Spreading of Semisolid Formulations
An Update

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Pharmaceutical semisolid preparations include ointments, pastes, cream emulsions, gels, and rigid foams. Their common property is the ability to cling to the application surface for a reasonable period of time before they are washed off or worn off. They usually serve as vehicles for topically applied drugs, as emollients, or as protective or occlusive dressings, or they may be applied to the skin and membranes such as the rectal, buccal, nasal, and vaginal mucosa, urethral membrane, external ear lining, or the cornea (1). These preparations are widely used as a means of altering the hydration state of the substrate (i.e., the skin or the mucous membrane) and for delivering the drugs (topical or systemic) by means of the topical–mucosal route.

One of the serious problems associated with the formulation and manufacture of topical–mucosal preparations is the establishment of reliable techniques for their characterization. The efficacy of a topical therapy depends on the patient spreading the drug formulation in an even layer to administer a standard dose. Spreadability is therefore an important characteristic of these formulations and is responsible for correct dosage transfer to the target site, ease of application on the substrate, extrudability from the package, and most important, consumer preference. This article discusses the various aspects of spreading, including the factors affecting it, the techniques available for its assessment, and various additives and interactions that can alter the spreadability of the final formulation.

A considerable problem associated with the manufacture of topically applied pharmaceutical products is the establishment of reliable techniques for their characterization. The efficacy of a topical therapy depends on the patient spreading the drug formulation in an even layer to administer a standard dose. Spreadability is therefore an important characteristic of these formulations and is responsible for correct dosage transfer to the target site, ease of application on the substrate, extrudability from the package, and most important, consumer preference. This article discusses the various aspects of spreading, including the factors affecting it, the techniques available for its assessment, and various additives and interactions that can alter the spreadability of the final formulation.

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culated using the following equation for plane laminar flow between two parallel plates:

\[ \frac{Y}{d} = \frac{v}{d} \]

in which \( v \) is the relative velocity of the plates (cm s\(^{-1}\)) and \( d \) is the distance between them (cm); that is, a measure of thickness of the film between the skin surfaces (3).

**Factors affecting spreading**

To assess the spreadability of a topical or a mucosal semisolid preparation, the important factors to consider include hardness or firmness of the formulation, the rate and time of shear produced upon smearing, and the temperature of the target site (3). The rate of spreading also depends on the viscosity of the formulation, the rate of evaporation of the solvent, and the rate of increase in viscosity with concentration that results from evaporation (6).

**Formulation characteristics.** Formulation characteristics, including viscosity, elasticity, and rheology, are the most important factors in the development and final behavior of semisolid formulations. Increasing the viscosity of the delivery vehicle increases its retention time at the target site but also decreases its spreadability. Therefore, consistency of these formulations (varying from fluid to very stiff texture) plays the most important role in their final behavior, including their spreading qualities on the substrate. Spreadability can be measured with various types of viscometers and varies according to the formulator’s requirement.

In suspension ointments, a logarithmic regression with a negative correlation was found between viscosity and degree of penetration, and a significant linear regression correlation was found between degree of penetration and spreadability (7). This correlation was further confirmed by Hegdahl and Gjerdet and Vennat, Gross, and Pourrat (8,9), who proved the existence of a strong negative correlation between the spreadability and viscosity of elastomeric materials. Also, spreadability of a formulation is inversely proportional to its cohesiveness because strong cohesive forces within a formulation retard its flowability and thereby its spreadability on the substrate. Therefore, the cohesiveness of the selected ingredients must be considered during the development of topical and mucosal formulations (10). In addition, each formulation must be specifically designed according to the desired purpose of its use, site of application, and patient acceptability. Spreadability of a formulation can be either increased or decreased as desired by the formulator to suit the end purpose.

Increasing the viscosity of timolol eye drops by adding sodium carboxymethylcellulose increased the effect three- to ninefold as compared with that of nonviscous drops. The ocular penetration increased as a result of longer corneal contact, and systemic absorption decreased as the result of slower spreading of the solution on the nasal mucosa (11). Nyman-Pantelidis et al. investigated the effect of viscosity on the retrograde spread of two enema formulations and found a statistically significant difference in the spread between the low-viscosity and the high-viscosity enema (12). The low-viscosity enema spread over a larger area in the lower colon, mainly in the first 15 min following administration. In contrast, the enema with higher viscosity spread over a very small part of the rectum and took a longer time to spread over the rectal mucosa. Also, the rate and extent of spreading was more variable with the latter formulations.

In another study, Ivens et al. compared the application and spreading of four different pharmaceutical vehicles, including solutions, ointments, creams, and low-viscosity creams, and found the spreadability and retention of the ointment to be better than those of the other three (13). Whereas the ointment spread evenly in the test area, other formulations were unevenly spread and provided a lower dose in the periphery. The rapid evaporation of water from creams and solutions influences the spreadability and results in an uneven topical dose within the treated area. The formulations also must be spread quickly and at multiple sites to ensure correct dosage. Besides having the advantage of spread, ointments have the disadvantage of stickiness, staining, and poor patient compliance.

