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Research Article

Influence of Colloidal Silicon Dioxide on Gel Strength, Robustness, and Adhesive Properties of Diclofenac Gel Formulation for Topical Application

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Abstract. The objective of this study is to identify the extent of stiffness, adhesiveness, and thixotropic character of a three-dimensional gel network of a 1% diclofenac sodium topical gel formulation in the presence and absence of colloidal silicon dioxide (CSD) and assess its ease of application and adhesiveness using both objective and subjective analysis. The 1% diclofenac gel was mixed with different amounts of CSD (*e.g.*, 0.5, 1, 2, 3, and 5% *w*/*w*) and allowed to equilibrate prior to testing. The texture analyzer in combination with a cone-cap assembly was used to objectively investigate the changes in spreadability and adhesiveness of the gel system before and after addition of CSD. Results indicate that an increase in pliability and adhesiveness at levels ≥2 to ≤5% *w*/*w* of CSD dispersed in the gel ensues. For subjective analysis, gels with (2% *w*/*w*) CSD and in the absence of CSD were uniformly applied to a 20-cm^2 (5 cm× 4 cm) surface area on the forearms of healthy volunteers and vehicle preferences by the volunteers regarding ease of application, durability on the skin, compliance, and feelings concerning its textural properties were assessed. It appears that changes in the gel formulation with the addition of CSD enhance gel viscosity and bonding to the skin. Results further show that changes in physical and rheological characteristics of gel containing 2% *w*/*w* CSD did not significantly change subject preferences for the gel preparations. These findings may help formulators to have additional options to develop more robust and cost-effective formulations.

KEY WORDS: colloidal silicon dioxide; gel-silica; texture analysis; thixotropic gel; topical gel.

INTRODUCTION

Some drugs are delivered topically for dermal treatment as opposed to transdermal which is for systemic use. In the former, drug must act locally as skin is compromised and the formulation is used to treat the diseased skin without entering the blood circulation, whereas in the latter case, the skin is intact and drug must enter the systemic circulation. In the case of topical gels, active drugs such as testosterone or anti-inflammatory agents (*i.e.*, diclofenac sodium) are used on the intact skin for local effect or possibly delivery to the dermis, deeper tissues, muscles, and blood capillaries in order to be therapeutically effective. Thus, it is essential to prolong duration of gel contact with the skin to ensure enough skin hydration and greater opportunity for the drug to penetrate through the more open pathways into the lower tissues. Occlusion is known to enhance efficacy of topical drugs (1,2). Therefore, increasing gel strength and viscosity may enhance gel properties and its resistance to rubbing off thus increasing skin hydration and by inference drug permeation into the skin (3).

Gels are defined as "semisolid systems consisting of either dispersions composed of small inorganic particles or large organic molecules interpenetrated by a liquid" (4). Presence of some degree of cross-linking between the dispersing phase and the solvated excipients in the formulation provides a three-dimensional network structure referred to as a "gel". The consequential internal associations and increases in viscosity are responsible for the semisolid state and resistance to movement. In the topical gel formulation, various polymeric materials, including polyacrylic acids (Carbomer) (5–7), sodium polyacrylamide (8), polyvinyl alcohol (9,10), and cellulose derivatives (11,12), are often used to obtain a viscous gel with network structure. However, the concentration of polymer is typically restricted to below 5% for safety concerns with pH preferably around 7 for optimum viscosity. In this study, we investigate the influence of various amounts of colloidal silicon dioxide (Aerosil®200) on the viscosity changes within a formulation, hoping to create a more viscous gel as colloidal silicon dioxide adsorbs large quantities of water without liquefying the system. This will lead to greater viscosity and thixotropic properties while keeping the polymer concentration below the restricted level of 5%. Increase in viscosity and rheological character of the gel may enhance occlusive properties of the applied gel, potentially allowing greater drug penetration into the deeper tissues (3).

Colloidal silicon dioxide (Aerosil®) is a fumed silica that has been extensively used as a glidant for powder flow in tableting. Furthermore, colloidal silicon dioxide has been successfully used to increase viscosity and impart thixotropic

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character to lipophilic ointments, non-aqueous suspensions, and certain pharmaceutical or cosmetic products. These effects are due to the formation of a three-dimensional network between the silica particles *via* hydrogen bonding (Fig. 1a) thus imparting paste-like consistency especially with oils such as peanut oil, silicone oil, isopropyl myristate, and other oils depending on the polarity of the oil (13).

Suspensions of silica particles in polymer solutions or gel systems are thixotropic, displaying a gradual increase in their stiffness on storage (at rest) due to the formation of a network as shown in Fig. 1c. When mechanical stress is applied (*e.g.*, rubbing of a gel on the skin surface or shearing), the three-dimensional network will break down and with passage of time, once again it recovers to the original firm structure under static condition (see Fig. 1c). Besides, the presence of polymer(s) in the gel formulation lends itself to additional interactions between silica particles and polymer chains complementing the thixotropic property of the system. Mechanistically, the adjacent polymer chains may cross-link with the contiguous silica particles, leading to the formation of a three-dimensional structure (Fig. 1c). The polymer chains may show a variety of conformations and adsorb at the surfaces of all particles in the system including silica particles. For example, carbomer polymers (polyacrylic acid) form acidic solution in water and can easily transform to a viscous gel state in an alkaline condition or when pH is greater than their pKa, resulting in formation of negative charges along the chains uncoiling the polymer chains and creating a more viscous solution. Moreover, increases in viscosity can be augmented when carboxyl groups of the polymer bind in a variety of forms to the surface silanol groups of colloidal silicon dioxide through hydrogen bonding (Fig. 1b). It is common in dispersed systems that they not only show this type of interactions but also show time-dependent particle/molecule interaction. As a result, bonds are created and a three-dimensional network structure is formed. Similarly, formation of a cross-linking network with increases in viscosity and consequently changes in thixotropic property often referred to as a "gel" is created. It is known that topical products require certain desirable characteristics including patient acceptability, spreadability, adhesiveness, resistance to rub-off and occlusive property, capacity to enhance drug liberation, and when needed, facilitate drug permeation into the skin (11).

