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Original Article

DERMATOLOGIC GELS SPREADABILITY MEASURING METHODS COMPARATIVE STUDY

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ABSTRACT

Objective: The main objective of our study is the comprehensive analysis and characterization of the existing spreadability evaluation strategies, the comparison of the obtained results reproducibility and convergence through the example of the 9 most widely used dermatological gels.

Methods: Dolobene®, Flucinar®, Ketorol®, Contractubex®, Dr. Theiss Venen gel®, Solcoseryl®, Deep Relief®, Hepatrombin® pharmacopoeia gel samples were analyzed using parallel-plate, "slip and drag", and viscometry methods. Analysis was performed in flow mode at 32±0.2 °C, over shear rates ranging from 0 to 350 s-1, increasing over a period of 1 20 s, and was maintained at the superior limit for 10 s and then decreased during the same period. At least 5 replicates of each sample were evaluated, and the upward flow curves were fitted using the Casson mathematical model.

Results: Solcoseryl® and Dolobene® showed the best spreadability in the parallel-plate method (3115.66±50.00 and 3316.63±50.00, respectively); Contractubex® and Dolobene showed the best spreadability in the "slip and drag" test (73.46±0.5 and 18.32±0.5, respectively); Solcoseryl® and Contractubex® showed the best spreadability in the viscometry test (43.86±0.5 and 76.92±0.5, respectively).

Conclusion: This study analyzed the existing methods for determining the spreadability using commercially available samples of the dermatological gels as examples. The viscometric and the "Slip and drag" methods use different characteristics of spreadability, giving a complex evaluation of the measured parameter *in vitro*. Therefore, the combination of these two methods has the greatest prospects for reliable determination of this indicator.

Keywords: Dermatological gels, Gels, Parallel-plate method, Rotational viscometry, Slip and drag, Spreadability

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INTRODUCTION

Currently, gels are the most demanded semi-solid dosage forms due to their optimal consumer characteristics. However, a significant problem for the development and production of gels is the search for reproducible and relevant ways to evaluate their characteristics. Regulatory documentation contains a narrow list of gel requirements and methods for their determination. Furthermore, dermatological gels' fundamental characteristic of spreadability, as well as a standard method for determination and optimums determination, are not mentioned in the world pharmacopeias [1].

The efficacy of topical therapy highly depends on the patient spreading the formulation in an even layer on the skin to deliver a standard drug dose. That is why spreadability is one of the most important characteristics of semi-solid dosage forms. Spreadability determines the delivery of the required drug dose to the place of use, ease of application, and extrudability from the primary package, affecting consumer preferences [2, 3].

The development of methods for spreadability determination was intensively conducted by a number of scientific groups from different countries from the mid-70s to the mid-90s of the XX century [2, 4]. Using modern equipment at the time and the available assortment of excipients, relevant techniques for evaluation of this characteristic was developed and the spreadability optimums that are still used in the development of new dosage forms were found. However, a significant expansion of the assortment of excipients for pharmaceutical technology and the improvement of analytical and technological methods makes it necessary to review and validate the methods for measuring the spreadability for their use in the modern dosage forms development following all the quality standards.

This study aims to analyze the existing scientific methods for determining the parameter "spreadability", werecharacterize them, and compare the reproducibility of the results of determination on the example of the ten most popular pharmaceuticals in the form of dermatological gels.

MATERIALS AND METHODS

Ten samples of the dermatological gels differing in the composition of gelling agents and excipients were selected as the objects of the study. Dolobene® was purchased from Merkle GmbH (Germany). Flucinar® was purchased from Jelfa S. A. (Poland) and Ketorol® was purchased from Dr. Reddy`s Laboratories LTD (India). Contractubex® was purchased from MERZ PHARMA GmbHand Co. KGaA (Germany). Solcoseryl® was purchased from MEDA PHARMACEUTICALS SWITZERLAND GmbH (Switzerland). Deep Relief® was purchased from Mentholatum Company Limited (Great Britain) and Hepatrombin® was purchased from Chemofarm A. D. (Serbia). Dolgit® was purchased from Dolorgit GmbH and Co. KG (Germany).