In a very recent study, a thermoreversible gel formulation was evaluated as a possible barrier to the transmission of pathogens that cause sexually transmitted diseases, including HIV and herpes simplex virus. It was found that this gel spread evenly in the vagina and coated the herpes virus or entrapped it in its micelles, thereby hindering its attachment to the target cells and inhibiting its infectivity (14).

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**Rate and time of shear.** Care must be taken that the operative rate of shear for rheological measurement is attained in a time comparable with the usual amount of time taken by the consumer to spread the preparation (3). In 1954, Kostenbauer and Martin approximated the rate of shear in the spreading of an ointment on a surface using the equation

\[ S = \frac{dv}{dr} \]

in which \( v \) is the velocity at which the ointment is being sheared and \( r \) is the thickness of the layer (15). They estimated the shearing rates for a pharmacist compounding an ointment with a spatula and for a consumer spreading an ointment on a surface such as skin as 200 s\(^{-1}\) and 120 s\(^{-1}\), respectively. A later study demonstrated that 120 s\(^{-1}\) was the point of greatest resistance to flow at low rates of shear for ointment bases, thus confirming the rates cited earlier (16). In addition, the later study concluded that the shearing region of 0–250 s\(^{-1}\) would be most relevant when characterizing the spreading properties of pharmaceutical semisolids.

Later, Langenbucher and Lange reported that for topical preparations, the apparent viscosity and spreading should be measured at 30–35 °C and at a shear rate of 104 s\(^{-1}\). This rate should be reached in a 10-s period (17).

**Temperature.** In a series of studies, Boylan obtained rheograms of 13 different pharmaceutical semisolids at various temperatures ranging from 20 to 35 °C using a Ferranti-Shirley cone-and-plate viscometer (16,18). Many of the preparations appeared to present a straight-line relationship between thixotropic area and temperature, but the viscosity of ointments is reduced by a factor of 0.5 for every 5 °C rise in temperature. He suggested that measurements for rheological properties should be made at several points in this temperature range to simulate most temperatures of use. However, a thin film of material rapidly warms to the respective temperature after spreading at
the target site. This temperature also may vary as a result of either increased blood flow induced by rubbing or of individual physiological conditions (17). Therefore, rheological experiments for correlation with spreadability must be performed at a suitable temperature according to the individual experiment.

**Site of application.** Pharmaceutical parameters of a formulation differ according to the target site of application. In the case of topical formulations, evaporation of water after application affects the spread and retention. Ointments prove better in such cases because evaporation is minimal because of their oily character, whereas solutions and creams tend to exhibit poor spreadability and rapid removal (13). In a very early study, Kostenbauer and Martin, after consulting several dermatologists, categorized pharmaceutical ointments into the following three classes:

- **Class I** consisted of ophthalmological ointments, which are the softest products and possess the lowest viscosities. These ointments spread at a shear rate as low as the action of a blink of an eye.
- **Class II** consisted of common medicated ointments, which although soft are stiff enough to stay at the point of application long enough to transfer the desired dose. They have a slightly higher viscosity than that of Class I ointments and require a moderate shear to spread.
- **Class III** consisted of protective ointments, which are hard and stiff so they remain at the site of moist ulcerative areas (15).

For preparations that are instilled in the mucosal cavities of the body such as the vagina or the eye, thinning of the vehicle by the cavity fluids also plays a role in their final behavior. In ocular formulations, thinning and drainage after mixing with tear fluids must be critically considered (19). Similarly, in vaginal formulations the vehicle’s compatibility with the vaginal fluids, their dilution after administration, and subsequent drainage depending on posture are important factors that govern their behavior. The rheological properties after administration determine the critical functions of spreading and retention over the vaginal surfaces. Gels are usually the most desirable dosage forms for this route. A study that compared four different contraceptive gels and statistically evaluated their shear thinning and viscoelasticity after application and subsequent dilution found that all gels that were tested exhibited non-Newtonian behavior, including shear thinning and viscoelasticity. The gels differed in their response to dilution with vaginal fluid simulant (20).

**Measurement of spreadability**

Acknowledging that each individual applies semisolid formulations to the skin with a slightly different motion, stroke, and rate, any rheological estimation of this process, however good, involves some degree of error. Nevertheless, good approximations can still be made. Tests and estimations are important to the development of semisolid formulations and can influence their final behavior.

Wood et al. developed several techniques to measure various rheological properties of pharmaceutical semisolids and lotions (21). They estimated the viscosity and elasticity required for extrusion of a formulation from a plastic bottle with respect to the bottle’s design, type of orifice, and thickness of the plastic. They also measured the shearing rates involved in high-speed tube filling and extrusion from collapsible tubes and assessed their effect on the formulation contained within. In another study they evaluated the increase in tackiness that occurs in some formulations as they dry and devised an empirical test to measure the cohesive–adhesive capability of skin surface during absorption after the rub-in.