In this work, we introduce a novel procedure and methodology using a texture analyzer with cone-cap assembly, which can be employed as a convenient and objective method to accurately and predictably measure both the spreadability and adhesiveness characters of formulated gels. It involves gradual penetration of the cone probe into a constant amount of sample (gel) placed in the cap, resulting in force-distance profile measurements which reflect the force required to spread the gel between the cone-cap surface areas as well as the force required to detach (*i.e.*, measure of adhesiveness) the cone from the cap when it is retracting to its original position. Additionally, formulation performance was also subjectively analyzed on the forearms of human subjects and results were compared with those obtained using the suggested method connected with texture analysis.

MATERIALS AND METHODS

Materials and Equipments

Commercially available Voltaren® gel (1% diclofenac sodium topical gel, manufactured by Novartis Inc.,

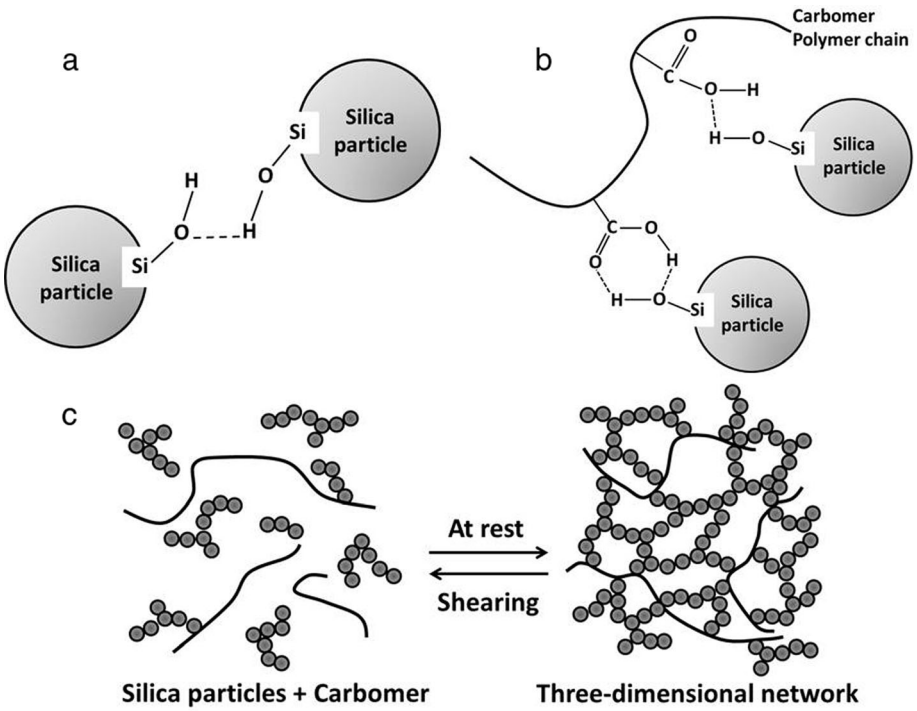

Fig. 1. **a** Hydrogen bonding between silica particles. **b** Likely formation of hydrogen bonding between silica particles and acid groups on polymer chains. **c** Time-dependent thixotropic property of the system when at rest or upon shearing

Parsippany, NJ, U.S.A.) was purchased and used as a model gel product for this study. Colloidal silicon dioxide with mean particle diameter of 12 nm (Aerosil®200, Evonik Degussa Corp., Parsippany, NJ), white mineral oil (Crompton Corp., Greenwich, CT.), and Carbomer (Carbopol®934, Lubrizol Inc., Cleveland, OH) were also purchased and used. TA.XT2i Texture Analyzer (Texture Technologies Corp., Scarsdale, NY) and synchro-lectric viscometer (Brookfield Inc., Stoughton, MA) were used to evaluate the changes in viscosity of certain preparations.

Composition of Topical 1% Diclofenac Gel

Diclofenac sodium 1% gel containing carbomer, homopolymer Type C, cocoyl caprylocaprate, fragrance, isopropyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, purified water, and ammonia solution was purchased from the pharmacy. To enhance gel viscosity, different amounts of colloidal silicon dioxide (*e.g.*, 0.5, 1, 2, 3, and 5% *w*/*w*) were dispersed in 20 g of the gel formulation by spatulation until homogeneous gel was formed. All the samples were allowed to equilibrate for at least 120 h at room temperature in sealed containers prior to analysis.