There are various methods for spreadability measuring in semi-solid dosage forms. It should be considered that each person applies ointment, gel, or cream to the skin with different strength, speed, and different movement which complicates the process of accurate determination of the spreadability and may introduce errors in the data obtained. However, this does not exclude the possibility of obtaining averaged results and determining optimum ranges.

Parallel-plate method

The most common method for measuring the spreadability is the parallel-plate method that has many variations. This method is simple, economical, and time-effective. It was first conducted by Keller during the development of a model for measuring the spreadability of suppository bases [4]. Hadi *et al.* evaluated the spreadability of polyethylene glycol ointment bases using an extensometer with sliding plates [5]. Later Vennat *et al.* validated the spreading diameter measurements of hydrogels based on cellulose derivatives and established the linear distribution of this diameter, this method has shown good reproducibility [6].

During the measurement using the parallel-plate method, 1 g of the sample prepared in 48 h before the test is placed between two glass plates 20 x 20 cm. A weight (50-500 g) of 125 g is placed on top for 1 minute. Then the diameter of the sample between the plates is measured [7-11].

There is a variation of the experiment in which the spreadability of various semi-solid dosage forms is determined by compressing the sample under several glass plates of known mass [values 12]. For example, 20 plates of known mass can be sequentially placed on a sample at 1 min intervals.

In these cases, spreadability is determined by the formula:

$$S_i = d^2 \times \frac{\pi}{4},$$

S_i–spreading area (mm^2) depending on mass, d–spreading area diameter (mm)

In their studies Panigrahi *et al.* used a similar system to characterize lincomycin hydrochloride gels [13].

The *"Slip and drag"* method is often used to determine the spreadability [12-14]. During the experiment, a test sample of a certain mass is placed on a glass plate, which is covered on top with another plate with an attached wooden block. A weight is placed on the upper plate for a while. After this, the weight is removed, a weighting agent is attached to the wooden block and the time that is needed for the upper plate to completely separate from the lower plate is measured.

In this case, spreadability is determined by the formula:

$$S = m \times \frac{l}{t},$$

S–sample spreadability, m–upper plate mass (g), l–glass plates length (cm), t–time taken to separate (s)

Thus, in the N. K. Dubey's work [14] the properties of the spreadability of the experimental sample of ointment with graphene nanoconjugate were studied. A sample of the ointment was spread between two glass plates of standard dimensions (7.5 cm), and a weight of 100.0 was placed on top. After a short exposure, a weight of 20.0 was attached to the upper plate, and the plates themselves were placed at an angle. The time interval during which the upper plate passes the distance of 7.5 cm and separates from the lower plate was measured.

There are many variations of the parallel-plate method. Most often, the mass of the test sample can change or the mass of the load attached to the sample, varying from 100 to 500 grams. Thus, the results of these spreadability determination studies cannot be correlated.

Subjective assessment

The subjective assessment method is based on a tactile assessment of sample spreadability by volunteers. This method is not expected to obtain accurate values but it shows the true spreadability as it is carried out using individual senses.

De Martine and Cussler predicted different subjective characteristics of the fluid structure, [15]. They stated that subjective spreadability and viscosity are perceived as shear stress felt on the fingers, while subjective stickiness of the sample is perceived as a time required to separate a finger from the sticky surface. Fig. 1 shows the correlation between the geometry of the fingers and two parallel plates.

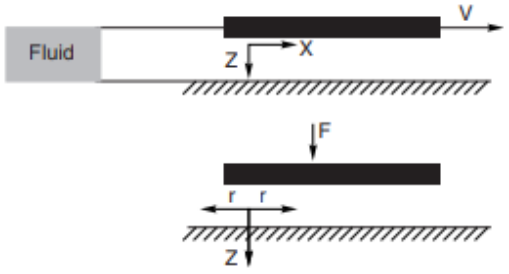

Fig. 1: Schematic representation of finger geometry as two parallel plates. V–finger velocity, Z–sample layer thickness, X–shear stress, F–shear force between fingers, R–finger radius [15]

It was found that subjective spreadability is inversely proportional to shear stress. It was also proportional to the ratio of sample viscosity to constant finger speed.