Several authors have assessed spreadability using the theoretical equation of plane laminar flow between parallel plates (17,22), whereas others have made evaluations with a correlation between non-Newtonian viscosities (23,24). The in vivo methods reported use techniques such as gamma scintigraphy (25) in addition to individual sensory assessment (17,26,27).

**Parallel-plate method.** The parallel-plate method is the most widely used method for determining and quantifying the spreadability of semisolid preparations. The advantages of the method are simplicity and relative lack of expense. Also, the assemblies can be designed and fabricated according to individual requirements of the type of data required, the route of administration, the surface area to be covered, and the model membranes to be considered. On the other hand, the method is less precise and sensitive, and the data it generates must be manually interpreted and presented.

The spreading behavior of various Witexol suppository bases was tested between two Plexiglas plates at 37 °C, and optimum bases were selected on the basis of their spreading properties (28). Hadi et al. (29) evaluated polyethylene glycol ointment bases for spreadability using a parallel-plate extensometer based on the sliding-plates design. Later, Vennat et al. validated the spreading-diameter measurements of hydrogels on the basis of cellulose derivatives and established the linearity of spreading-diameter measurement (30,31). The linear relationship between spreading diameter, viscosity, and the concentration of gelling agent depended on the cellulose derivative. The linear relationship between viscosity and spreading diameter was independent of the derivative. Good repeatability and reproducibility of the spreading measurement was found. The spreading capacity of the gel formulations was measured 48 h after preparation by measuring the spreading diameter of 1 g of the gel between two 20 × 20 cm glass plates after 1 min. The mass of the upper plate was standardized at 125 g. Panigrahi et al. used a similar apparatus to assess the spreadability of lyncomycin hydrochloride gels (32). The following equation was used for the purpose:

$$S = m \times \frac{1}{t}$$

in which S is the spreadability of the gel formulation, m is the weight (g) tied on the upper plate, l is the length (cm) of the glass plates, and t is the time taken (s) for the plates to slide the entire length.

DePaula et al. determined the spreadability of various ointment formulations by compressing the sample under several glass plates of known weight (33). Twenty plates were subsequently placed over the sample at 1-min intervals. The spreading areas reached by the sample were measured in millimeters.
in the vertical and the horizontal axes. The results were expressed in terms of the spreading area as a function of the applied mass according to the following equation:

\[ S_1 = d^2 \times \frac{\pi}{4} \]

in which \( S_1 \) is the spreading area (mm\(^2\)) resulting from the applied mass \( i \) (g), and \( d \) is the mean diameter (mm) reached by the sample. The spreading area was plotted against the plate weight to obtain the spreading profiles.

In another study, Arvouet-Grand et al. determined the spreadability of various oil-in-water creams by pressing 1 g of a sample between two 20 \( \times \) 20 cm horizontal plates, the upper of which weighed 125 g (34). The spread diameter (\( \phi \)) was measured after 1 min. Under these experimental conditions, they applied the term semistiff creams to samples with \( \phi \leq 50 \text{ mm} \) and semifluid creams to those with \( \phi > 50 \text{ mm} \) but \( < 70 \text{ mm} \). Lardy et al. recently used a very similar method to evaluate the spreadability of various test hydrogels (35). The 1 \( \pm \) 0.01 g gel sample was placed between two 20-cm\(^2\) horizontal glass plates, and \( \phi \) was measured after 1 min. The mass of the upper plate was 125 \( \pm \) 1 g. The study temperature was maintained at 21 \( \pm \) 0.5 \( ^\circ\)C, and the gels were evaluated 48 h after their preparation. They were finally graded from fluid to very stiff on the basis of the value of \( \phi \) obtained. Principal component analysis, a powerful statistical method, was used to demonstrate the relationships among the various parameters that describe the consistency of the hydrogels and their spreadability.

Lucero et al. used a Ranvier-type manual microtome to study the compression deformation (i.e., spreading) of hydrophilic gels of \( \alpha \)-tocopherol (36). The microtome that was used had a perfectly flat 5-cm-diameter plate, a 1.2-cm-diameter screw bore, and a 0.68-mm thread. A sequence of masses of 80, 150, 300, and 500 g equivalent to compression stresses of 3302, 6191, 12383, and 20638 dynes/cm\(^2\) respectively, were placed on the cylinder of a 77-mm\(^3\) sample under ambient conditions. The duration of each application of force was 1 min of compression with 30-s rest intervals. To evaluate the resulting deformation by each of the stresses, photographic plates were printed with the areas of spreading produced using a lamp of constant intensity placed at the same location. Also, these areas were determined by a direct reading of the perimeter by means of a planimeter.

**Subjective assessment.** As the name suggests, subjective assessment is based on the sensory assessment of human volunteers. This mode of measurement is closest to the true spreadability assessment because the results are generated from the individual feel of the formulation. However, because it requires human assessment it is unpredictable and variable, and the element of reproducibility is reduced because the individual attributes of the subjects are involved. Therefore an element of bias always exists.