Texture Analysis

The measure of spreadability and adhesiveness (represented by retraction force) of gel formulation was investigated using a Texture Analyzer (XT2i) with cone-cap assembly, with a typical force-distance (F-D) profiling shown in Fig. 2. The instrument was calibrated for force and distance measurement at room temperature. The 45° cap was partly filled with 1 g gel or gel-silica mixture and set on the platform of the analyzer prior to F-D profiling. A corresponding 45° cone was used as a probe to spread (shear) and detect dynamics of spreading and retracting forces as it moved vertically toward the bottom of the cap followed by withdrawal to its original point. The cone and cap assembly were aligned coaxially. During the test, the cone probe travels downward (*i.e.*, compression mode) at a speed of 3 mm/s until it reaches the distance of 1 mm from the bottom of the cap. This is immediately followed by an upward movement of the probe (*i.e.*, retraction mode) at a speed of 10 mm/s. Force-distance profiles representing total work done to spread 1 g of gel in between the cone-cap surfaces and total work required to detach from the spread gel were obtained in each case. The total work done (W) is equivalent to the area under the force-distance curve and is described by Eq. (1):

$$W = \int F \cdot \mathbf{d}D \ldots\ldots\ldots\ldots \quad (1)$$

Where W is the total work done by the probe, F is the force applied, and dD is the total distance traveled by the probe (*i.e.*, displacement).

Gel Strength and Robustness Study

In order to examine the thixotropic/rheological property of the gel-silica mixture over time, 1 g of the mixture of diclofenac gel with 2% *w*/*w* colloidal silicon dioxide homogeneously dispersed in it was placed in the 45° cap immediately after gentle stirring, followed by texture profiling as described above. Additional samples containing 2% *w*/*w* colloidal silicon dioxide were also prepared and placed in different containers, sealed, and stored at room temperature to re-equilibrate for further analysis. Individual samples were gently removed periodically and placed in a cone-cap assembly after 2, 6, 12, 24, 48, 72, and 120 h and subjected to texture profiling to assess gel strength and time-dependent recovery of the gel.

Viscosity Measurements

To determine the influence of colloidal silicon dioxide and its interaction with polar or non-polar systems on viscosity, mixtures of mineral oil and different amounts of colloidal silicon dioxide (*e.g.*, 0.5, 1, 2, 3, and 5% *w*/*v*) and the mixtures of 0.1% carbopol solution in water and different amounts of colloidal silicon dioxide (*e.g.*, 0.2, 0.4, 0.6, 0.8, and 1% *w*/*v*) were prepared and analyzed. The measurement of viscosity of the prepared mixtures was determined using a Brookfield Viscometer equipped with a disk-type spindle (RV spindle). The viscosity of the gel was obtained by multiplication of the dial reading with corresponding factor provided in the manufacturer's chart.

Topical Application to the Forearms of Human Volunteer and Assessment

A consent form was obtained from the volunteers (N=6), and diclofenac gel 1% and the mixture of diclofenac gel 1% with 2% colloidal silicon dioxide homogeneously dispersed in it were applied to a 20-cm^2 (5 cm×4 cm) surface area on the forearms for performance assessment. The study was blinded and subjects were asked about their preferences and perceptions for either of the two gel formulations applied. On a scale of 1 to 10, various subject assessments regarding ease of application, durability on the skin, compliance, and feelings concerning its textural properties were collected and statistically analyzed.

RESULTS AND DISCUSSION

The texture analysis (TA) profile using cone-cap assembly indicates that a linear increase in gel strength with corresponding increases in stiffness at levels of ≥ 2 to $\leq 5\%$ *w*/*w* colloidal silicon dioxide dispersed in the 1% diclofenac gel ensues. Figure 3 shows the compression force and the retraction force increases observed with the increasing concentration of colloidal silicon dioxide based on texture profiling. Profiles clearly show that colloidal silicon dioxide is able to increase the overall textural properties of topical gels as the total work (*i.e.*, area under the F-D curves) required in both compression and retraction modes increase correspondingly. Figure 4a shows that increases in peak force *vs.* colloidal silicon dioxide concentration is linear up to 5% levels (r^2=0.9930 and r^2=0.9908 for compression and retraction forces, respectively). Figure 4b illustrates the total work done during compression (r^2=0.9801) and retraction (r^2=0.9713) based on F-D area under the curves. The slope of the lines in the case of retraction force measurements is slightly shallower due to differences in probe speed (*i.e.*, 3 mm/s for compression

