Expert Opinion

Vaginal gel drug delivery systems: understanding rheological characteristics and performance

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Introduction: Vaginal gels are used for a wide range of clinical and pharmaceutical applications. Gel performance *in vivo,* including spreading ability, retention and drug release behavior, is closely related to rheological properties. Hence, a comprehensive rheological characterization of candidate gel formulations is important in screening and designing appropriate vaginal gels to achieve optimal clinical performance.

Areas covered: In this review, the basic destructive (flow) and non-destructive (oscillation and creep) techniques, commonly used in the assessment of gels, are introduced. The main rheological properties discussed in this work include viscosity, storage modulus, loss modulus, loss tangent and strain growth under small stress loads. In particular, this paper reviews the rheological methods used in characterizing vaginal gels and discusses the factors that may influence rheological performance. Recent advances in rheological methods, the use of advanced rheological methods and the challenges facing formulation scientists are also reviewed.

Expert opinion: The complex and dynamic environment of the vagina requires a comprehensive understanding of the rheological performance of vaginal gels. The establishment of suitable rheological tests to appropriately define such characteristics may facilitate the selection of a gel that avoids leakage. The ideal gel platform must provide adequate coating with minimal leakage. This is extremely difficult to obtain as it requires the formulation of a gel with a suitable viscoelastic balance.

Keywords: gels, rheological methods, vaginal drug delivery

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1. Introduction

Vaginal gels have been used to administer locally acting compounds such as antimicrobials, labor-inducing agents, spermicides, prostoglandins and steroids [1]. Moreover, as vaginal administration provides a large surface area for absorption, a rich blood supply, avoidance of first-pass metabolism and relatively high drug permeability, gels have also been used as a convenient way of administering systemically acting drugs [2,3]. Gels as vaginal delivery vehicles offer ease of application, high levels of patient acceptability and are inexpensive to produce. However, sustained drug release is often difficult to achieve due to limited retention as a result of the self-cleansing action of the vaginal tract. Therefore, it is common for gels to require multiple daily dosing to obtain optimal clinical efficacy.

Vaginal gels are multi-component systems comprising a polymer network in which aqueous fluid is 'trapped' forming a gel matrix. This gives rise to a unique

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gel property referred to as viscoelasticity wherein the gel possesses both solid and liquid character. Consequently, *in vivo* performance may vary depending on the value of the stress applied to the gel, the timescale over which the stress is applied and many other factors [4]. Polymer gels may be classified according to the nature of the continuous network that provides connectivity throughout the matrix. Chemical gels are formed by covalently bonding linear polymer chains, forming permanent or irreversible networks that will not disperse freely but rather swell to a certain extent. This is the basis of hydrogels that are used extensively as implantable drug delivery platforms [5]. Conversely, physical gels, which form the majority of vaginal gels, are formed by secondary forces and/or by polymer/polymer entanglements. These gels are reversible, and may be 'switched' between the sol and gel state by changes in temperature [6], pH [7], solvent composition [8] and the addition of ions [9].

Commercially accepted vaginal gels are aesthetically pleasing, non-toxic, physically/chemically stable and release the active ingredient to suit the clinical application [10]. Furthermore, vaginal gels must be cosmetically elegant and easy to apply. Once applied, gels are required to reside at the application site for a defined period allowing for controlled delivery of the active ingredient. In order to adequately administer drugs via the intravaginal route, delivery vehicles should be designed with the anatomical and physiological features of the vagina in mind. For example, the volume, composition and pH of vaginal fluids, and the forces the gel experiences *in vivo*, should be considered when designing gels as these factors play a pivotal role in defining drug release properties. Such variables will affect gel distribution and retention. Moreover, formulation of a vaginal gel drug delivery system possessing optimal characteristics not only requires understanding the effects of *in vivo* conditions but additionally a trade-off between spreading and retention. This was acknowledged in a recent article published by Owen *et al.* [11] wherein the success of a vaginal gel was deemed to be dependent on the propensity to spread along the vaginal canal and coat the vaginal epithelium. However, improved spreading was acknowledged to increase the likelihood of leakage, decreasing patient acceptability. Therefore, in order to achieve the delicate balance between spreading and retention thus achieving maximum clinical efficacy, it is important that the rheological performance of vaginal gels is fully characterized. This should involve a fundamental understanding of the relationship among spreading dynamics, retention, applied gel volume and *in vivo* conditions and their effects on rheological performance [12,13]. Consequently, a fundamental understanding of rheological theory, the characterization methods used to define rheological properties and an appreciation of how gel structure can vary in the dynamic vaginal environment is necessary in order to develop optimized vaginal gel products. Therefore, the aim of this review is to provide an overview of the fundamental rheological properties of gel systems so as to provide a basis for the development of more innovative, structured gels, offering improved clinical efficacy.

2. Vaginal environment: implications for gel-based delivery systems

An appreciation of vaginal anatomy and physiology is essential to the design and optimization of vaginal gels. Formulation scientists must be cognizant of how the anatomical and physiological features of the vagina influence gel spreading, distribution, retention and leakage. Vaginal fluids, semen and their pH values are key factors that can alter rheological properties of gels [14]. In general terms, increased vaginal fluid volume and/or the presence of semen will dilute polymeric structure and hence decrease the elasticity and rigidity of a gel. This could increase gel leakage. However, one must also consider the higher pH value of semen, relative to vaginal fluids, which has the potential to increase the rheological structure of poly-anionic gels or further decrease the structure or poly-cationic gels. In both cases, we would expect therapeutic efficacy to be affected. Therefore, knowledge of *in vivo* conditions allows for the development of robust vaginal gels and hence offers a way in which gel structure can be tailored to optimize therapeutic performance.

