reacts by showing friction (24). The product itself could have the ability to modify the skin's friction properties by hydrating it. According to experimental reports, COF rises to higher levels when the skin is well-hydrated (27). This phenomenon can be explained by the fact that hydrated skin is softer and provides a greater contact area between the measuring probe and the skin. Additionally, water itself may exhibit an adhesive force that induces a probe to overcome greater resistance to initiate a movement (27).

Chewing and swallowing is another example of physiological tribology processes. The teeth are responsible for grinding food, leading to slow wear. On the other hand, the tongue is a muscle that allows the movement of food in the mouth, and the secreted saliva facilitates the swallowing process (24, 28). The lubricant properties of saliva are crucial for the oral processing of food, food supplements and drugs, and consequently it is also related to the sensory and textural experience known as the "mouthfeel" (29). In this context, tribology finds its application in the field of (per)oral and orodispersible drug preparations.

The following sections of the paper will focus on the actual application of tribological phenomena for the development and characterization of medicinal (diverse application/administration routes) and cosmetic products.

Tribological assessment of oral dosage forms

Palatability is one of the characteristics of oral dosage forms that are important both for adherence and efficacy. It is defined as the product acceptance by the patient and is directly related to the taste, smell, texture, and sensation in the mouth after the administration of an oral drug (19, 30, 31). The *EMA Guideline on pharmaceutical development of medicines for paediatric use* emphasized the importance of palatability, especially for pediatric oral preparations (30). However, the document failed to recommend the methodologies to be used to assess it, other than relying on adult panels and literature.

Food science commonly uses tribology at an early development phase to examine food behaviour, evaluate mouthfeel and subsequently obtain the product with the most desired perception properties (8). This is recognized as a potentially useful approach for the pharmaceutical industry as well, knowing that several sensory and texture properties that patients perceive when taking oral medications are identical to food, including (but not limited to) hardness, softness, grittiness, creaminess, stickiness and slipperiness (19). Tribology has also been used to measure phenomena related to properties such as creaminess, lubricity and coating. However, so far, only a few studies have investigated the possibility of using tribology for these purposes (9, 19), implying that further research in this area is necessary to obtain optimal test conditions with clear interpretations.

In their work, Hofmanova et al. considered tribology as the most appropriate method to study texture sensations associated with solid oral dosage forms (19). They focused on the examination of slipperiness and stickiness of HPMC-coated tablets. As a function of time, COF was measured for whole tablets. The COF has been inversely related to slipperiness and is therefore relevant to the human perception of what is "slippery". It is important to note that the results were subsequently compared with *in vivo* data. In this part of the study, volunteers rated the tablets with different coatings as more or less slippery. It was found that their assessment was consistent with the results of the performed surface tribology test (19). These results imply the merit of tribology during the formulation phase of solid oral dosage forms in order to create a formulation with the desired mouthfeel.

Batchelor et al., on the other hand, focused their work on using tribology to evaluate the texture of liquid oral drugs, mainly oral suspensions (9). The palatability of these preparations is a critical quality attribute for all patient groups, but particularly for children and the elderly as population groups heavily relying on liquid oral dosage forms (30, 32). They measured COF as a function of velocity, and the results were presented in the form of a Stribeck curve for different authorized drugs (containing paracetamol, lactulose or co-trimoxazole). It was found that the friction measurements provided better insight into the texture differences between the samples. In fact, the boundary and mixed lubrication regime were identified as the critical tribological parameters for oral drugs, due to the fact that spreading the medicine in the mouth and swallowing generally fail to produce high shear rates. The same study benefitted from certain previous knowledge on the texture of the samples, enabling the categorization of some samples as oily and slippery, and others as gritty. Overall, both studies (9, 19) have shown that tribological tests provided results and conclusions corresponding to the instrumental or *in vivo* ones. Still, by itself, a tribological study can provide some general conclusions about oral drugs' properties and performance, but in combination with rheological and other tests it could be an excellent tool for developing formulations with the desired mouthfeel.