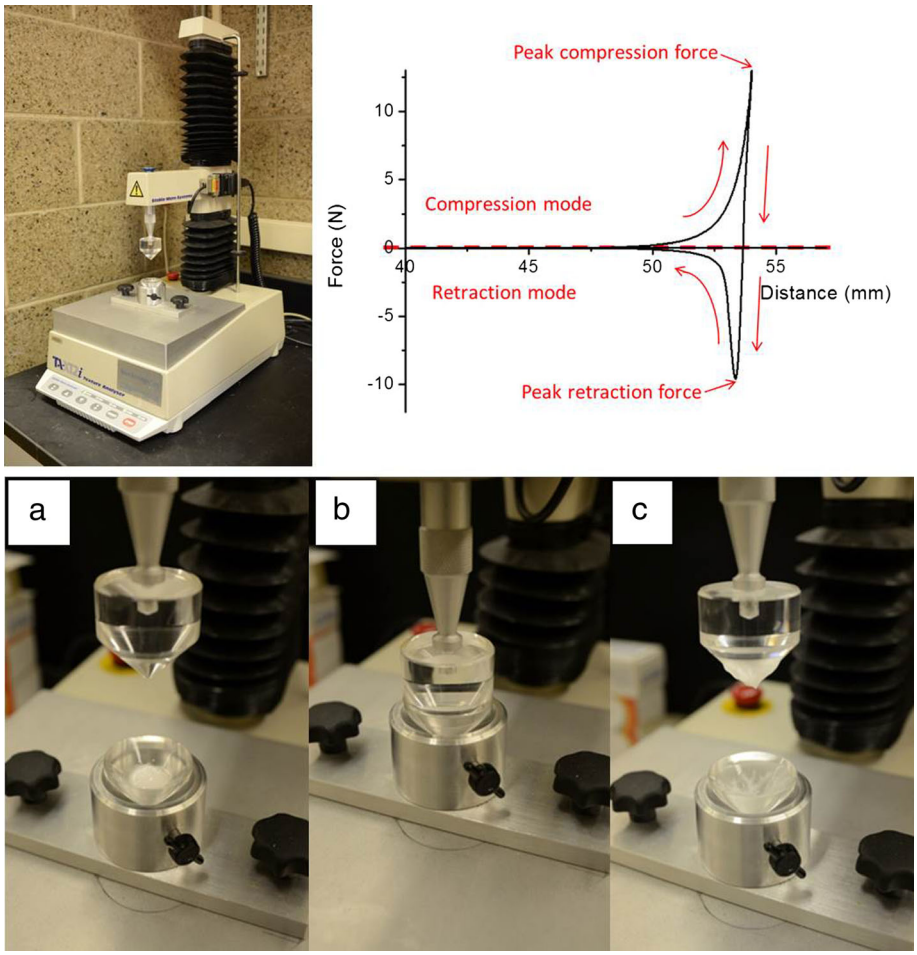

Fig. 2. Type of probes (cone-cap) used for measurement of gel behavior under mechanical force (shearing stress). **a** Downward movement (*i.e.*, compression mode) at speed of 3 mm/s. **b** Full distance traveled to reach the 1 mm of the cap depth. **c** Upward movement (*i.e.*, retraction mode) at speed of 10 mm/s. A typical force-distance profiles with *arrows* describing the direction of probe movement during the application of mechanical force (compression) on the gel and retraction force

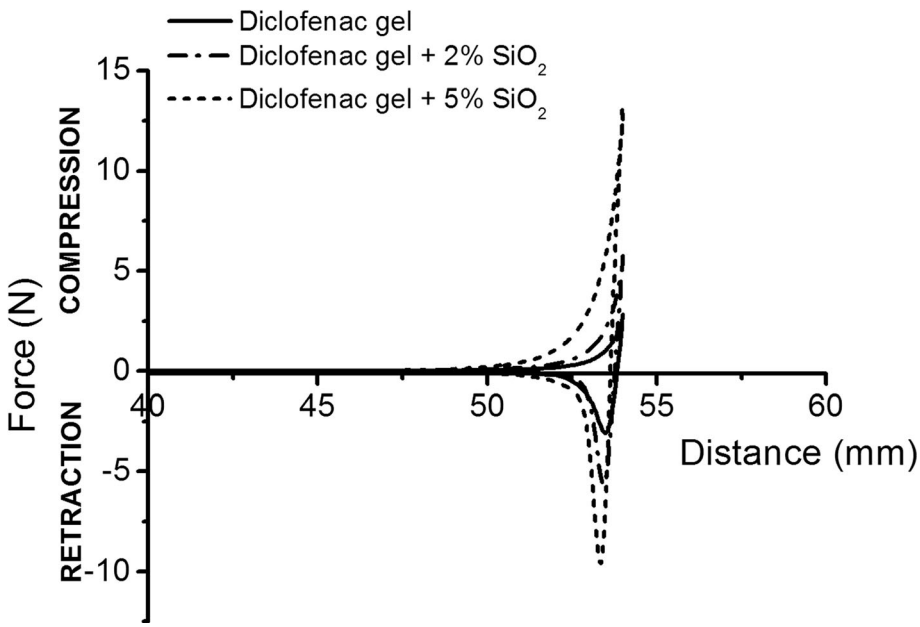

Fig. 3. Force-displacement (F-D) profiles of diclofenac gel, diclofenac gel with 2% colloidal silicon dioxide, and diclofenac gel with 5% colloidal silicon dioxide