The vagina is often described as a slightly S-shaped collapsible tube (2 – 5 cm diameter) possessing two distinct sections, a lower convex region and an almost horizontal (130° to the lower axis) upper region [15-17]. The vaginal canal extends from the lower part of the uterine cervix to the external region of the vulva (labia minor) through a posterior length of 7 – 9 cm [18]. The vaginal wall is composed of four distinctive layers: the stratified mucosa, submucosa, muscularis and the tunica adventitia [1,19]. Recently, squeezing flow between vaginal walls has been reported to significantly affect gel spreading and distribution. This has the potential to affect intravaginal surface area coverage/coating and contribute to the therapeutic efficacy of vaginal gels [20]. Moreover, shearing rates experienced *in vivo* will have a significant influence on viscoelastic gels and, hence, their spreading and retention. Shear rates experienced *in vivo* are estimated to be $< 0.1\ s^{-1}$ during passive seepage between epithelial surfaces. Therefore, the use of non-destructive rheological techniques may be justified in order to exam the influence of small stresses/strains at extended time periods. Additionally, destructive rheological methods may be used as a complementary tool to provide a comprehensive view of how candidate gels perform under a range of shear stress environments caused by movements of the vaginal epithelial surfaces, gravitational and capillary flow, and sexual intercourse [21].

The rheological structure of vaginal gels is regarded as an important factor affecting *in vivo* distribution. It is desirable, therefore, to define those factors that can alter *in vivo* rheological performance. Vaginal fluids in particular have the potential to significantly alter rheological properties and drug release pattern as fluid volume and composition are dynamic,

complex and periodical [22]. The vaginal epithelium is in constant contact with fluid, mainly formed from transudate, passing through the vaginal wall from the blood vessels. The fluid is a mixture of vulval secretions from sebaceous glands and sweat glands and cervical mucus produced by glandular units within the cervical canal. Cervical mucus, a major component of vaginal fluid, is significantly influenced by the menstrual cycle. Changing estrogen levels during menstruation will alter fluid volume, composition and physical characteristics. During ovulation, vaginal fluid volume is increased due to mixing with uterine, oviductal, follicular and peritoneal fluids. This drives an increase in pH, fibrosity and mucin content, but a decrease in viscosity, cellularity and albumin concentration [23]. Additionally, the composition and volume of vaginal fluids is influenced by sexual arousal. In a sexually aroused state, the vagina is further lubricated through the release of vasoactive peptides that increase arteriolar dilatation [24]. Dilution by increased fluid volume would be expected to decrease gel viscosity, increase spreading and reduce retention time [25].

The vaginal pH of healthy, reproductive age women ranges from 4 to 5 [23]. The slightly acidic environment (maintained by the presence of lactic acid produced by *Lactobacillus acidophilus*) is a highly important defense mechanism as it offers natural resistance to the colonization of pyrogenic organisms. Vaginal pH may be affected by the presence of cervical mucus and also by the amount of lubricating vaginal fluids. Vaginal pH rises during the menstrual cycle and also following coitus due to the presence of semen, which is slightly alkaline. Furthermore, hygiene products often result in vaginal pH increase due to alteration of local microflora, which allows proliferation of pathogenic bacteria and yeast [26]. Obviously, the dissolution and absorption of drug molecules possessing ionizable functional groups will be significantly affected by vaginal pH. Moreover, polymeric gels possessing ionizable functional groups would be affected by increasing/decreasing pH values. In a study by [21], the rheological properties of four commercially available spermicidal gels (polyacrylic acid (PAA) derivatives and two cellulose ether derivatives) were assessed following dilution with a vaginal fluid simulant (pH 4.2) and a semen simulant (pH 7.7) across a range of biologically relevant shear rates. The rheological properties of PAA gels are known to be dependent on the type of diluent used [27]. Interestingly, PAA viscosities after dilution with a semen simulant were significantly greater than after comparable dilution with simulated vaginal fluid. Cellulose ether derivatives were not as dependent on environmental pH. The authors do suggest that the differing response following dilution could lead to differences in the extent and durability of epithelial coating. Given the significance of vaginal environment on gel performance, it is essential that characterization methods incorporate a range of carefully selected simulated fluids. In doing so, a more comprehensive understanding of gel behavior may be obtained [28].

3. Non-destructive rheological characterization methods

The rheological characterization of vaginal gels is often complicated by their inherent viscoelastic nature. Using techniques such as oscillatory and creep rheology, it is possible to quantify both the viscous and elastic properties of gels at different timescales and thus to understand the dynamic and structural properties of these systems. Although complex, viscoelasticity is of special interest for vaginal drug delivery as modulation of the viscous–elastic balance allows for the formulation of gels that possess high levels of elasticity yet still retain viscous flow character under high stress loads [29]. Therefore, through careful choice of excipients, gels may be engineered to offer ease of application, adequate intravaginal spreading and increased residence due to an improved ability to resist *in vivo* stresses, particularly following dilution [30]. Oscillatory and creep analysis are the most common non-destructive techniques used to characterize the viscoelastic properties of gels.

3.1 Oscillatory rheological analysis

Oscillatory analysis is a dynamic mechanical technique involving the application of a sinusoidal strain (or stress) of frequency, f (measured in hertz (Hz) or radians/second (rad sec^{-1})), to a sample, whilst measuring the stress (or strain) response [31]. Characteristically, these tests are useful in generating information on the response of materials at very short times and may, therefore, be used to compliment creep analysis [32,33]. Moreover, such tests are useful in understanding the relationship between viscous flow and elasticity at small stress values, that is, those typical during passive seepage between epithelial surfaces [21].

Typically, oscillatory rheology is performed within the small strain range, that is, the applied strain is small enough so that a linear relationship between stress and strain exists. This is termed the linear viscoelastic region (LVR). On application of a small strain to a gel, the response may not be instantaneous and will be dependent on how elastic or viscous the material may be. A highly elastic gel would exhibit a near linear relationship between the stress and strain and both signals would largely be in phase. The exact opposite behavior is expected of a highly liquid formulation. The relationship between the stress and strain will again be linear but the two will be out of phase by 90°. Such a system would be expected to have excellent spreading characteristics. It follows then that a viscoelastic material will lie somewhere between these two extremes. The stress responses of a viscous liquid, an elastic solid and a viscoelastic gel, following the application of a constant strain, are depicted in **Figure 1** and appropriately described using the mathematical equations presented. The principle rheological parameters derived from an oscillatory rheogram are the storage modulus (G′), the loss modulus (G″) and the loss tangent (tan d). The loss tangent is the ratio of loss modulus:storage modulus (G″:G′) and values of tan δ < 1 are indicative of an elastic gel structure.