Tribology can provide insightful information on other oral dosage forms as well, especially for pharmaceutical preparations that tend to stay in the oral cavity a little longer (i.e., oromucosal films, oromucosal gels, medicated chewing-gums, etc.), or for those that disintegrate in the oral cavity (i.e., orodispersible tablets) (9). In that context, Łyszczarz et al. used tribology to estimate the texture and mouthfeel of aripiprazol orodispersible films (20), while Desai et al. studied sulforhodamine B-coloured orodispersible films (33).

Tribological assessment of topical drugs and cosmetic products

The skin is the largest organ in the human body, and in addition to a number of physiological functions, it is also the place where many drugs and cosmetic treatments exert their effect (34). Before registration/authorization, topical drugs must pass a variety of official (pharmacopeial) and unofficial characterization tests, discerning their critical quality attributes (35). So far, none of the regulatory bodies explicitly list tribology among the requested characterization methods (36-38). However, the latest EMA *Draft guideline on quality and equivalence of topical products* requires a discussion of some novel product aspects (39). Namely, the transformation of the product upon skin application needs to be assessed.

During and after administration, some ingredients evaporate from the skin surface, some are absorbed by the skin, and others are left on top of the skin, forming a residual layer. The formulation undergoes certain structural modifications known as vehicle/base "metamorphosis" or "transformation", and what is left on the skin following all of these modifications is known as the residual formulation (40). Film forming systems (FFS) are one of the best examples of pharmaceutical systems that go through this process. A recent study performed by our group dealt with the development and characterization of FFS based on hydrophobic polymethacrylate copolymers and/or hydroxypropyl cellulose (41), and it was observed that tribology could be a very informative methodology for the evaluation of these systems. By monitoring the COF, it was possible to identify the exact time point of the first phase transformation (solution to film), while the subsequent measuring points revealed the films' skin substantivity, i.e., resilience to friction that the probe exerts on the fully formed films. The investigation of long-term tribological behavior (during 24 hours) provided interesting information on structural modifications that happen to films over time (41).

Savary et al. investigated formulation factors responsible for the "skinfeel" of topical preparations (21). One of the things they investigated is the amount of formulation residue left after application, which has a significant impact on the textural characteristics.

Comparisons were made among three different emulsions and gels. By plotting the COF with time (graphic representation given in Figure 2) and comparing it between formulation types, it is possible to observe the differences in the amount of oily residue. Emulsion systems generally show a larger amount of residue when compared to gels, which is manifested by a decrease in COF. The explanation lies in the fact that emulsion residues are more greasy and slippery, and thus lead to better skin lubrication (42).

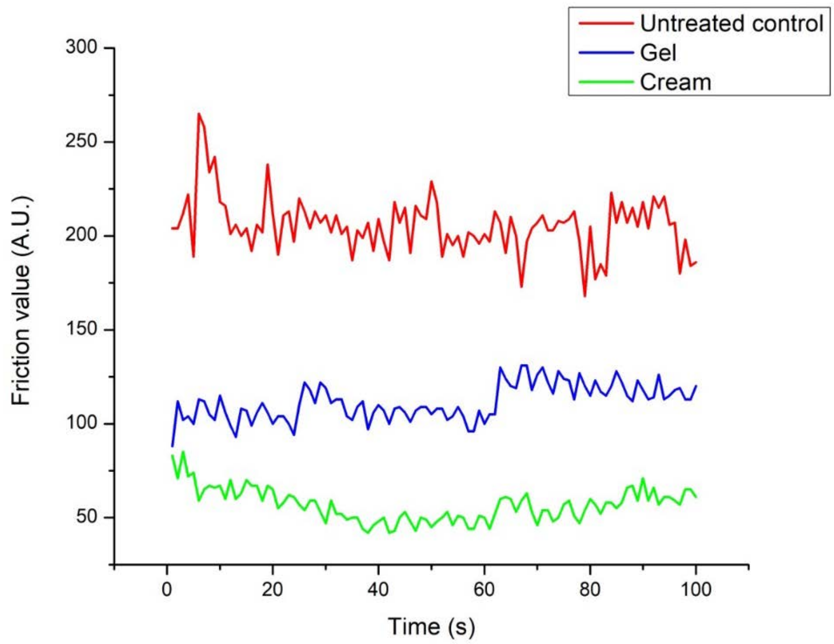


Figure 2. Typical changes of the friction parameter with time for the bare forearm skin and different formulation types (a gel vs. a cream)