The work of Aust *et al.* on the sensory approach study for evaluating semi-solid dosage forms included a selection of 9 participants who evaluated various characteristics of the dosage form including spreadability [16]. Participants applied test samples to the inner surface of the forearm and reported a numerical evaluation.

Master-curve method

The master-curve method combines the advantages of subjective analysis and instrumental measurement methods. It was introduced by Barry *et al.* who proposed combining a sensory assessment of spreadability with the concept of a master curve derived from a rheological measurement of the viscosity of test samples [2, 3].

This method is used to determine the relationship between shear stress and shear rate which affected the application of topical preparations to the skin, based on master curves for lipophilic and hydrophilic preparations, including oil-in-water emulsions and aqueous gels.

A group of volunteers was asked to compare a series of experimental samples prepared on various bases and varying in consistency from well-flowing liquids to hard semi-solid substances with different Newtonian silicone oils of different viscosities.

Participants were offered to evaluate the proposed compositions on two scales: on a subjective scale from 1 to 5 where 5 is the most pleasant feeling of the sample, or on a scale from 1 to 5 where a rating of 1 denoted an excessively liquid consistency of the sample, 2-a liquid, but acceptable consistency, 3-optimal, 4-thick but acceptable, 5-excessively thick consistency. Participants also needed to indicate which silicone oil most resembled a sample according to the spreading characteristics.

Participants applied samples to the inner surface of the forearm. The average skin temperature was 34 °C, the shear rate varied from approximately 300 to 2500 s-1, and the shear stress ranged from 40 to 6000 Pa.

On a Ferranti-Shirley viscometer of the "cone to plate" type, rheograms of silicone oils and test samples were obtained, intersections of rheograms of samples and silicone oils made it possible to evaluate the shear conditions that apply during the application of the dosage forms to the skin.

These data, superimposed on the master curve, revealed the optimal and preferred conditions for spreading for maximum patient comfort (fig. 2). The data obtained indicate a dynamic relationship between shear rate, relative viscosity, and the thickness of the oil strip on the skin.

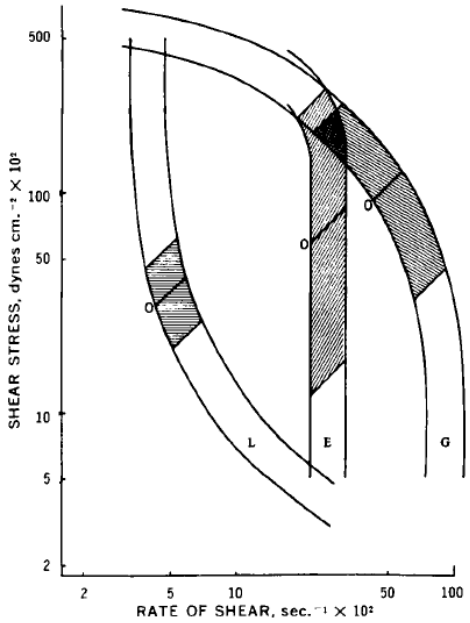

Fig. 2: A combination of master curves for lipophilic (L) and hydrophilic gels (G) and oil-in-water emulsions show the most acceptable viscosity range for spreading on the skin (shaded area) and optimal viscosity value (line 0) [2]

Viscometry

Viscometers are one of the oldest and most common tools for spreadability measuring. They measure spreadability as a function of viscosity. "Cone to plate" viscometers are considered to be the best instruments for spreadability measurement, in particular the Ferranti-Shirley viscometer. The main advantages of this method obtain getting a multi-point rheogram, easily supported shear rate and geometry, closely simulating the application of a sample in a circular motion. The disadvantage is slippage between the rotating part of the viscometer and the sample during the measurement. However, viscometers allow measuring the spreading properties of semi-solid dosage forms with high reproducibility.