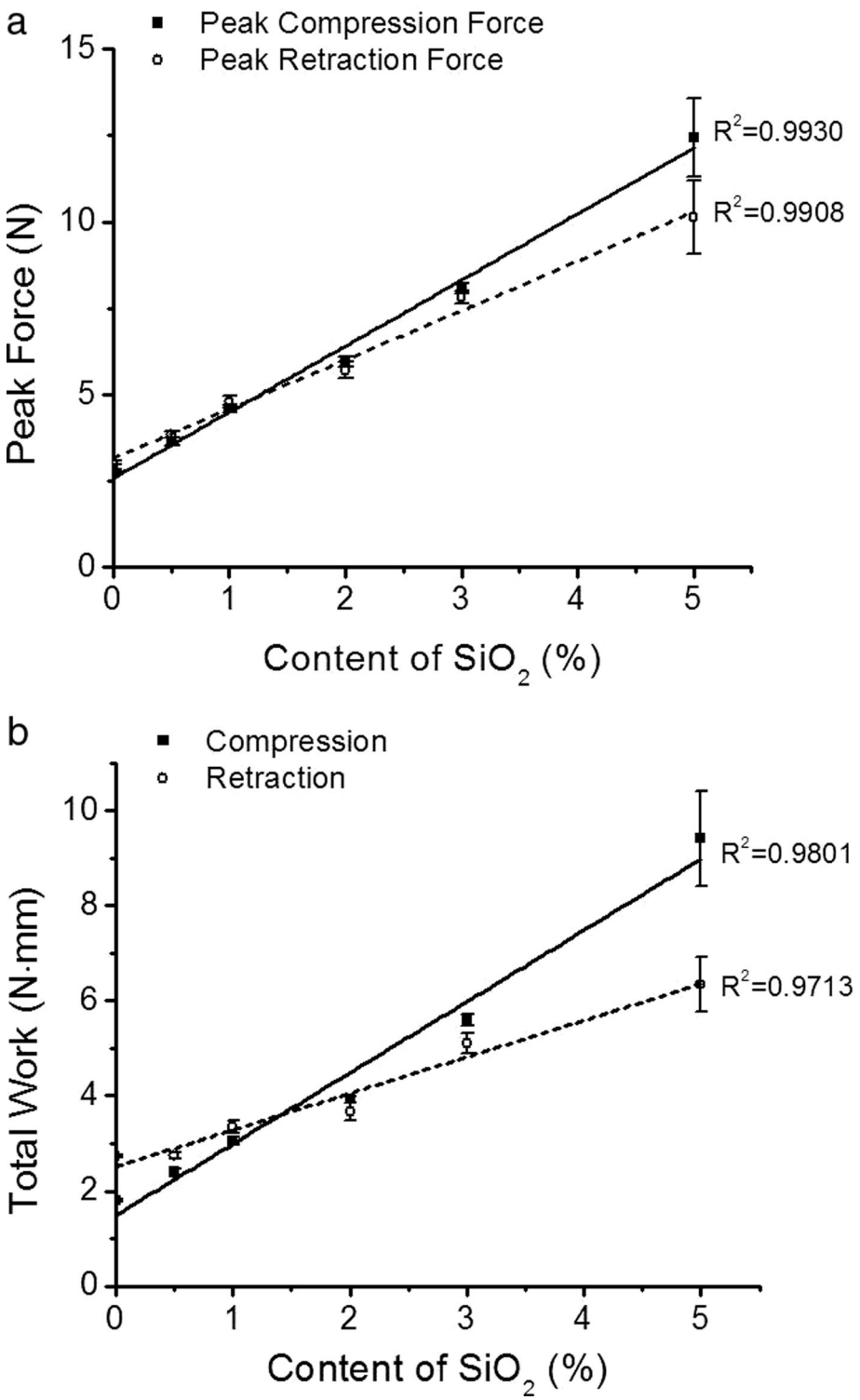

Fig. 4. **a** Increases in peak compression force and peak retraction force as concentration of colloidal silicon dioxide is increased. **b** Total work done to mechanically spread the gel between cone-cap assembly and retract the probe to its original position

vs. 10 mm/s for retraction). The retraction speed was specifically set at a higher rate as gels are required to set or recover in a more rapid manner once spread or applied to the surface(s). However, the overall profiles shown in Fig. 4a, b appear to be consistent and slope differences shown in Fig. 4 can also be discerned from the slope of the compression and retraction curves shown in Fig. 3. These data suggest that gels examined with the described methodology characterizes mechanical shearing analogous to those experienced when gels are topically rubbed and applied over the skin.