Slika 2. Uobičajene promene frikcionog parametra tokom vremena za čistu kožu podlaktice i kožu tretiranu različitim formulacijama (gel vs. krem)

This type of testing is particularly important in the development phase of topical formulations, both pharmaceutical and cosmetic ones, since the preparation needs to possess favorable textural characteristics in order to be acceptable to the patient/user (43). The sensation that the preparation leaves on the skin is among those characteristics and is a direct result of the performance of the residual formulation. Namely, while applying a preparation, the patient will rub in the product until she/he feels a tactile change in its structure. This is a sign for her/him that the preparation has been absorbed and that there is no need for further rubbing (21, 40). The vibrations that trigger mechanoreceptors located in the deeper structures of the skin are responsible for this feeling. The mechanoreceptors capture more vibrations when there is higher friction on the finger that is spreading the product (44). This knowledge prompted scientists to study variations in skin texture before and after the application of a moisturizing agent, by measuring the vibrations made as a result of friction (10).

Furthermore, tribology may be used for in-depth examination of a topical formulation's lubricating and textural properties (21). The tactile sensation that topical products produce after application could also be described by tribology, considering the fact that significant correlation has been found between sensory perception and the changes in skin friction (44-45). The tactile perception that a patient/consumer perceives during the application of a topical product can be described in three phases: *i.* the first phase is described as the slippery phase - the product is applied in a relatively thick layer and shows hydrodynamic or mixed lubrication behaviour; *ii.* the second phase is described as the "sticky" phase - the skin becomes moisturised and, as a consequence, COF increases and a greater adhesive force occurs between the skin and the applied preparation; in the end, *iii.* some water evaporates from the skin surface, adhesive force decreases and preparations become "moist" and "smooth" (45).

Mahdi et al. compared the lubricating properties of commercially available Voltaren® gel and several gellan gum formulations using a tribology test (15). For these goals, soft tribology was applied and the Stribeck curves of the samples were compared, suggesting that tribological testing can identify the lubricating behavior of a material under circumstances that simulate *in vivo* conditions when a product is applied to the skin. This is especially important for preparations that have good lubrication identified as a critical quality attribute, such as ultrasound gels or dry eye preparations (46, 47).

An overview of the scientific papers that encompass tribological tests reveals that they are almost never used independently, but mostly as an integral part of a larger group of tests, commonly including rheological and/or textural characterization. Moreover, some publications have combined tribological tests with electrical measurements such as impedance (48). Uniting different methodologies provides a broader picture and gives more information about the properties and performance of topical pharmaceutical/cosmetic products. Sivamani et al. studied the variability of skin types based on different age, gender and ethnicity by using a frictometer probe (49). The differences were captured by simultaneous measurement of COF and electrical impedance. Furthermore, the ratio of the amplitude and mean values measured for the COF was calculated from these parameters. This is how the stickiness of skin surfaces was evaluated. They also evaluated the differences in the surface characteristics of the skin before and after treatment with different topical preparations. Overall, this study shows how tribological tests can be utilized for evaluating untreated skin surfaces, in addition to being used to characterize different topical products (15, 21).

Although tribology shows potential in this field of study, the absence of a standardized test procedure limits its wider application. As is the case with many other methods, the results obtained from tribological studies are valuable only in the context of comparison between samples.

Tribological assessment of artificial cartilages

Articular cartilage is a biological load-bearing material able to withstand damage and wear and provide frictionless movement (18). Cartilage is an avascular, alymphatic and aneural tissue which, when damaged, is not susceptible to regeneration. Therefore, degenerative diseases such as rheumatoid arthritis and osteoarthritis, which often lead to cartilage destruction, are a major problem faced by a large percentage of the elderly population (50, 51). While these patients are routinely given symptoms-treating medications, articular cartilage replacement is one of the potential long-term solutions (52).