Penetrometers can also be used to determine the spreadability. Spreadability value, in this case, is determined by the formula:

$$P_0 = \frac{m \times K_b}{(d_p) \times n_j},$$

P_0–sample flow rate, d_p–cone penetration depth, m–mass of the cone and other moving parts of the instrument, n_j–a constant of approximately 2.

Three methods for determining spreadability were selected for the study — the parallel-plate method, the "slip and drag" method, and the viscometric method for determining the spreading value as the reciprocal of the yield strength.

In the "parallel plate" experiment two glass plates 200 × 200 mm in size and 164.0±0.5 g in weight were used. 2.00±0.01 g of the analyzed sample was placed in the center of the lower plate, the second 164.0±0.5 g plate was mounted on top. Spreadability in mm^2 was calculated by the formula:

$$S_i = d^2 \times \frac{\pi}{4},$$

Where S_i–spreading area (mm^2) depending on mass, d–spreading area diameter, (mm) [12].

The "slip and drag" experiment was also conducted using two glass plates, the lower one with a size of 200 × 200 mm and a mass of 164.0±0.5 g and the upper one with a size of 100 × 100 mm and a mass of 75.91±0.02 g. The mass of the weighing agent was 50.0±0.1 g. The distance that the upper plate had to slip for separation was 9.0 cm. The spreadability [kg·m/s·10·4] was calculated for the samples that showed the separation of the upper plate from the lower one by the formula:

$$S = m \times \frac{l}{t},$$

Where S–sample spreadability, m–upper plate mass, l–glass plates length, t–time taken to separate

In the experiment on the determination of the spreadability by the viscometric method a Lamy Rheology RM 200 rotational coaxial viscometer (France) with a cylinder-in-cylinder measuring, MS-DIN system 33 was used. The rheological characteristics were determined in the range of shear rates from 0 to 350 s^{-1} [17]. RHEOMATIK software (ver. T, Lamy Rheology, France) was used for the experiment. Approximation of the results was carried out using the Casson equation

$$\sigma^{\frac{1}{2}} = \sigma_\gamma^{\frac{1}{2}} + (\eta_\rho \gamma)^{\frac{1}{2}},$$

σ_γ–yield strength;

η_ρ–plastic viscosity;

γ–shear rate.

The Casson fluid model refers to equations with yield strength and can be used to evaluate the rheological properties of materials that do not flow at low shear rates or have such high viscosity values that they can be neglected in technological applications [17, 18].

RESULTS

At the first stage of the study, the values of plastic viscosity and yield strength of the samples were determined according to the Casson fluid model. It was shown that the studied industrially manufactured samples can be conditionally divided into systems with high (Solcoseryl®, Dolgit®, Ketorol®), medium (Deep Relief®, Dr. Taiss Venen®) and low (Contractubex®, Flucinar®, Dolobene®, Hepatrombin®) viscosity values (table 1). Dolgit® sample had shown the highest yield strength (187.20±0.5), which is expected to negatively affect its spreadability.

Table 1: Plastic viscosity and yield strength values according to the casson fluid model

Sample	Plastic viscosity, (Pa·s)	Yield strength, (Pa)
Deep Relief®	0.321±0.05	46.40±0.5
Solcoseryl®	0.494±0.05	22.80±0.5
Dolgit®	0.480±0.05	187.20±0.5
Contractubex®	0.112±0.05	13.00±0.5
Flucinar®	0.185±0.05	52.40±0.5
Ketorol®	0.558±0.05	69.90±0.5
Dr. Taiss Venen®	0.357±0.05	75.50±0.5
Hepatrombin®	0.234±0.05	72.20±0.5
Dolobene®	0.212±0.05	38.00±0.5

Then the spreadability of the analyzed gels was determined by three methods (table 2).