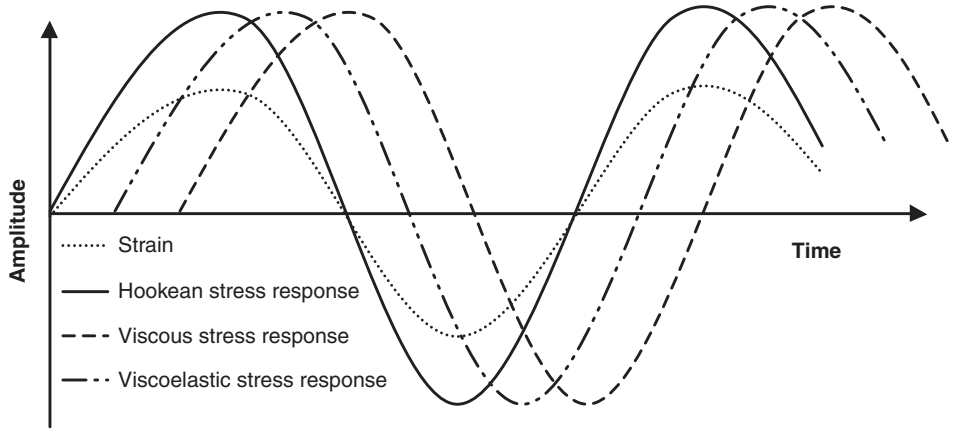


Figure 1. Representative stress responses for elastic, viscous and viscoelastic materials.

There are generally three main modes of operation that may be used in oscillatory analysis, namely, frequency, time and temperature sweep methods [34-36]. Frequency sweeps are the most commonly used [32,37-38] and potentially the most useful regarding the quantity and quality of information obtained. Frequency sweep experiments involve measurement of the stress at a range of frequencies performed at a constant strain and temperature [39]. The fundamental information derived from this mode of analysis may provide an insight into the structural properties of the material under investigation. Characteristically, the shape of the rheogram is often related to the structure of the material [40]. Chemically cross-linked gels, for example, will exhibit a storage modulus that is frequency independent whereas physical gels such as those used for vaginal delivery are frequency dependent. This is extremely important, as there will be frequency ranges at which vaginal gels would behave predominantly as liquids or solids under small stress loads. This has significant implications for spreading and retention within the vaginal vault and allows for a more complete understanding of gel behavior in small stress environments. Formulations designed for vaginal use should be easy to administer and exhibit retention at the site of application. Following administration, these formulations should exhibit elastic properties to optimize retention and offer controlled drug release [30]. Using oscillatory analysis, the effect of formulation composition on elastic structure can be thoroughly examined. Moreover, this technique may also be used to determine elastic structure in simulated vaginal fluids and thus provide relevant information relating to *in vivo* performance [37].

Oscillatory analysis also provides a useful tool for examination of gel structure across a range of timescales using the time–temperature superposition [27,41-42]. The result of such experiments is a 'master' curve that describes the material property of interest at a specific temperature over a broad time/frequency scale. Additionally, oscillatory analysis may be performed at a range of temperatures. This is particularly useful in characterizing gel platforms that use a 'temperature switch' to drive *in situ* gelation at 37°C. In a recent article published by our group, we used temperature-sweep oscillatory analysis to define the thermo-gelling properties of gels manufactured from a polyoxyethylene-polyoxypropylene copolymer [33]. Importantly, a predominantly viscous material ($G'' > G'$) was observed below the gelling temperature facilitating application to the required site. Conversely, above the sol–gel transition temperature, the formulations exhibited high elasticity ($\tan d < 1$, $G''<<G'$) rendering them potentially useful as platforms for controlled topical drug delivery offering increased resistance to *in vivo* deformation.

3.2 Creep rheological analysis

Creep experiments involve recording strain response as a function of time after the application of an instantaneous, unidirectional stress [43-45]. At the end of a defined time period, t, the stress is removed whilst measurement of the strain is continued. The time-dependent strain response following application of a constant stress is termed creep rheology. After removal of the stress, if there has been no viscous flow during the application of the stress, the strain is gradually recovered and falls to zero. If there has been viscous flow of the material under the applied stress, the recovery will be incomplete and a typical creep curve will exhibit two distinct zones of physical response, the creep and the recovery zones [46,47]. A characteristic creep curve/recovery is depicted in **Figure 2**. Interestingly, there is a major deficit of literature describing the use of creep rheology to characterize vaginal gels. Conversely, creep rheology has been used extensively to characterize a range of gel-based pharmaceutical materials [48-50]. In relation to vaginal gels, creep rheology is a useful tool in determining the balance of viscous–elastic character within a viscoelastic gel and how this balance may shift as a function of time under the application of small stress values. As previously reported, shear rates within the vagina can range from 0.1 to 1000 s^{-1}. The lower shear rate values

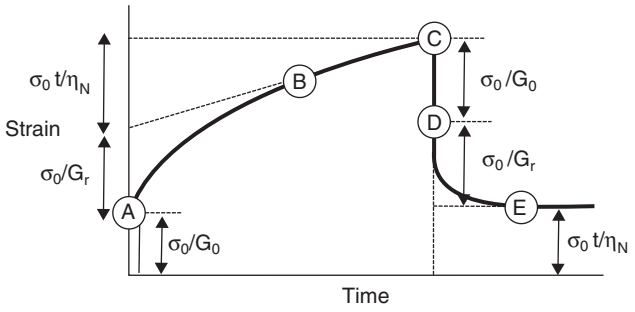


Figure 2. Creep experiments involve recording the strain response as a function of time after the application of an instantaneous, unidirectional stress. At the end of a defined time period, t, the stress is removed whilst measurement of the strain is continued. Creep and recovery refer to the former and latter steps, respectively.

are representative of the stresses experienced during seepage between epithelial surfaces. Whilst destructive techniques (flow rheology) provide information on how the formulation may respond during high shear rates, such as those experienced during application or during sexual intercourse, these techniques provide no valuable information with regard to the viscous–elastic balance in low stress circumstances. Following application of low stresses, even a highly elastic gel may begin to flow at extended time periods. This is critical for vaginal formulations as increased flow would increase the propensity for leakage.