Artificial cartilages need to be composed of materials resembling natural ones, but able to withstand wear and tear better. The major challenge is to develop a lubricant biomaterial that is sufficiently resistant. Synovial fluid normally consists of hyaluronic acid, lubricin and phospholipids. Hyaluronic acid and lubricin have been found to work as antiadhesion components to reduce the wear of cartilage, while phospholipids are responsible for reducing the friction. Accordingly, many biomaterials developed in this vein also have these or similar molecules in their composition (51).

One of the critical quality attributes of artificial cartilage is durability, so tests able to examine hardness and tendency to wear are indispensable. By testing lubrication behavior and COF of the different materials, it is possible to determine whether a biomaterial shows optimal tribological behavior. Moreover, in the developing phase of intraarticular injection formulations, tribology may be a tool able to predict pharmacodynamic behavior of these dosage forms (53).

The first use of tribology in this area was in 1936, when Jones et al. measured the COF of a horse's joint. They came to the conclusion that the synovial fluid was responsible for reducing the COF from 0.27 in a dry joint to 0.02 in a lubricated one (52). Since then, tribology has been an indispensable part of the formulation of new systems for the intraarticularly delivery of medicines, design of the materials used as artificial joints, or for cartilage replacement in diseases with a high degree of damage.

Ultra-high-molecular weight polyethylene (UHMWPE) is the most common material included in the composition of artificial joints (16, 24). Because of the high wear, it is often modified by other materials that show less wear and better lubricating properties. Molo et al. modified the polyethylene surface with biocompatible phospholipid polymer 2-methacryloyloxyethyl phosphorylcholine (MPC), and thus got a joint with much better tribological characteristics (17). There are many other examples of combinations used in conjunction with UHMWPE, including hydrophilic acrylic acid (54), Sr/Zn-doped CPP/GNS (55), nanodiamonds (56), etc. In addition to UHMWPE, the characteristics of other materials, such as TiAl6V4 and CoCr28Mo alloys, have also been investigated (11). For all these studies, tribological parameters like COF and wear volume were the main parameters for comparison and characterization.

Table I summarizes the usage of tribology tests for characterization of different pharmaceutical and cosmetic preparations, with main conclusions, measurement principles, and future application perspectives.

Table I Summary representation of a variety of dosage forms examined through tribology tests with key conclusions and perspectives for future use

Tabela I Sumiran prikaz različitih farmaceutskih oblika/kozmetičkih proizvoda ispitivanih tribološkim testovima sa osnovnim zaključcima i perspektivom za buduću upotrebu

Dosage form/Type of cosmetic product	Measured parameters	Conclusions	Perspectives	References
Coated tablets	COF as function of time	COF was inversely related to slipperiness of coating material	Results obtained by the tribological test were comparable with *in vivo* evaluation of "mouthfeel" characteristic of oral preparation and has the perspective to replace it in the formulation development phase	19
Oral suspensions	COF as a function of velocity	Tribology provided good insight into texture characteristics of oral liquid preparation comparable with *in vivo* data		9
Orodispersible films	COF between the interacting surfaces in relative motion	Measuring of COF gave information of sensory perception in the mouth after the disintegration of orodispersible films	Novel method that could support the development of orodispersible films with focus on patient acceptability	20,33
Emulsions and gels	COF as function of time	Type and amount of residue after application of topical products can be assessed with friction measurement	Skinfeel evaluation must be determined during the development phase of topical formulations. Tribology stands out among other methodologies for these purposes	21
Film-forming systems	COF as a function of time	Through a tribological study, it was possible to observe the substantivity of the formed films	Tribology could contribute to the understanding of the transformation process of FFS, in addition to determining the substantivity and durability of FFS on the skin (recommended frequency of use)	41
Emollients / moisturizing substances and products	Amplitude of vibration produced as a result of skin friction	Treated skin has shown a decrease of vibration amplitude which was correlated with decrease of friction force	Tribology could be implemented in cosmetic products' research in order to develop new skin hydrating products	10
Gels	Stribeck curves	Results can identify a material's lubricating behavior under circumstances that simulate *in vivo* conditions when a product is applied to the skin	Especially important for development of novel excipients with lubrication properties and characterization of ultrasound gels or dry eye preparations	15
Glycerin and petrolatum	COF in combination with electrical impedance	This method was capable to capture a variety of different skin types and treated and untreated skin	Combination of friction and electrical impedance measurement gave a broader picture of skin properties after topical administration of hydrating agents	49
Injectable solution (intraarticular injection)	COF and dynamic creep	By using tribological measurements, hyaluronic acid and dopamine together demonstrated properties superior to hyaluronic acid alone	Tribology established as the most superior methodology in characterization of intraarticular injections	53