Table 2: Spreadability values of the samples

Sample	Parallel-plate spreadability, (mm^2)	"Slip and drag" spreadability, ($kg \cdot m/s \cdot 10^{-4}$)	Viscometry spreadability, (mPa^{-1})
Deep Relief®	2289.06±50.00	7.59±0.5	21.55±0.5
Solcoseryl®	3115.66±50.00	4.93±0.5	43.86±0.5
Dolgit®	1074.66±50.00	-*	5.34±0.5
Contractubex®	2732.59±50.00	73.46±0.5	76.92±0.5
Flucinar®	2640.74±50.00	-	19.08±0.5
Ketorol®	2374.63±50.00	6.21±0.5	14.31±0.5
Dr. Taiss Venen®	2826.00±50.00	-*	13.25±0.5
Hepatrombin®	1074.66±50.00	-*	13.85±0.5
Dolobene®	3316.63±50.00	18.32±0.5	26.32±0.5

*-glass plates did not separate during the experiment

According to the results: Solcoseryl® and Dolobene® showed the best spreadability in the parallel-plate method (3115.66±50.00 and 3316.63±50.00 respectively); Contractubex® and Dolobene showed the best spreadability in the "slip and drag" test (73.46±0.5 and 18.32±0.5 respectively); Solcoseryl® and Contractubex® showed the best spreadability in the viscometry test (43.86±0.5 and 76.92±0.5 respectively). Thus, the obtained data are consistent with each other, which may indicate the relevance of the selected methods.

However, the results obtained cannot serve as industrially manufactured gels qualitative assessment approach. Depending on the pharmacological effect of the gels for topical use, differentiation of the spreadability optimums is necessary. For example, for vasoprotectives and NSAIDs the additional shear force is required when applying pharmaceutical compositions with low spreadability values, it will increase blood flow and accelerate the onset of the therapeutic effect. It distinguishes them from preparations applied to the wounds which should be quickly and evenly spread over the affected area without additional shear stress.

DISCUSSION

Modern researchers involved in topical semi-solid dosage forms quality assessment use a limited set of techniques to test the spreadability (various modifications of the parallel-plate method or the "slip and drag" method are most often used) [5-15]. In each same study, the conditions of the experiment are often subjected to significant or minor changes (parameters such as the exposure time of the load, the mass of the load, the mass of the dosage form, and the size of the glass plates). This particular problem does not allow to compare the analysis of the results and determines the optimums for the spreadability parameter.

The registration of spreadability "optimal values" is extremely important. Often researchers conduct only comparative studies of the pool of sample spreadability during their screening in the development phase. However, this approach does not allow a complex evaluation and spreadability level ranking of the experimental sample in the pool of similar products for the dermatological application. The idea of commercially available sample utilization as spreadability standards is presented in the works of Qushawy M. and Iglesias N [19, 20]. The experimental samples obtained were compared in parallel tests with the Voltaren®, Emulgel®, [19], and Daktarin® [20]. These products were well-established as preparations with optimal consumer characteristics.

While the number of experimental studies concerning the parameter measurement remains at an appropriate level, the lack of fundamental works attempting to systematize the available experimental methods for spreadability evaluation, their validation, and determination of optimal values, negatively affects the spread of the practice of studying the spreadability parameter, as well as the introduction of the criterion "spreadability" in the lists of standardization criteria of the global regulatory documentation.

A PubMed search for the period from 2010 to 2020 revealed more than 600 publications using different methods to determine the bioavailability. However, no comparative studies reviewing known techniques for the parameter measurement and attempting to compare their biorelevant characteristics were performed.

Thus, a review of the currently available and most popular techniques for determining this parameter, studying the similarity of the results obtained for commercially available dermatological medicines is important for choosing the most relevant techniques or creating recommendations for the use of a complex assessment of the spreadability parameter by studying several known methods.

It has been established that the most suitable of the analyzed methods for determining the spreadability in terms of screening of the samples with the best performance is the "slip and drag" method-according to the ability of the upper plate to move under the influence of the weight of the attached load and the final separation of the plates, we can judge the ability of the sample to quickly and evenly spread on the surface. The unit of the spreadability, in this case, is an impulse that regards not only the area of the spreading of the sample over the surface (as in the classical interpretation of the parallel-plate method) or shear stress required for even spreading (viscometric method) but also the speed of spreading over the surface. It should be noted that none of the analyzed samples, which did not show separation of the parallel plates in the "slip and drag" method, had high spreading values determined by two alternative methods.