A creep curve typically consists of three distinct subregions (depending albeit on the elastic–viscous balance and observation time) containing information regarding the viscoelastic properties of a material. A comprehensive understanding of these regions may be achieved using mechanical models constructed from springs and dashpots used to represent elastic and viscous responses, respectively. At the most basic level, viscoelasticity may be represented using a combination of a spring and a dashpot connected in series (Maxwell model) or in parallel (Kelvin-Voigt model). Although both provide a useful first approximation of viscoelasticity, gels are better represented using combinations of the Maxwell and the Kelvin-Voigt models as shown in **Figure 3** (Burgers' model of viscoelasticity). These more complex mechanical models may be used to eradicate the difficulties encountered when attempting to describe the creep, recovery and relaxation processes involved in the viscoelastic analysis of vaginal gel platforms. If viscoelasticity of vaginal gels is considered to be, at least on a basic level, represented by the Burgers' mechanical model then the application of a small stress would be expected to result in an instantaneous elastic response, equivalent to σ_0/G_0. This instantaneous response is due to extension of the residual spring of the Maxwell unit (Region O-A, **Figure 3**). The instantaneous strain is fully recoverable and due to the elasticity of the material, that is, the stretching of primary bonds [51]. Consequently, using such information it becomes possible to quantify the elasticity within a vaginal gel. A highly elastic gel will roll rather than spread and thus coverage within the vagina may be less likely. Moreover, high levels of elasticity may prove difficult in applying of the gel as increased shearing stresses would be required to produce sufficient flow to expel the gel from an applicator. The second region of a creep curve (A-B, **Figure 2**) represents the retarded elastic response of the individual Kelvin-Voigt unit. This represents the breaking and reforming of secondary bonds within the material. Within more advanced mechanical models it is possible to include several Kelvin-Voigt units as an attempt to model the various rates at which different secondary polymeric bonds break and reform. The third region (B-C, **Figure 2**) of a creep curve is due to the extension of the Maxwell dashpot. In this section of a creep curve, Newtonian flow occurs and the strain increases as a function of time and is inversely related to viscosity. The rate of change of strain as a function of time (slope) within this region may be used to define the residual viscosity. This governs the degree of non-recoverable viscous deformation and may be used to define the resistance of the gel to viscous deformation and also to identify an approximate time point (extrapolation of Point B to the X-axis) at which vaginal gels begin to flow following the application of small stresses. At the onset point of this linear region, the physically entangled gel system starts to 'unravel' and polymer chains begin to slip past one another. In terms of vaginal gel performance, such information is extremely useful in understanding the effect of small *in vivo* stresses, such as those typically involved in passive seepage between epithelial surfaces.

Following removal of the applied stress (s_0), a gel that has been exposed to a small stress, which lies within the LVR, will exhibit a recovery curve that would be expected to consist of similar regions to the creep portion [44,46]. An instantaneous recovery of the elastic energy (Maxwell spring) will occur (region C-D, **Figure 2**), followed by a more gradual recovery (Kelvin-Voigt units) of the viscoelastic components (region D-E, **Figure 2**). At this point, equilibrium is reached and there will be no further recovery. The strain gap, that is, the distance (along the Y-axis) from the equilibrium strain to the strain baseline, is attributed to viscous deformation and is non-recoverable. This energy loss will be dependent on the viscosity of the system under investigation and the duration and magnitude of the applied stress.

4. Destructive rheological characterization methods

Destructive rheological test methods involve applying stress or strain values that exceed the LVR. Although destructive in nature, these tests are extremely important in understanding the effects of high stress environments. For example, continuous shear experiments will provide a useful marker for how easily a gel formulation may be expelled from an applicator or if it is more likely to leak following sexual intercourse.

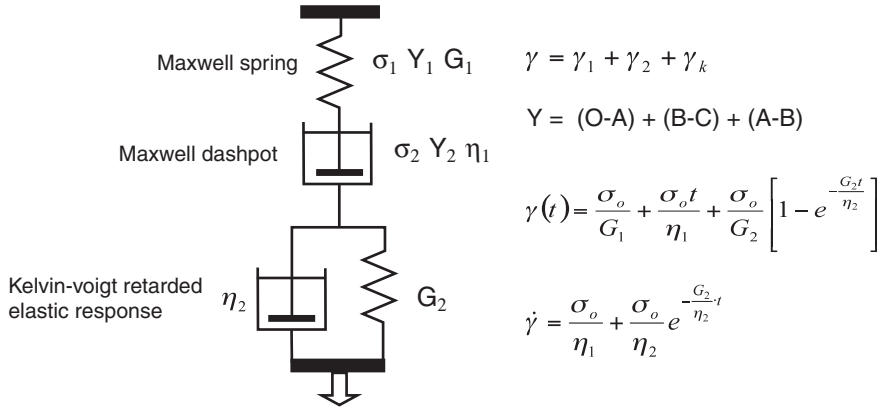


Figure 3. The Burgers' model of viscoelasticity is useful to define in a basic way the creep and recovery responses of viscoelastic materials.

The viscosity, a fundamental property of gel structure, is the most common rheological parameter determined using continuous shear experiments. Viscosity may be determined from the slope of a shear rate versus shear stress plot (flow rheogram) following the application of either a unidirectional controlled stress or strain whilst recording the resultant strain or stress, respectively [52]. The most common rheological method used to determine flow behavior involves enclosing a gel between two surfaces that rotate relative to one another about a common axis. Although, the gradient of a flow curve can be used to define viscosity, this only holds true for Newtonian materials. The flow character of non-Newtonian materials is more complex and the viscosity is known to change as a function of shear rate [53].