Overview of the measuring equipment and test conditions

The equipment choice and test conditions depend on the study aim and the dosage form that needs to be tested. For example, for assessing oral preparations, test conditions are set to simulate the swallowing step or the short stay inside the oral cavity. In vitro studies that mimic the ingestion of oral dosage forms are usually designed so that the temperature is set at 20 or 25°C (i.e., close to room temperature) (9, 19). It is a rational choice, considering the fact that oral drugs have a short residence time inside the mouth. On the other hand, the apparatus used for topical preparations simulates the movements made when rubbing the product against the skin, and experiment is performed at approximately 32°C, which is considered to be the average skin temperature. Important parameters that are set during the measurement are the force with which the probe presses the sample (i.e., normal load), the duration of the measurement, velocity and the type of probe movement (e.g., rotational, linear or sinusoidal) (15, 48). The most frequently applied devices and their fundamental operating principles are outlined in Tables II and III, and discussed in the following sections.

Apparatus for tribological testing of oral dosage forms

Due to an insufficient number of studies dealing with this issue, there is also little variation in the device principles that have been modified for these applications. However, certain differences may be discerned in the apparatus used for investigating solid dosage forms on the one hand, and films and liquid dosage forms on the other. The apparatus consists of a top and bottom steel geometry, with a suitable space between them for the sample. Although a majority of the consulted studies were performed with distilled water as the saliva-mimicking lubricant, the studies investigating oral liquid formulations or some coating materials were performed without a lubricant. The force load was in the 1-2 N range because previous research had shown that similar forces are exerted in oral conditions when swallowing food or medicines. The velocity was increased over time, and the top plate/ball moved while the bottom plate remained stationary (9, 19, 20). In some studies, these steel components were covered with a film made of various materials to simulate *in vivo* conditions as closely as possible. The bottom and/or upper parts may be covered with a hydrocolloid-based thin dressing (19) or modified with a compliant poly-(dimethylsiloxane) (PDMS) coating (57). Such modifications attempt to mimic, e.g., the roughness of the tongue or the oral cavity mucosa.

One research team created a system that closely resembles what happens in the oral cavity and could be applicable to tribological testing in the food industry as well. They claim that traditional friction measurement devices are unsuitable for simulating the oral environment. As a result, a system that employed a sinusoidal motion was devised and agar gel was introduced as the sample substrate. Agar gel has physical and geometric properties similar to the human tongue, while the sinusoidal motion best represents the movement phenomena in the oral cavity (58).

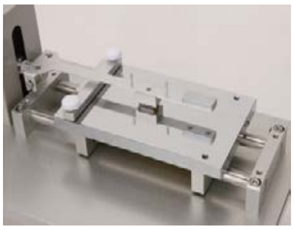
Table II Overview of the used apparatus and test conditions in the frictional measurement of topical products

Tabela II Pregled uređaja i uslova ispitivanja frikcije preparata koji se primenjuju na koži