The parallel-plate method, which has become widespread in research and pharmaceutical development of new semi-solid dosage forms, because it does not require special equipment, is more suitable for a quantitative comparative assessment of the spreadability of dermatological semi-solid dosage forms. The low or high values of the spreadability according to the results of this method can be judged only in comparison with the pool of samples. The variation of the method with applying the test sample to a glass plate application and sequentially mounting similar-sized plates on top of each other has significant advantages in correlation with physiological spreading compared to mounting a load of a certain mass on top of the second parallel plate since it provides equal shear stress to the sample spread between the plates. By varying the number and mass of parallel plates, it is possible to *in vitro* simulate a range of shear stress in which the yield strength of the analyzed gels will fit.

Low values of spreadability obtained from the parallel-plate method for some of the analyzed samples (Dolgit®, Hepatrombin®) are likely to be associated with high yield strengths of these samples (table 2) which did not fit the shear stress range created by the model from parallel plates in the experiment.

The viscometric method for determining spreadability is also based on the ability of a gel sample to flow like a fluid with a plastic-type of flow after applying shear stress of a certain value (above the yield strength). This method requires sophisticated apparatus; nevertheless, it is the most accurate, reproducible, and validated. For samples with low yield strengths (table 2), high optimum spreadability is characteristic-these results are correlated according to the results of all experiments. Deep Relief®, Solcoseryl®, Contractubex®, and Dolobene®, whose viscometric spreadability values are higher than 20.0 mPa^{-1}, showed satisfactory results in the parallel-plate method and "slip and drag" method.

However, the Ketorol® sample with an average spreadability determined by the viscometric method (14.31±0.5mPa-1) was also acceptable by the spreadability results obtained from two alternative methods. It is important to note that Ketorol® had the highest value of plastic viscosity from the pool of the analyzed gels and the average yield strength (table 2). Thus, it cannot be reliably claimed that the values of the spreadability above 20 mPa-1 obtained from the viscometry can be reliable to judge the optimality of this indicator. For a final conclusion on the spreadability optimum, it is necessary to study a larger pool of samples of various compositions.

According to the results of the experiments and analysis of scientific publications, the most widely known methods for determining spreadability were evaluated (table 4).

Among the benefits of **the *"parallel-plate"* method** is simplicity, cost-effectiveness and quick obtaining of the results. At the same time, there is no standardized method of conducting the experiment, and the weight of the load installed on top varies in different experiments and has no scientific justification.

The model used in **the *"slip and drag"* method** allows to consider not only the spreading surface of the sample and the necessary shear stress but also the velocity parameter. However, the disadvantages of the method also include the lack of a standardized methodology, justification of the mass of the load on the leverage mechanism.

The *"master-curve"* method involves a combination of the subjective analysis with the rheological approach to the measurement of spreadability, the possibility of linking consumer preferences with the rheological properties of the sample. The

disadvantages of the method include the complexity of the experiment, inaccuracy in the subjective assessment. Measurements at low shear rates (about 1 s^{-1}) do not give a correct idea of the rheological properties of the sample due to the design features of the measuring geometries [9].

The use of ***viscometry*** to assess the spreadability allows obtaining the most accurate numerical values due to hardware, high reproducibility. Calculation of the spreadability as the reciprocal of the yield strength is carried out when measuring in a wide range of shear rates and levels the influence of the features of the measuring geometries, compared to the "master-curve" method. However, it is necessary to adjust the optimum values when using different ranges of shear rates and rheological models to approximate the results.

Thus, it should be noted that none of the described methods is completely reliable and correlates with the conditions of spreading *in vivo*. To determine this indicator, it is recommended to use a combination of the most reproducible and correlating with physiological conditions methods, for example, viscometric and "slip and drag".

CONCLUSION

The most promising option for the reliable determination of the spreadability is the combination of the viscometric method and the "slip and drag" method. It uses various spreading characteristics and allows comprehensively evaluating the *in vitro* measured parameter. To confirm or refute the possibility of finding the rheological optimums of spreadability, it is necessary to continue the study of both topical drugs and dosage forms in the development process, mono-and multicomponent bases, and pharmaceutical compositions.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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