Many factors are known to affect the viscosity of polymeric gels. These may include formulation parameters, such as polymer molecular mass/weight distribution, polymer concentration and polymer chemical structure. Also, it is important to fully consider the effects of vaginal environment, such as vaginal fluid volume, pH and shear rate/stress experienced *in vivo*, on gel structure. Understanding these effects will undoubtedly facilitate the selection of optimal gel platforms.

Typically, gels exhibit a viscosity that is dependent on the magnitude of the stress or the rate of shear that is applied. As previously discussed, the relationship between the shear stress and the shear rate obtained from continuous shear analysis is presented in the form of a flow rheogram. When the plot is linear, the behavior of the liquid is defined as simple and termed Newtonian [54]. Although Newtonian behavior is observed for many low molecular mass molecules (examples being glycerol and water), this response is limited to a very short range of shear rates (low shear stress values) for aqueous polymer gels. Materials that display a change in the viscosity as a function of shear stress/shear rate are referred to as non-Newtonian. These materials may be sub-divided into one of three categories as illustrated in **Figure 4**. The complex nature of non-Newtonian behavior requires mathematical expressions with additional parameters to that described by Newton's law [55]. Non-Newtonian flow behavior may be categorized into one of three phenotypes, plastic, pseudoplastic and dilatant. Pharmaceutical vaginal gel systems are typically pseudoplastic in nature [56]. Consequently, we provide an extensive description of this type of flow behavior in the subsequent section.

4.1 Pseudoplastic flow

Pseudoplasticity is characterized by a viscosity that continuously decreases as the shear rate increases. A typical flow curve for such a material will proceed from the origin with the shear stress increasing to a lesser extent than the shear rate (**Figure 4B**); thus, the viscosity will decrease. This will continue until a limiting high shear rate viscosity is obtained [57]. Polymer chains dispersed in aqueous fluid have an ability to form an extended 3D physical network through the association (hydrogen bonding, electrostatics and dipole–dipole interactions) or entanglement of molecular chains. The relative decrease in viscosity with increasing shear rate is a result of structural rearrangement and disentanglement or disruption of this network. Intermolecular associations (Van der Waals' forces) such as dipole–dipole interactions, London dispersion forces and hydrogen bonding interactions are destroyed as the material is sheared and hence the viscosity decreases. Due to the continuously changing viscosity, the slope of the tangent at any point in a flow curve yields what is defined as the apparent viscosity (η_a) [46]. Consequently, flow rheology may be used to define viscosity at a range of shear rates. Moreover, the results obtained from such an experiment may also be used to determine the viscosity at zero shear (zero rate viscosity, η_o) using mathematical expressions such as the Cross and Carreau models [58,59]. Most often, pseudoplasticity is mathematically modeled using a Power law equation. Interestingly, the power law model may be used to describe shear-thinning or shear thickening flow depending on the value of the power law index, n [60]. If n is > 1, the

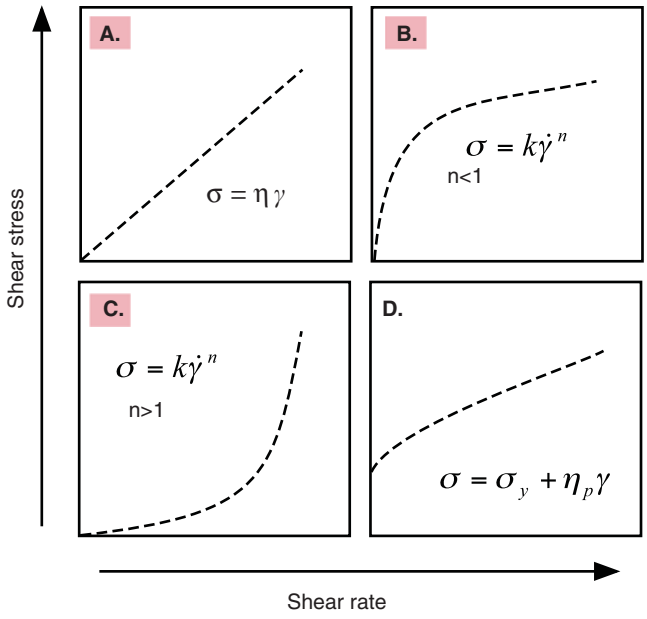


Figure 4. Rheograms depicting (A) Newtonian, **(B)** pseudoplastic, **(C)** dilatant and **(D)** plastic flow behavior.

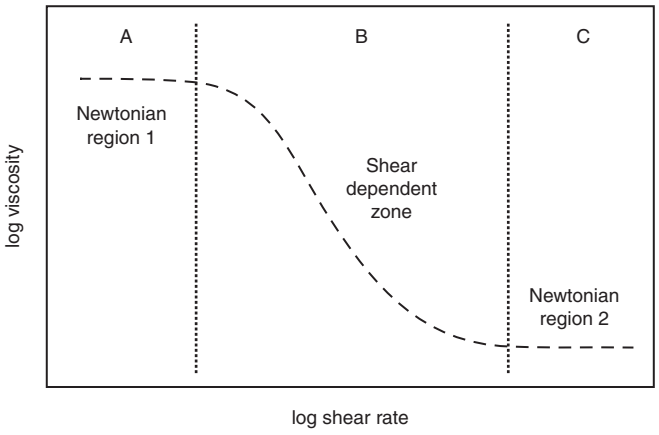
viscosity increases with increasing shear rate (dilatant flow). However, if the power law index is < 1, this expression also provides an adequate prediction of shear-thinning (pseudoplastic) behavior. In general, it can be assumed that a vaginal gel with a lower viscosity would spread at a faster rate and to a greater extent across vaginal surfaces [21]. Given that vaginal gels are pseudoplastic, it can be expected that increased spreading would occur at higher shear rates (during coitus) or following dilution with vaginal fluids or semen (decreased polymer:fluid ratio and thus viscosity). This has the significant disadvantage of increasing the likelihood of leakage of the product.