Used apparatus	Type of the examined pharmaceutical dosage form/cosmetic product	Top geometry	Bottom geometry	Velocity	Type of probe movement	Normal load	Temperature	Reference
Frictiometer FR 700 (Courage + Khazaka electronic GmbH, Köln, Germany)	Emulsions vs. gels	Smooth Teflon disk	Inner surface of forearm	900 rpm	Rotation	Unspecified	Skin temperature	21
Mini traction machine MTM2 (PCS Instruments, London, UK)	Gels with diclofenac	Stainless steel ball	Silicone disc	1-1000 mm/s	Unspecified	4 N	32°C	15
Frictiometer FR 770 (Courage-Khazaka electronic GmbH, Köln, Germany)	N/A (measured various age, sex and ethnicity-related skin conditions)	Flat Teflon probe	Dorsal surface of the hand, the forehead, the canthus	255 rpm	Rotation	0.7 N	16-20°C	61
Custom-made for the purpose of the experiment	Moisturizing cream with vaseline	Artificial finger of liquid plastic	Pig skin, Syntethic skin, PMMA membrane	10-30 mm/s	Linear	50-200 mN	Room temperature	10
UMT Series Micro-Tribometer (UMT Campbell, CA, USA)	Moisturizing creams	Cylindrical copper probe	Forearm skin	0.4 mm/s	Linear	Measured	Skin temperature	48
		Stainless steel ball	Dorsal surface of the finger, abdominal skin samples	5 mm/min				49
KES-SE Frictional Analyzer (KATO TECH Co. Ltd., Kyoto, Japan) + arm holder	N/A (examination of moisture influence upon addition of water)	Fingerprint contact probe	Forearm skin	1.1 mm/s	Linear	0.244 N	Skin temperature	62
Sinusoidal motion friction evaluation system made for the purpose of experiment	Moisturizing agents: Glycerol and water	Fingerprint-similar probe	Forearm skin	2.1 rad/s	Sinusoidal	0.98 N	25°C	63

Table III Technical data on commonly used instruments belonging to the tribology sphere

Tabela III Tehničke informacije o najčešće korišćenim tribološkim uređajima

Tribometer device type	Appearance of the device	Measurement principle	Velocity range/ Dimension of the device	Pressure/ Measurement area	Reference
Frictiometer FR 700 (Courage + Khazaka electronic GmbH, Köln, Germany)		A constant rotational speed is applied onto the skin by the friction probe. The torque is measured.	13 cm	0.7 N/ ø 16 mm	64
Mini traction machine MTM2 (PCS Instruments, London, UK)		The ball is loaded against the face of the disc, and the ball and disc are driven independently to create a mixed rolling/sliding contact. The frictional force between the ball and disc is measured by a force transducer. This system can mimic the physical perception of spreading the preparation on the skin/in the mouth and demonstrate lubrication behaviour of the pharmaceutical product.	-4 to 4 ms^{-1}/ 19.05 mm (3/4 inch) steel ball and a 46 mm diameter steel disc	0-75 N	65
KES-SE Frictional Analyzer (KATO TECH Co. Ltd., Kyoto, Japan) + arm holder		Imitating hand movements, the device mechanically slides over the surface of the sample thereby detecting the COF. The sensor unit’s design features a load and surface treatment that mimics a fingertip, allowing for quantification similar to that of the human finger.	0.1 - 10 mm/s W320 × D180 × H220 (mm)	10 ×10 mm	66

Discovery HR-2 with Tribo-Rheometry Accessory (TA Instruments, USA)		Measurement of the COF between two solid surfaces which come in the near contact during rotational movement of the apparatus elements. Surfaces can be modified or attached with various pharmaceutical products (i.e., tablets, coatings material, etc.)	0-300 rad/s	50N	67

Apparatus for tribological testing of topical products

As tribology is more frequently used to characterize topical than oral pharmaceuticals, there is much more variety in the used apparatus and test conditions. However, the basic measurement principle of the applied tribometers is somewhat similar (sample space within the top and bottom geometry). While some studies used synthetic skin or other types of skin constructs as the bottom geometry (10, 15), even more research was classified as “in vivo”, introducing different parts of the human body as the bottom geometry (e.g., forearm skin, forehead skin or dorsal surface of the finger) (21, 48). The top geometry is the probe, made of metal or a suitable material imitating the surface properties as a human finger. The measuring probe either rotates or slides, linearly or sinusoidally, along the skin. In some measurements, the normal load was set to a predetermined, constant value, whereas others required further calculation of the coefficient of friction. Table II gives an overview of the various measurement conditions.