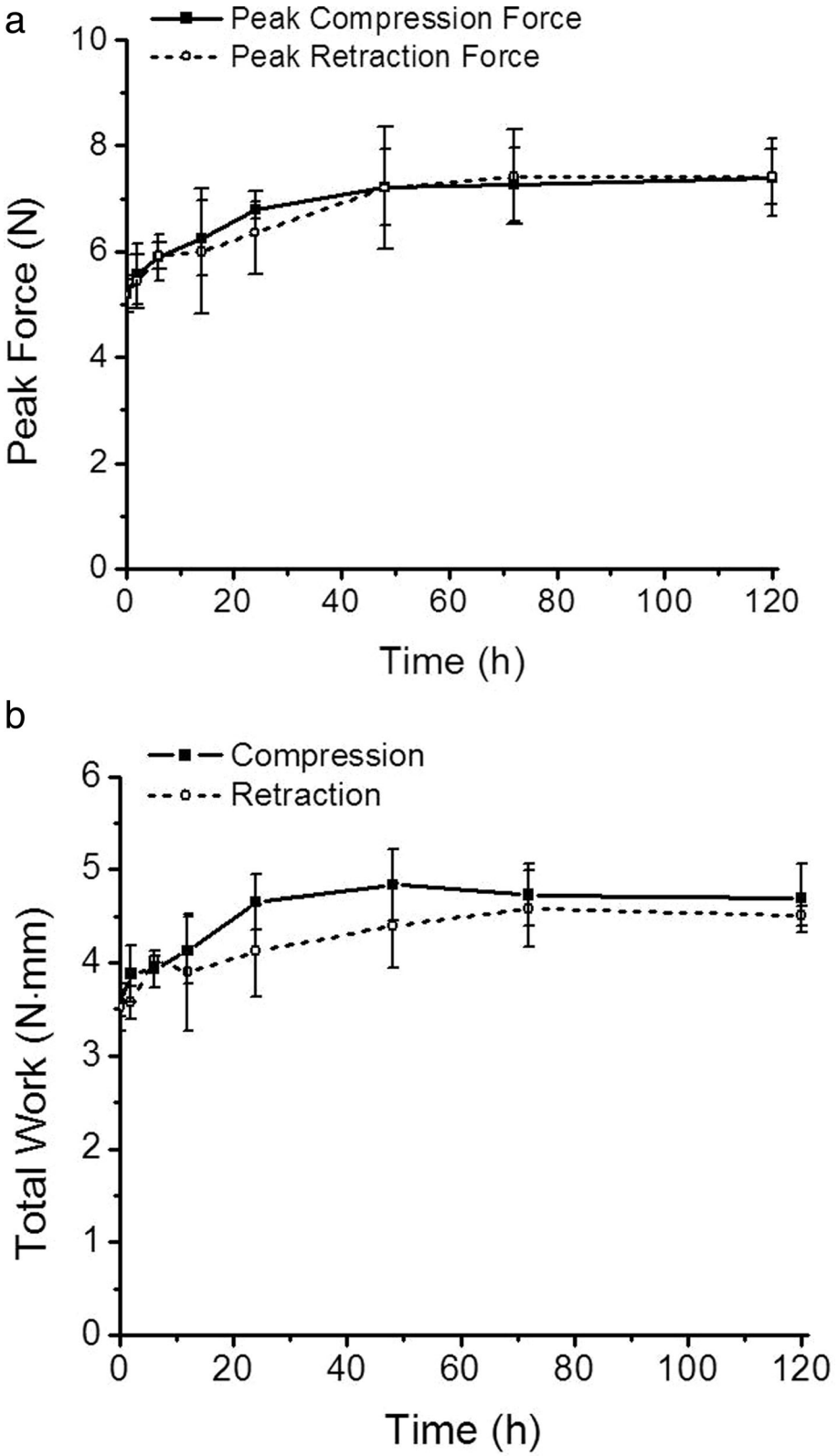

Fig. 5. Changes in peak compression force and peak retraction force (**a**) and total work done (**b**) on the gels (stored up to 120 h) as a function of time for 1% diclofenac gel containing 2% *w/w* colloidal silicon dioxide dispersed in the gel system

The result of the thixotropic study (*i.e.*, time-dependent changes during 120 h of storage at room temperature) further showed that both peak compression forces and peak retraction forces as well as total work done on the gel systems increased and

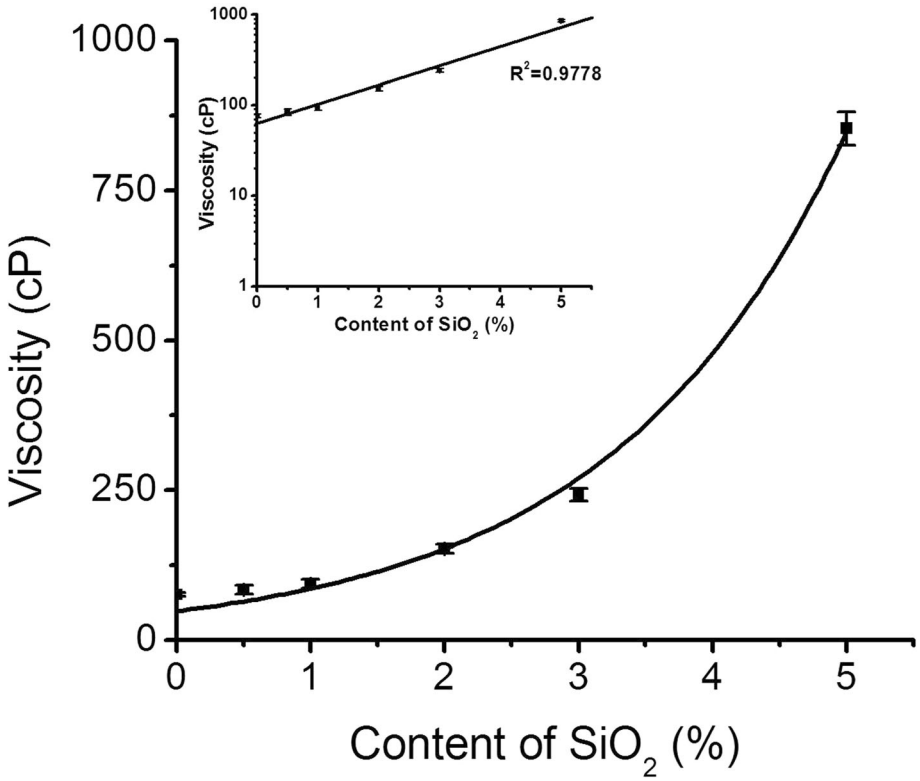

Fig. 6. Influence of colloidal silicon dioxide on changes in viscosity of mineral oil. *Inset* represents the logarithmic plot of the same data

stabilized upon storage (see Fig. 5). The recovery changes were more rapid in the initial stage, indicating a more rapid restructuring and regaining of the three-dimensional organization in the gel system followed by a much slower (*i.e.*, reaching a plateau after about 48 h) restructuring over a prolonged time period. It appears that under shearing, the hydrogen bonding