4.2 Time effects in flow rheology

The assumption that a given shear rate results in a corresponding shear stress that will remain constant as long as the shear rate is maintained is not necessarily correct. Indeed, it is quite common for non-Newtonian materials to exhibit shear stresses that are dependent on the time over which a stress is applied [47,61]. The viscosity can, therefore, increase or decrease as a function of the time of shearing. This phenomenon is known as thixotropy. Thixotropy is defined as 'an isothermal and comparatively slow recovery, on standing of a material, of a consistency lost through shearing' [62]. In essence, there will be a decrease in the viscosity under a particular shear stress that will be followed by a gradual recovery of structure on removal of the shearing stress. An anti-thixotropic response may be identified as one where there will be a gradual increase in viscosity under a particular shear stress that will be recovered on removal [60]. A common method to assess thixotropy is to use an up/down stress sweep. Gels that are thixotropic will exhibit a 'hysteresis loop' wherein the up/down rheograms will differ. Interpretation of such data must be done with extreme care as hysteresis loops are strongly dependent on sample history and are subject to instrumental artifacts [63].

4.3 Generalized flow behavior

The majority of vaginal gels exhibit non-Newtonian flow behavior, each being characterized by a unique flow rheogram. These rheograms will vary dramatically depending on the nature of the system; however, the majority may be described by a generalized flow rheogram (**Figure 5**) with three characteristic regions. Characteristically, at very low and very high shear rates, the viscosity will be independent of the rate of shear, that is, Newtonian. The Newtonian viscosities at very low and very high shear rates are termed the zero rate viscosity (ZRV) and the infinite shear viscosity (ISV), respectively [64]. The inter-connection between these two regions is the shear-thinning area of the rheogram. This is the region that is most commonly observed experimentally [65]. At lower shear rate values, there is a Newtonian plateau (region A) where the shear rates experienced are not large enough to cause any major polymer chain restructuring and the network of chain entanglements is not significantly altered [66]. The second region is where there is a continuous decrease in the viscosity as a function of shear rate. Under this range of shear rate values, polymer chains become mobile and begin to slide past one another as a result of the destruction of inter and intra chain bonds [55]. This region is best described by the power law expression, which may be fitted to experimental data over 2 or 3 decades of shear rate. This two parameter model is the most commonly used empirical equation for pseudoplastic materials. The power law equation fails to



Cross model $$\eta = \eta_\infty + \frac{\eta_0 - \eta_\infty}{+ (\tau \cdot \gamma)^m}$$

Carreau model $$\frac{\eta - \eta_\infty}{\eta_0 - \eta_\infty} = \frac{1}{\left(1 + (K_1\gamma)^2\right)^{\frac{m_1}{2}}}$$

Figure 5. Generalized flow rheogram and descriptive mathematical models for a pseudoplastic material.

describe flow behavior outside of the shear thinning region and consequently cannot describe the viscosity within the upper or lower Newtonian zones [60]. However, there are models used to describe the complete flow rheogram, that is, both Newtonian regions and the shear dependent zone. Two of the most commonly used models are the Cross and the Carreau models (**Figure 5**). The advantage of the Cross and Carreau models is that they predict the ZRV or the ISV based on an experimentally observed portion of the curve. The Cross and Carreau models are useful to examine the complete rheological landscape of a vaginal gel and are very useful as a comparative tool for experiments performed under different shearing conditions, providing the most comprehensive description of 'flow' behavior [46]. Interestingly, the use of these models may be limited as the introduction of rheometers with extended shear stress ranges and an ability to perform experiments at shear rates as low as 10^{-7} s^{-1} means that the complete flow rheogram for many materials should be obtainable; however, they may still be used as a comparative tool [55].

5. Pharmaceutical applications of rheological methods

Flow methods can be used to assess the influence of *in vivo* conditions and gel composition/administered volume on spreading, distribution and coating properties. In an article published by Kieweg and Katz [67], squeezing flow behavior of vaginal gels, as a function of applied volume, squeezing force and squeezing time, was investigated and modeled to express spreading ability of vaginal gels. Squeezing flow was dependent on polymer type. Cellulose-based gels were best described using a partial-slip power model whereas for PAA gels, rotational viscometry measurements utilizing a Herschel-Bulkley flow model led to a reasonably accurate prediction of squeezing flow. Moreover, the authors concluded that yield stress (determined from the y-intercept of **Figure 4D**) is a strong determinant of squeezing flow mechanics. In a more recent study by Szeri *et al.* [20], vaginal gel rheology, luminal biomechanical properties and gravitational forces were listed as the key parameters influencing coating mechanics. In this study, the authors present a single dimensionless number, independent of viscosity, as a way of characterizing the relative influences of squeezing and gravitational acceleration on the shape of spreading. This was applicable only in Newtonian systems. The extent of squeezing flow of vaginal gels has been shown to be driven by the extent and dilution rate of a gel. In general, a high dilution rate would promote rapid flow in the vaginal vault. In contrast, a low dilution rate has the propensity to limit intravaginal flow [67]. The effects of dilution by vaginal fluids or semen on squeezing flow behavior can be attributed to alternation of gel viscosity: increased flow, distribution and coating area. The detrimental effect of dilution has been previously described by Owen *et al.* [68]. In this early work, continuous shear analysis was used to screen and optimize vaginal gels based on flow response. Flow behavior was modeled using the power law and the extent of shear thinning behavior defined by the pseudoplastic index (**Figure 4B**). Following dilution, the pseudoplastic index tended towards unity and the consistency (y-intercept) decreased, suggesting a transition from a non-Newtonian shear-dependent gel to a

lower viscosity, Newtonian, shear-independent gel [68]. In more recent work by Lai *et al.* [14], vaginal gels exhibiting a yield stress resisted flow; however, dilution with simulated vaginal fluid or semen caused a rapid loss of yield stress and an increase in coating area.

Additionally, valuable and complementary information regarding gel spreading and leakage can be obtained using MRI and γ scintigraphy studies [69]. The *in vivo* spreading of commercially available products, KY Jelly and Replens, has been tested by Mauck *et al.* [70]. MRI and scintigraphy confirmed that ambulation accelerated spreading of KY Jelly in terms of linear coverage and coated area after insertion. Interestingly, in a related study by Lai *et al.* [14], Replens, characterized by flow rheology, exhibited a yield stress and thus resisted free flow whereas KY Jelly did not exhibit a yield stress. Consequently, during ambulation, the generation of small *in vivo* stresses was sufficient to facilitate flow of KY Jelly. Conversely, the established stresses set up following ambulation were not sufficient to overcome the yield stress value of Replens and hence resisted *in vivo* flow. Thus, as the distribution properties of gels are considered a critical factor influencing acceptability and clinical efficacy of vaginal gels, rheological properties have an important role to play in predicting gel behavior.