In addition to frictometers (Table III), some papers report the use of more sophisticated techniques such as atomic force spectroscopy and nanoindentation for the measurement of surface behavior (friction, adhesive force and wear) at the nanoscale. The probes of these devices are sharp-tipped cantilevers with a radius <10 nm that enable the simulation of a single touch point. These devices have been used for characterizing tactile properties of some 3D skin models (59), while their application for the characterization of topical preparations is still limited, and is mentioned in only a few papers (45, 60).

Conclusion

Tribology is an emerging method in the field of pharmacy and cosmetology. Despite the fact that it has the potential to be a unique method of characterization able to explain the surface behavior of materials even at the development phase of new preparations, its application has so far been limited to the context of comparative tests. There are predictions regarding the areas of research in which it could be particularly useful, i.e., the investigation of mouthfeel of oral preparations (both solid and liquid), and a somewhat broader characterization of topical pharmaceutical and cosmetic products. For now, it finds the widest application in the field of characterization of intra-articular injections and materials intended for the production of artificial cartilages.

Wider application of tribological tests is limited by the absence of a unique research protocol. In some studies, for example, the COF is used as a measure of friction, whereas in others interpretations are made based on different profiles of the Stribeck curve. It is therefore necessary to determine a standardized research protocol in which the test conditions and parameters to be measured are clearly defined, and from which certain conclusions can later be drawn.

There is no doubt that the future of tribology lies in the investigation of new phenomena. Hence, it may find its use in metamorphosis research as a regulatory recognized process through which various topical formulations pass during the application.

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Doprinos triboloških testova sveobuhvatnoj karakterizaciji medicinskih i kozmetičkih proizvoda

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Kratak sadržaj

Tribologija se bavi izučavanjem uticaja i događaja koji se dešavaju na površinama dveju materija/objekata koji su u direktnom ili indirektnom kontaktu, uključujući procese trenja, podmazivanja i/ili habanja (trošenja). Naime, primećeno je da je merenjem frikcije moguće ispitati teksturna svojstva (per)oralnih farmaceutskih preparata i doprineti razumevanju njihove palatabilnosti. S druge strane, nešto duži niz godina se tribološka ispitivanja izvode u cilju karakterizacije preparata (farmaceutskih, kozmetičkih) koji se primenjuju na koži, dajući time kompletniju sliku o taktilnim i teksturnim osobinama ovih preparata. Ipak, dobijeni rezultati se uobičajeno razmatraju zajedno sa onim dobijenim tokom reoloških, teksturnih i/ili biofizičkih studija. Takođe, materijali od kojih su napravljeni veštački zglobovi i zglobne hrskavice su primer triboloških sistema koji su razvijani i optimizovani na način da imaju slične karakteristike prirodnim sistemima, a za čiji je razvoj i karakterizaciju neophodno ispitivanje frikcije, lubrikacije i trošenja. Kako je polje primene triboloških ispitivanja široko i provlači se kroz, u tehnološkom smislu, izrazito različite farmaceutske oblike, posledično će i aparatura koja se koristi u te svrhe pokazivati veliki diverzitet, te je deo ovog rada posvećen i pregledu specifičnosti uređaja za ispitivanje triboloških parametara, sa posebnim osvrtom na primenjene protokole ispitivanja. Na kraju, dat je osvrt na potencijalne primene triboloških studija za ispitivanje novootkrivenih fenomena, poput transformacije/metamorfoze vehikuluma/podloge topikalnih preparata.

Ključne reči: frikcija, (per)oralni farmaceutski oblici, farmaceutski oblici za primenu na koži, kozmetički proizvodi, veštački zglob/hrskavica

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