Lagenbucher and Lange described *spreadability* as a measure of viscosity correlated to subjective preference. Oils with viscosities ranging between 0 and 10 P at 35 \( ^\circ\)C were presented to test subjects who rated the ease with which the formulation could be spread on the backs of their hands. The scores obtained were plotted against the viscosity of the sample. The most-acceptable viscosity does not mean the most-viscous sample but the one with the best spreadability according to the test subjects (17).

DeMartine and Cussler predicted various subjective attributes of liquid texture (26). They stated that subjective spreadability and viscosity are perceived as the shear stress on the fingers, whereas subjective stickiness of a formulation is perceived as the time frame during which the finger is pulled away from the sticky surface. Figure 1 shows a correlation between finger geometry and two parallel plates. Assuming that when fingers move against each other in an oscillating motion with constant amplitude and for a constant period of time, the finger velocity varies little with changes in objective liquid viscosity. First they developed equations for the thickness of the fluid film on the fingers as a function of time, and then using those equations they developed more equations for predicting spreadability, viscosity, and stickiness. Subjective spreadability was found to be inversely proportional to the shear stress. It was also proportional to the ratio of viscosity of the sample to the steady velocity of the fingers. For each textural characteristic, the study used panels of between 15 and 24 members of both sexes ranging in age from 20 to 50 years who had not been trained before the present work.

Aust et al.’s study of sensory or skin-feel approach for the evaluation of creams and lotions included a panel of nine judges who rated various skin-feel attributes, including spreading characteristics (27). The participants applied the test formulations to the inside surface of their forearm and scored the attributes numerically.

Solutions, ointments, creams, and low-viscosity creams were tested on 29 healthy volunteers who applied a fixed amount (0.1 g) to the abdominal skin to assess the best vehicle for topical therapy. Ointment proved to be the vehicle of choice because it ensured even spreading and retention and therefore a correct dose transfer (13).

**Master-curve method.** The master-curve method combines the advantages of both the subjective assessment of spreadability and the use of instrumental measurements. It was brought forward by Barry et al. who, in their many studies, coupled the sensory assessment of spreadability with the master-curve concept derived from rheological measurement of viscosities of the test samples (3,37–40). The method determined the relationship...
between the shear stress and the shear rate that operated during the spreading of topical preparations on the skin by deriving from the master curves for lipophilic preparations and hydrophilic preparations, including oil-in-water emulsions and aqueous gels (3, 38). A panel of volunteers compared a series of formulations that varied in consistency from mobile liquids to stiff semisolids with a range of Newtonian silicone oils of various viscosities. The participants spread the materials on the inner surface of their forearm. The mean temperature of the participants’ inner surface of the forearm was approximately 34 °C, the rates of shear varied approximately from 400 to 2500 s⁻¹, and the shear stresses varied from 40 to 6000 Nm⁻². The panel indicated which oil appeared to possess the same spreading properties as each test formulation. Flow curves of the materials were obtained with a Ferranti–Shirley cone-and-plate viscometer and the intersection of the rheogram of the test formulation, and the selected Newtonian oil provided estimates of the shearing conditions that operate during spreading of the dermatological formulation on the skin. A double logarithmic plot of shear stress against shear rate provided a master curve. The preferred region of this master curve was bounded by ~ 400–700 s⁻¹ and 200–700 Nm⁻². The panel then rated the same preparation in terms of preferred spreadability. These data, superimposed on the master curve, suggested the optimum and preferred spreading conditions for maximum patient acceptability. The data obtained indicated a dynamic relationship between the rate of shear, the relative viscosity, and the thickness of the oil film on the skin.

This procedure for continuous shear rheometry provides a sound basis for assessing the rheological behavior of a material under moderate shear conditions (see Figure 2). Suzuki et al. showed that the sensory-perceived property of the product consistency, and therefore spreadability, is closely related to Barry’s ground state (i.e., the state in which the structure of the viscoelastic material is flexed but not destroyed) (23).

In vivo studies. In vivo studies are the best possible assessment method for any pharmaceutical research. Little work has been done in vivo for the measurement of spreadability of semisolids, but a few animal and human study data are available. These studies bypass all elements of bias and instrumental limitations and give an accurate picture in terms of the biological environment.

Animal models. Grant and Liversidge, in an attempt to assess the rheological behavior of fatty suppository bases and their spreading characteristics, developed a method using rats (41). The rats were deprived of food for 24 h, and their intestine was completely purged to remove any fecal pellets. The suppository then was inserted into the rectum, and the rectum was sealed with a cyanoacrylate ester adhesive. The rats then were placed in a cage with food and euthanized after the allotted time. The dead animals were dissected, and the distance of ingestion of the suppository base containing dye was measured from the external anal sphincter.

Richardson et al. studied the distribution and retention of a novel bioadhesive intravaginal delivery system based on HYAFF (a chemically modified hyaluronic acid ester) microspheres in a sheep model (42). In a preliminary experiment, the dimensions of the ovine vaginal cavity were outlined and imaged by gamma scintigraphy after administration of a suitable volume of ⁹⁹ᵐTc-Technitium (⁹⁹ᵐTc)-labeled gellan gum. The gum solution gels after administration into the vagina and is hence able to fully fill and outline the cavity. The data collected then was used for subsequent comparison with the distribution of the radiolabeled HYAFF formulations. In other groups of sheep, ⁹⁹ᵐTc-HYAFF microspheres were either administered as a dry powder or suspended in a vaginal pessary, and the distribution and intensity of radioactivity in the genital tract was measured during a period of 12 h.