Oscillatory rheology is a useful technique to characterize the viscoelastic properties of gels. The scientific literature has many examples of how oscillatory rheology may be used to define elastic–viscous balance within a gel and the importance of oscillatory properties in understanding the performance of a gel at an applied site. In an early study by Andrews *et al.* [71], oscillatory rheology was used to characterize novel candidate ophthalmic viscosurgical devices based on binary interactive polymer gels. Rheological synergy was observed in binary gels and suggested a structure-building interaction between parent polymers. Using oscillatory techniques, the authors were able to confirm that binary systems possessed viscoelastic properties similar to commercially available gels and thus appropriate for the maintenance of the ocular space. In a later study, Andrews and Jones [72] used oscillatory rheology to describe the rheological properties of hydroxyethylcellulose (HEC) and polycarbophil (PC) gels designed for improved drug delivery to mucosal sites. Oscillatory rheology was used to define the storage modulus (G') and loss modulus (G'') before and after dilution with phosphate buffer saline. Dilution with PBS altered rheological structure; however, binary HEC and PC interactive systems, particularly those containing higher concentrations of HEC, still exhibited predominantly elastic properties (high G′ and low tan d). In light of this, it was suggested that the rheological properties of binary interactive systems offered particular promise as platforms for topical mucosal drug delivery systems. Further work in the area by Jones *et al.* [33] has described the use of oscillatory rheology to characterize PAA gels designed as bioactive implants for the improved treatment of infectious diseases of the oral cavity. Oscillatory rheology was used to identify gels wherein there was a significant entanglement between polymeric chains increasing elasticity, and thus viscoelastic response. A good correlation was observed between the viscoelastic properties and drug release suggesting oscillatory rheology along with other complementary methods provides important information pertaining to the nonclinical and clinical use of gel systems.

Interestingly, despite the extensive use of oscillatory to characterize topically applied gels, there are limited articles within the literature describing the use of this method in characterizing vaginal gels. A number of more recently published papers have gone some way to address this deficit. Oscillatory rheology has been used by das Neves *et al.* [73] to investigate the rheological features of vaginal hydrophilic polymer gels and determine the relationship between rheological properties and gel composition and their relevance to therapeutic efficacy. All gels were viscoelastic and characterized by a predominant elastic response. The extent of elasticity, and indeed general rheological behavior, was strongly dependent on the type of gelling agent used. The authors conclude that there is a strong correlation between rheological properties and therapeutic performance. Interestingly, Hombachi *et al.* [29] used oscillatory rheology to facilitate the design of a novel vaginal delivery system for nystatin based on L-cysteine and cysteamine. Oscillatory rheology was used to characterize the viscoelastic properties of the vaginal systems and correlated well with the extent of free thiol groups on the polymer comprising the gel matrix.

The most recent work ustilizing oscillatory rheology describes the formulation and characterization of rheologically structured vehicles (RSVs) designed for improved drug delivery to the vagina [37]. In this study, interactive, multicomponent, polymeric platforms were manufactured and characterized before and after dilution with simulated vaginal fluid to mimic *in vivo* dilution. The performance of the RSVs was dependent on the mucoadhesive material used. RSVs containing PC were more rheologically structured than comparator formulations containing gantrez. Dilution with simulated vaginal fluids significantly decreased rheological structure, although RSVs still retained a highly elastic structure ($G' > G''$ and tan $\delta < 1$). Furthermore, RSVs exhibited sustained drug release properties that were shown to be dependent on their rheological structure. A subsequent, follow-on paper by the same group [13] developed these RSVs as delivery systems for vaginal mucosal vaccination using a HIV-1 envelope glycoprotein (CN54gp140). Oscillatory properties were evaluated *in vitro*, and the distribution, antigenicity and release of CN54gp140 were analyzed by ELISA. CN54gp140 was uniformly distributed within the RSVs and continuously released *in vitro* in an antigenically intact form over a 24 h period. Vaginal administration to rabbits induced specific serum IgG, and IgG and IgA in genital tract secretions. The combination of high levels of elasticity and the release properties was deemed acceptable to render the RSVs as a viable delivery modality for vaginal

immunization. Although oscillatory rheology has not been used routinely to characterize vaginal gels, over the last number of years there has been an increase in the usage of this method. In addition to providing information on the viscous/elastic character within a gel, oscillatory rheology may also be used to gather important information on how a gel may distribute intravaginally during application of small, repetitive, frictional forces. This behavior may be modeled using *in vitro* oscillatory tests and facilitate the design of vaginal gels with an optimal balance between elastic (G′) and viscous (G″) character to improve gel performance *in vivo*.