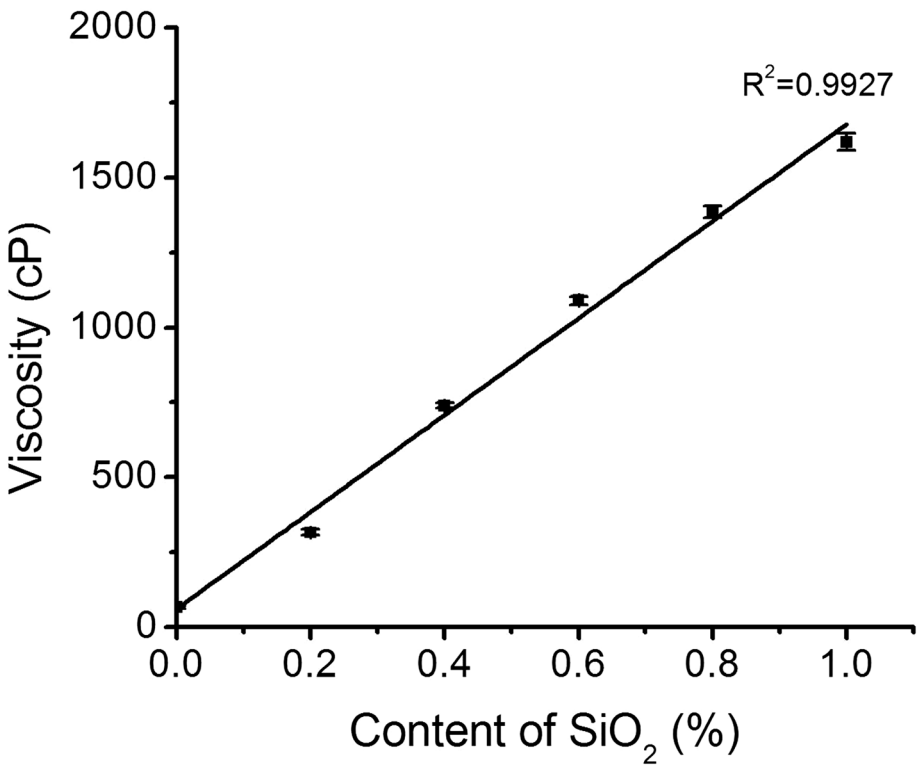

Fig. 7. Influence of colloidal silicon dioxide on changes in viscosity of 0.1% Carbopol solution