Human volunteers. In studies on human volunteers, the noninvasive technique of gamma scintigraphy has proved to be a very valuable means to assess novel formulations aimed at optimizing retention and spread locally or in systemic drug delivery. This technique is the most effective method for studying the spreading and retention of pharmaceutical semisolids for insertion in mucosal cavities.

Nyman-Pantelidis et al. investigated the retrograde spread of two budesonide enema formulations with different viscosities (12). Three female and two male patients were given the enema formulations containing budesonide and an unabsorbable radioactive marker (⁹⁹ᵐTc-labeled human serum albumin microlloid), and the spread was monitored by gamma scintigraphy. In a similar study, Wilding et al. used the same technique to evaluate the colonic spreading of a rectal foam enema in patients with quiescent ulcerative colitis (43). A single administration of a mesalazine foam enema containing ⁹⁹ᵐTc was conducted on 10 patients, and the spread of labeled Tc was assessed during a period of 4 h by gamma scintigraphy.

Brown et al. assessed the vaginal spreading and clearance of...
a radiolabeled, fatty-based pessary formulation and a putative, bioadhesive gel formulation (Replens, Columbia Laboratories Inc., Aventura, FL) in six healthy postmenopausal female volunteers during a 6-h period using gamma scintigraphy (25). The study was also designed to investigate whether any of the formulation was capable of migrating across the cervix into the upper genital tract. The formulations were administered into the posterior fornix of the volunteers, and immediately a sanitary dressing was applied to contain any leakage of the formulation. Dispersion and spreading of the formulation within the vagina was monitored throughout the study day using a gamma camera within a 40-cm field of view and fitted with a low-energy parallel hole collimator. Anterior and posterior images of 60-s duration were acquired at predetermined intervals. For analysis, the images were displayed on a color monitor, and the extent of spreading was assessed in terms of the anatomical location of the tracer. It was also observed that following placement of the formulation in the posterior fornix, no spread into the cavity of the uterus or beyond was observed in any of the volunteers for either the pessary or the gel formulation.

**Miscellaneous methods.** In addition to the methods previously described for spreadability measurement, some techniques or instruments originally designed for other purposes have been used for the measurement of spreadability of semisolids. Four of the instruments are described in this section.

**Viscometers and penetrometers.** Viscometers are by far the oldest and most widely used instruments for the measurement of spreadability. They measure spreadability as a function of viscosity of the formulation. Cone-and-plate viscometers are best suited for estimating the viscosity of semisolids. The Ferranti-Shirley cone-and-plate viscometer was used by Boylan as early as 1967 to evaluate the spreading properties of semisolids, and he described various advantages and disadvantages of using the instrument for this purpose. The advantages included the provision of a multipoint rheogram, the ease of maintaining a constant shearing rate for an indefinite period of time, and a shearing geometry that closely duplicates that of the application of the materials with a circular motion on the skin. In addition, it subjects all portions of the sample to uniform shearing stress. The disadvantages included slippage between the rotating portion of the viscometer and the sample during measurement. However, rheological procedures by which the spreading properties of pharmaceutical semisolids can be reproducibly measured were presented (18). In addition, Barry et al. in their series of studies mentioned previously in this article correlated sensory assessment of spreadability to viscosity measured using a Ferranti-Shirley viscometer.

Penetrometers, usually used to measure the viscosity and consistency of semisolids, also can be used to determine the spreadability of semisolids (44). The following equation can be used to yield the spreadability index of a formulation using a cone penetrometer:

\[
\text{Spreadability Index} = \frac{H}{R^2}
\]

where H is the height of the cone penetrometer and R is the radius of the cone. This equation provides a quantitative measure of the spreadability of a semisolid formulation.
in which $P_0$ is the yield value for the sample (g/cm$^2$), $d_p$ is the depth of penetration of the cone (cm), $m$ is the weight of the cone plus the weight of other moving parts of the instrument (g), and $n_i$ is the constant ($\approx 2$), the precise value of which depends on the properties of the sample. $K_b$ can be calculated using the following equation:

$$K_b = \left(\frac{1}{n_i}\right) \cos(2\alpha) \cot(\alpha)$$

in which $\alpha$ is the half-life of the cone angle.

Extending the yield values obtained from the penetrometer, the spreadability index can be calculated using the following equation:

$$S_i = P_0(u) - 0.75(P_0[u] - P_0[w])$$

in which $S_i$ is the spreadability index, $P_0(u)$ is the yield value before working the sample, and $P_0[w]$ is the yield value after working the sample on a roller mill for 30 min. The factor 0.75 is derived from a comparison of penetrometer data with panel participants’ assessment of spreadability.

Various other penetrometers also have been used to determine a statistical correlation coefficient between spreadability and firmness, including a needle penetrometer, a cone penetrometer, a sectiometer, and a FIRA-NIRD extruder. Spreadability data obtained in this way agreed closely with the consumer-panel assessment of the same formulations, and in fact the instrumental technique proved to be more sensitive to small variations in spreadability. A highly significant correlation was identified between instrumental measurements of spreadability and hardness, the latter being assessed using a sectiometer (44). The regression equation used was

Resistance to spreading (g) = 90.9 + 2.63 \times \text{hardness (mg)}

The standard deviation was 43.4 g, and confidence limits at 5% significance levels were given as $\pm$ 86.7 g. It was concluded that although the most important factor affecting spreadability was hardness, certain other factors may also exert minor influences.

**Texture analyzers.** Texture profile analysis (TPA) was used by researchers to determine the mechanical and physical properties of semisolid systems (4,10). These properties include compressibility, cohesiveness, adhesiveness, hardness, and physical properties. The texture analyzer (model TA-XT2, Stable Microsystems, Surrey, UK) has an analytical probe that is depressed two times into the sample at a defined rate to a desired depth, allowing a predefined recovery period between the end of the first and the beginning of the second compressions. The TPA characteristics of the sample are evaluated from the resultant force–time curve. This precise and convenient method allows a small sample to provide a large amount of data pertaining to the physical properties of the semisolid formulations in a desired form. The data can be statistically evaluated and presented with ease.

**Spread meters.** Spread meters are specially designed to measure spreading of semisolid preparations. These mechanized and improvised parallel-plate instruments provide accurate, reproducible, and statistically relevant data.

Tamura et al. used a spread meter having a 115.5-g glass plate (Rigosha and Co. Ltd., Tokyo, Japan) for the assessment of spreadability of an oil-in-water–type cyclosporine gel ointment (45). Spread diameters of the samples were measured at 1 min after the beginning of compression at 20 °C. In another study, a spread meter (model 419, Rigosha and Co. Ltd., Tokyo, Japan) was used to measure the spreadability of gel ointments of indomethacin. A 0.45-mL sample of the ointment was placed in the sample hole on the spread meter. The spread diameter measured after 1 min was read at 25 °C. This spread area was used as an index of spreadability (46).

**Improvement of spreadability**

Because spreadability is such an important factor in the development of a wide variety of dosage forms ranging from topical and mucosal semisolids to lotions and drops, specific efforts are required to achieve the desired formulation characteristics. Various pharmaceutical excipients have been used to improve the lubricity and spreadability of topical–mucosal formulations. These include various polymers, surface active agents, and many other miscellaneous materials.

**Polymers.** Various polymers have been added to formulations to improve their spreadability. Product cohesiveness has been found to be significantly affected by its degree of polymeric concentration, and in nearly all cases increased polymer concentration has led to increased viscosity of the formulation. Thermal gelation temperatures also play an important part in a formulation’s behavior. Therefore the selection of polymer combinations and their relative ratios plays a very important role in formulation development and must be carefully considered to achieve the desired spreadability.

When various hydroxyethylcellulose (HEC) gels were formulated alone and in combination with polyvinylpyrrolidone (PVP) and polycarbophil (PC), it was observed that increasing the concentration of HEC from 1 to 3% led to increased hardness and cohesiveness, and a further increase from 3 to 5% had an opposite effect. When PVP or PC were used in combination with HEC, product cohesiveness depended on the individual polymer ratios (10).

For hydroxypropyl methylcellulose (HPMC) gels, Ferrari et al. reported that the gel strength or cohesiveness increased as the concentration of the polymer was increased (47). In a quantitative evaluation of the changes of dynamic surface tension and therefore the spreading behavior of HPMC aqueous solutions, various concentrations of the same were tested against Avicel PH-101 (FMC Corp., Philadelphia, PA) tablets. It was observed that by increasing the concentration of HPMC and thereby increasing the viscosity, the dynamic contact angle values also increased, thus decreasing the spreading behavior of the polymer solution on the tablet surface. It was also noted that the presence of a hydrophilic–type plasticizer improves the spreading pattern (48). McTaggart and Halbert suggested that the gel strength of HPMC gels is related to the degree of cross-linking in the polymer network (49).
To identify optimum bases for vaginal suppositories with spreading (upon melting) as a parameter, it was determined that Suppocire NA was the best lipophilic base and polyethylene glycol (PEG), a macrogel with low molecular weight, was the best hydrophilic base. The use of Suppocire was strongly recommended for formulating suppositories for the treatment of vaginitis (50). Hadi further stated that the type and amount of PEG used greatly affects the spreadability of ointment bases (29). PEG 2000 and PEG 6000 showed the best results as suppository bases in a comparative study of PEGs of various grades. PEG 200 and PEG 400 have been used to impart desired flow properties to ophthalmic ointments (51). Semisynthetic glycerides, as with Witespols (HS, H15, W25) (Condea Chemie, Hamburg, Germany), which consist of solid lipid nanoparticles, and Suppocires (AIM, NAI, A, AP) (Gattefossé, Weil-Am-Rhein, Germany), which consist of semisynthetic glycerides (C8–C18), have been studied as suppository bases, and the Suppocires showed better spreading properties (52).