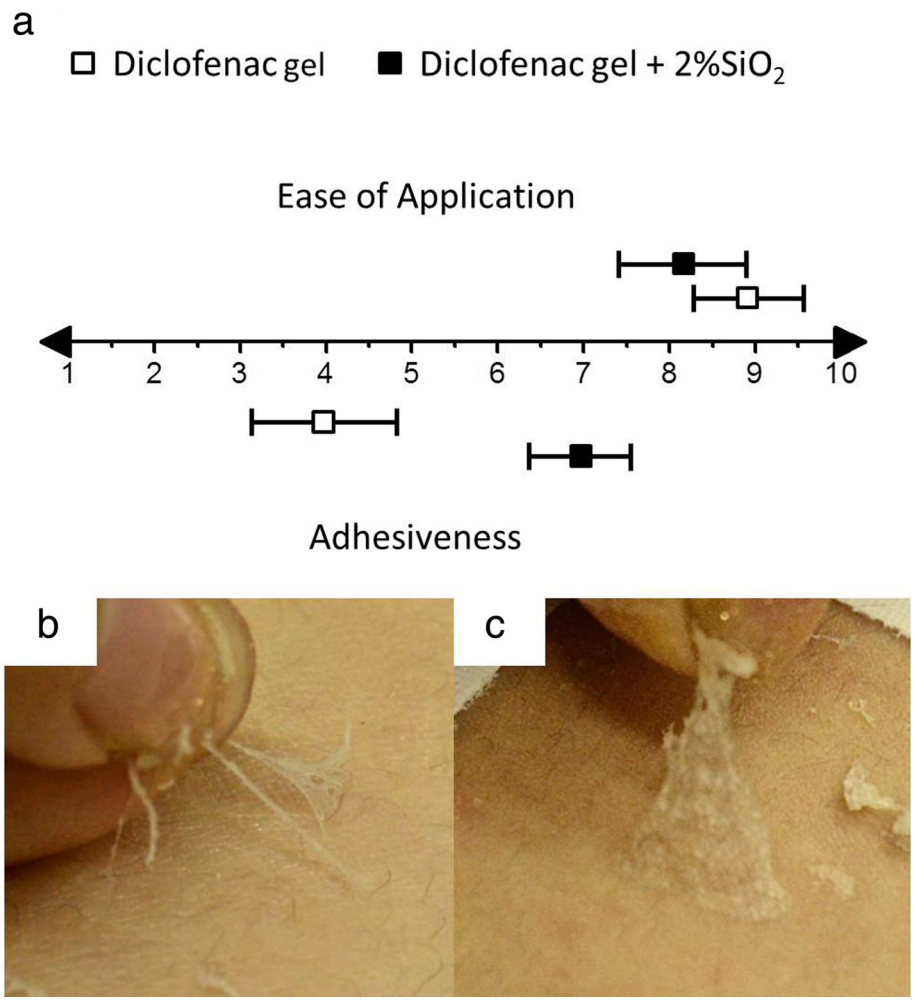

Fig. 8. Subjective and comparative assessment of diclofenac gel 1% (reference) and diclofenac gel+2% colloidal silicon dioxide on the forearms of human subjects (N=6), with respect to ease of application and adhesiveness character on a scale of 1–10 (**a**). *Photos* show comparative thickness and adhesiveness of formed films after 50 min for 1% diclofenac gel (**b**) and 1% diclofenac gel with 2% CSD dispersed in the system (**c**)

between silica particles and other components are broken down with a more fluid-like low viscosity system. While upon storage in the absence of mechanical forces, silica particles re-join again and the three-dimensional network rebuilds fairly quickly, resulting in a rapid recovery with increases in system restructuring with time. Thus, the dispersions of silica particles in the gel tend to enhance the thixotropic properties of the system initially followed by a gradual increase in gel strength upon storage (Fig. 5) due to the formation of similar network illustrated in Fig. 1. The viscoelastic nature and rheological character of such systems suggest that these gels tend to be valuable as topical delivery systems.

To examine the influence of a vehicle in the presence of colloidal silicon dioxide, the mixtures of mineral oil and colloidal silicon dioxide and the mixtures of 0.1% carbopol solution and colloidal silicon dioxide were investigated using a high performance rotational viscometer. Results illustrate an increase in viscosity for both the mineral oil-silica mixture and 0.1% carbopol-silica mixture (Figs. 6 and 7). When colloidal silicon dioxide is dispersed in the non-polar vehicle, for example, mineral oil, the available silanol groups can easily interact with each other *via* hydrogen bonding with a visible formation of three-dimensional structure (*i.e.*, thickened). Similar thickening or paste-like consistency can also happen with other oils such as peanut oil, isopropyl myristate, and silicon oil (13). The degree to which an increase in viscosity occurs is contingent on the extent of polarity of the oil. In this study, the viscosity of mineral oil-silica mixture is increased exponentially while for 0.1% carbopol mixture with dispersed colloidal silicon dioxide, increases in viscosity were more modest and linear, suggesting a more predictable performance in the formulation of the gels making them amenable in topical delivery systems. The solubility of carbopol in water depends on the interaction of polar groups of the polymer with water in an alkaline environment generating sufficient energy to disentangle the polymer chains from the solid state, allowing silica particles to interact with the available charges along the chain. Thus, carboxyl groups of the polymer interact with the surface silanol group of the silica particles through

hydrogen bonding with potential for cross-linking between reciprocal polymer chains. Consequently, a three-dimensional structure is formed accounting for increases in the system viscosity.

Performance assessment by using standard 1% diclofenac gel as a reference showed that inclusion of 2% colloidal silicon dioxide significantly enhanced gel viscosity, bonding to the skin, resistance to rubbing off, as well as an increased capacity to cause occlusion by forming a thicker film on the forearms of the subjects (Fig. 8). Application of silica-containing gels onto the forearms was comparable to that of standard gel in terms of subject compliance, ease of spreading, and comfort based on the subjective assessment on a scale of 1–10 with the descriptors extremely disagreeable, moderately disagreeable, slightly disagreeable, neutral, slightly agreeable, moderately agreeable, and extremely agreeable. Results show that changes in physical and rheological characteristics of gel containing 2% *w*/*w* colloidal silicon dioxide (CSD) did not significantly change subject preferences for the gel preparations ($P>0.05$) although adhesiveness to the forearm was superior in the presence of 2% CSD.

CONCLUSION

Non-Newtonian rheological properties of topical products such as viscosity can affect their drug delivery (14). Semisolids with high viscosity can effectively display high diffusion rates when compared to products of relatively lower viscosity. Acceptable criteria and methods for testing topically applied drug products is divided into those that assess general product quality attributes and those that assess product performance (4). Results of this study show that the novel procedure and methodology described using a texture analyzer with cone-cap assembly can be employed as a convenient and objective method to accurately and predictably measure both the spreadability and adhesiveness character of formulated gels. Changes in the gel formulation with the addition of colloidal silicon dioxide appear to enhance viscosity and bonding to the skin. The composition of the system allows for significant formation of hydrogen bonds mediated by the collective interaction of non-polar and polar constituents of the gel matrix including CSD, thus increasing viscosity and imparting thixotropic properties. This implies that greater occlusivity can ensue, which may enhance drug penetration into the skin and deeper tissues and possibly improve drug effect as suggested in the literature (3,4). The thixotropic performance of the gel-silica mixture is advantageous both during filling and packaging as well as when topically applied, since the viscosity decreases when shearing and restores on standing. Improved thixotropic properties and enhancement in viscosity and bonding to the skin as assessed by subject analysis may allow for reduction in application frequency and consequently improvement in patient compliance. These findings may help formulators to have additional options to develop more robust and cost-effective topical products for various API's and formulations.

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