A comparison of the spreadability of various light-bodied elastomeric and reversible hydrocolloid impression materials showed that polysulfide had the maximum spreading ability, followed by silicones, hydrocolloids, and polyether materials (8).

DePaula et al. prepared ointments of Achyrocline satureioides spray-dried extracts with various adjuvants, including colloidal silicone dioxide, MCC plus colloidal silicone dioxide (1:1), and β-cyclodextrin plus colloidal silicone dioxide (1:1), each in a glyceryl monostearate base (33). The physical properties, including spreading, viscosity, and pH were compared, and it was concluded that the best spreading area was reached by the ointment prepared with the spray-dried extract containing MCC plus colloidal silicone dioxide. Silicone dioxide alone gave the lowest value, indicating the desireability of incorporating this polymer (33).

An FAPG base (Syntex Pharmaceuticals Limited, St. Ives House, Maidenhead, Berks, UK), which is a mixture of propylene glycol, stearyl alcohol, polyethylene glycol, and glycerine combined to form a gel-like structure with a crystalline network, was investigated as a vehicle for dermatological formulations, and its rheological properties have been studied. This base is a mixture of propylene glycol, stearyl alcohol, PEG, and glycerol combined to form a gel-like structure with a crystalline network. Patient acceptance of skin spreadability was assessed using the master-curve concept. The spreading properties were close to the preferred values for maximum patient acceptance (3,38,40).

Surfactants. Surfactants, or surface-active agents, are amphiphilic compounds that form oriented monolayers at interfaces and exhibit higher equilibrium concentrations at interfaces than do those in a bulk solution. They exhibit several characteristics, including detergency, foaming, wetting, emulsifying, solubilizing, and dispersing. These agents are an integral part of the formulation of disperse systems for drugs and cosmetics and impart the desired physical characteristics and physical stability to these systems. Overall, they are responsible for the rheological properties of a formulation (53). Grant and Liversidge demonstrated the importance of the rheological properties of a suppository base in terms of the release and absorption of the drugs entrapped within (41). Softigen 701 (Condea Chemie), which is a polyethylene glycol–caprylic glyceride, and stearyl heptanoate are agents known to enhance the spreading of Witepsol suppository bases (28). In water-in-oil ointment bases with high water content, Miglyol gel (stearalkonium hectorite-propylene carbonate) (Condea Chemie), which is an ester of saturated coconut and palm kernel oil–derived caprylic–capric fatty acids; Span 80 (sorbitan monoleate); and Imwitor 780K (isostearyl diglyceryl succinate) (Condea Chemie), which is an ester from diglycerol isoctearic acid and succinic acid, were found to be the best emulsifying agents for imparting favorable consistency, low thixotropy, and good spreadability to the bases (54). On the other hand, spreadability was found to decrease with the increasing levels of te- gins (glyceryl esters) when they were incorporated in lipophilic bases (55). In yet another study, Eros and Hunyadvari investigated the effect of spans (sorbitans) on the physical properties of ointments and concluded that the spreading of an ointment decreases with the increasing length of the carbon chain of the fatty acid residues of the sorbitans (56).

Sodium dodecyl sulphate as a salivary substitute was used to improve the lubricity of the saliva at a bovine enamel interface, and it reduced the interocclusal friction (57). Statherin, which is a salivary acidic proline-rich protein and is another excipient used as a boundary lubricant on enamel, exhibits comparable lubricity to amphipathic molecules such as Gramicidin-S and sodium dodecyl sulphate (58). Various organomodified silicone emulsifiers have also been shown to improve spreading and lubricity along with other formulation parameters in topical formulations (59). Polyoxyethylated glycerides (e.g., Nikkol TMGS-5, Nikko Chemicals Co. Ltd., Tokyo, Japan) have been used as emulsifiers and spreading agents in various oral solutions and hydrogel ointments (45, 60).

Fluorocarbons. Fluorocarbons and fluorocarbon moieties comprise a vast family of synthetic compounds. They have recently found numerous applications in the pharmaceutical industry because of their special properties, including exceptional chemical and biological inertness, low surface tension, excellent spreading characteristics, unique hydro- and lipophobicity, high density, high fluidity, absence of protons, and magnetic susceptibility similar to that of water. Fluorinated lipids and fluorinated surfactants can be used to elaborate and stabilize various colloidal systems such as various types of emulsions, vesicles, and tubules as well as have the potential to be used for controlled-release drug delivery. Fluorinated amphiphiles have helped provide a variety of stable reverse and multiple emulsions and gels with excellent spreading properties. These compounds, with their polar heads, are significantly more surface active than their hydrocarbon analogues and thus display a greater tendency to form well-ordered stable supramolecular assemblies (61–63). Their potential as pulmonary, topical, and ophthalmological drug delivery agents and as skin protection barriers is being investigated widely (64).

Miscellaneous. It has been observed that the levels of colloidal silicone oxide–dioxides, which are >2% in suppository bases, inhibit the spreading of molten suppositories. However, with triglyceride bases and with cocoa butter, as much as 3% silica can be added to improve the flow characteristics of molten sup-
positories (65). Colloidal silicone dioxide, coupled with β-cyclodextrin or microcrystalline cellulose, was shown to enhance the oil-index values of an herbal ointment, thereby imparting better spreading properties (33). Glycerine, when added to formulations, also helped impart the desired rheological characteristics (66). Cyclomethicone has been widely used as a base fluid to formulate a variety of cosmetic and toiletry preparations because it imparts desirable lubricating and spreading properties (67).

A comparative study of the hygroscopicity and viscosity of glycerine, propylene glycol, and sorbitol and their effects on the moisture loss, spreading, and stability of nonionic and ionic oil-in-water lotions and cream emulsions found that all these polyols offered protection against water loss and provided emolliency, good spreadability, and stability to both lotions and creams. The effect varied with the concentration and relative humidity of the polyol used, and sorbitol offered the best results.

Low doses of eucalyptus oil have been used to improve the surface properties of various surfactants including ALEC (Abbott Labs, North Chicago, IL), which is a combination of dipalmityl lecithin and phosphatidyl glycerol; Exo-surf (Abbott Labs), which is a synthetic surfactant containing cetyl alcohol, colfosceril palmitate, and tyloxapol; beractant (Survanta, Abbott Labs), which is an exogenous surfactant; and a binary mixture of dipalmitoylphosphatidylcholine and phosphatidylethanolamine (2:3). Eucalyptus oil–enriched surfactants form an open membranous structure, thereby exhibiting better surface activity (68).

Lucero et al. described the effects of two antioxidants—ascorbic acid (AA) and butylated hydroxytoluene (BHT)—on the spreadability of α-tocopherol gel formulations (36,69). Carbomer 940 (DFS Products, Honiton, Devon, UK) was used as the gelling agent. α-Tocopherol gels were individually prepared with the two antioxidants and one without an antioxidant, and the three preparations were compared for their spreading characteristics. Both AA and BHT reacted with the carbomer and exhibited significantly different properties. In gels with BHT, hydrogen bonds were produced between the hydroxyl groups of α-tocopherol and those of BHT and the free radicals –C=O of the carbomer, thereby leading to an unwinding of the polymer resin and an accompanying rise in the viscosity and thickening and hence reduced spreading. In gels with AA a repulsion is created between the like (negative) charges originating in AA and the carbomer, leading to the loss of spiral structure of the resin and thus higher viscosity. However, this union still exhibits a statistically significant and improved spreading because the repulsion of the like charges forms hydrogen bonds between the hydroxyl groups of dehydroascorbic acid (an intermediate formed by oxidation of AA) and the carboxyls of the polymer. This union is very easily broken under pressure because of the nature of these bonds. This formulation therefore exhibits very good spreading characteristics.
Phospholipids such as phosphatidylcholine and triolein in their hydrated, liquid crystalline state gave large values of spreading pressures, thereby enhancing the spreadability of vesicular formulations (70,71). The use of physiological lipids that are normally present in the tear fluid (i.e., phospholipids, saturated and unsaturated fatty acids, and triglycerides) in eye drops provides better spreading behavior of these formulations in the eye because of the small size of the lipid particles (53).

The addition of neutral oils such as Miglyol 812 and Estasan, which is a medium-chain triglyceride consisting of glyceryl tricaprylate-caprate, each in a 5% concentration, had a favorable effect on the spreading properties of a vaginal suppository base (72).

Various drugs can also modify the spreading properties of the base of a topical preparation, thereby altering its rheological properties. Sodium valproate, when added to fatty bases, increases the viscosity notably and therefore necessitates the use of a spreadability aid. The addition of sodium valproate was found to increase the viscosity of Witepsol H-15/Span 80 and Suppocire As2–aerosil combinations when formulating suppositories. The active substance suspended in the molten base provides nuclei for the crystallization of high-melting-point glycerides, thus accelerating the separation and subsequent sedimentation of the suspended matter, altering the flow properties of the formulation (73).

Conclusion
Spreadability is a very important property in the development of semisolid preparations meant for topical–mucosal routes. Because it is responsible for the overall performance of a formulation, it must be carefully taken into consideration and procedures must be devised for its effective measurement during the formulation development stages. To date, little effort has been directed toward this issue and more work must be applied to its study.

On the basis of existing literature, an appropriate method for the evaluation of spreadability can be chosen or custom-designed according to the formulator’s need. Various polymers, plasticizers, and other materials can be incorporated into a formulation to alter its spreading characteristics. The polymers that can be used, their compatibility with the active ingredient, the prospective route of administration, and the rate and time of shear are among the most important parameters to be considered at the time of formulation development. The method to be used for assessing the spreadability must be selected carefully and modified according to individual requirements.

References
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