Creep rheology is a second non-destructive technique that provides information relating to the viscoelastic structure of gel materials. Interestingly, there are no reports within the scientific literature utilizing creep rheology to characterize vaginal gel systems. Given the valuable information creep rheology generates it is difficult to fully understand the reasons behind this. One reason may be the long experiment duration relative to flow/oscillatory rheological tests. Although there is a lack of information within the scientific literature relating to vaginal gels, this technique has been used to characterize gels used for alternative pharmaceutical applications. In a study by Wille *et al.* [74], creep rheology was used to effectively screen tooth-bleaching materials. Similar to vaginal gels, these materials require ease of application, but should have a high viscosity at low stresses in order to be retained. A balance of elasticity and viscosity is required to aid retention and suitable degree of elasticity may also aid retention thereby maximizing efficacy. The materials exhibited pseudoplastic behavior at high stress values and high levels of elasticity, measured using creep analysis, at low stress values. In more recent work, de Paula *et al.* [75] used creep rheology to characterize anionic collagen gels. Rheological studies confirmed the presence of viscoelasticity and, moreover, creep experiments were used to screen formulations providing a useful tool to identify those that are less elastic and more susceptible to deformation using small stresses at extended time periods (hours). The rheological properties of Carbopol 971 and 974 in a tetra-glycol, water-miscible co-solvent were characterized using creep methods [76]. Increased gel structure, as a function of increasing temperature, was reported and high levels of elasticity (initial strain jump during creep test) were shown to give rise to sustained release of model drug compounds. In a recent study by Jones *et al.* [49], the rheological properties of PAA organogels designed as platforms for drug delivery to the oral cavity were characterized using creep rheology. Increased elastic structuring was associated with organogels prepared using glycerol and PEG 400 due to their interaction with adjacent carboxylic acid groups on each chain and on adjacent chains. All organogels exhibited a greater network structure than aqueous PAA gels. The enhanced network structure, which may be engineered through choice of polymer concentration/solvent type, was deemed clinically useful for the delivery of drugs to the oral cavity. Undoubtedly, creep analysis provides useful information that may facilitate the design of vaginal gels. During creep analysis, a constant shear stress is applied to a gel and the strain growth is measured. This provides a method of quantifying instantaneous elastic strain, the viscoelastic strain and the viscous strain under constant stress loads. In relation to vaginal gels, the time point at which the gel enters the viscous strain region is of particular importance as at this point the material is effectively behaving like a liquid, even under a small stress load. This may help to define the spreading and leakage of vaginal gels under small stress loads, commonly experienced intravaginally.

Gels designed for intravaginal use need to possess rheological properties that facilitate ease of application and *in vivo* spreading yet offer sufficient elastic structure to provide sustained drug delivery and enhanced retention. Importantly, gels need to be robust enough to retain their rheological structure during usage (ambulation, seepage between epithelial surfaces and during sexual intercourse) and following dilution with vaginal fluids. Given the dynamic nature of the vaginal environment and the range of shearing stresses experienced by gels *in vivo*, characterization should be performed in the context of the rheological demands of these systems. This should involve the presence of diluting vaginal fluids and the inherent effects on the rheological properties. This would thereby provide an indication of the possible persistence of the gel during usage. Largely, the choice of rheological test will be dependent on the parameter(s) that one wishes to investigate. Of significant interest are the structural rheological properties of vaginal semisolids following application of low stresses/strains, particularly given the effect these may have on drug release properties and passive seepage between epithelial surfaces. Moreover, the flow rheological properties are of primary interest because they have been shown to largely govern the ease of application and dispersion of semisolids. Usefully, creep experiments will provide information on prolonged retention, under constant small stress loads, at the site of application.

6. Conclusion

The spreading and retention characteristics of vaginal gels are largely governed by the rheological properties. Even with a comprehensive understanding of the *in vitro* rheological characteristics of a gel platform, prediction of the intravaginal performance is extremely complex [1]. This may be attributed to the dynamic vaginal environment in which the gel must function. The ingress of vaginal fluids and semen, variation in local pH and the range of *in vivo* stresses the formulation may be subjected to all significantly alter rheological structure and hence performance. Undoubtedly, leakage of vaginal gels is generally accepted as being one of the major disadvantages of these platforms. Consequently, vaginal residence is of particular importance as the physiological conditions imposed by the protective mechanisms within the vagina limit the efficacy of gel formulations. The self-cleansing mechanisms, in addition to normal physiological functions, effectively limit

contact between the gel and the vaginal epithelium. In light of this information, gel optimization should be conducted in simulated environments that allow for elucidation of these interactions. Over the last few years, the limited retention of vaginal gels has been addressed through the use of mucoadhesive polymers. Although mucoadhesive polymers may significantly increase adhesion, when used alone to formulate a gel their rheological properties are frequently insufficient to offer optimal resistance to dilution and *in vivo* stresses. Consequently, single polymer gels typically offer sub-optimal clinical performance. Vaginal gels should be highly elastic, even following dilution, as these properties govern drug release properties and leakage. Furthermore, pseudoplasticity would offer stress-induced viscosity depression and hence ensure ease of application. This is difficult to achieve using single polymer gels. Therefore, gels offering greater clinical promise may be achieved through the combination of mucoadhesive and gel structuring polymers within a binary or higher polymer platform [33,56]. In this respect, recent work by our group has examined the potential of ternary polymer systems designed to offer enhanced rheological structure. In doing so, we have expanded the formulation options for effective vaginal administration of gel platforms. As a result, our work has shown the potential of vaginal gels to be dependent on advances in rheological characterization and formulation science that will promote effective stability, delivery, protection and prolonged exposure of emerging biopharmaceutics to target cells [13,37].

7. Expert opinion

The distribution and leakage of vaginal gels is directly related to therapeutic efficacy. The use of a gel with a low viscosity would facilitate spreading and hence contact with the vaginal epithelium. However, a low viscosity gel would be expected to have a limited residence time due to the inability of the gel to resist dilution from vaginal fluids and semen. Moreover, a low viscosity gel ($\tan \delta > 1$) would be unable to 'absorb' *in vivo* stresses without causing destruction of polymer gel entanglements and thus would be expected to leak rapidly. Conversely, a highly elastic gel ($\tan \delta << 1$) would offer greater resistance to dilution and *in vivo* stresses; however, application and intravaginal spreading would be limited. Therefore, optimal clinical performance may only be achieved when the elastic–viscous balance is carefully controlled. Although initial research in this field has focused primarily on the use of destructive rheological methods (flow rheology), over the last decade there has been greater appreciation of the need to understand the viscoelasticity of vaginal gels and elucidate the relationship among these properties, gel composition and clinical efficacy. The performance of a vaginal gel can be evaluated with respect to a number of properties, including spreadability, coating and retention. The establishment of suitable rheological tests to appropriately define such characteristics may facilitate the selection of a gel that avoids leakage. The ideal gel platform must provide adequate coating with minimal leakage. This is extremely difficult to obtain as it requires the formulation of a gel with a suitable viscoelastic balance. Undoubtedly, the performance of a vaginal gel and the properties significantly influencing *in vivo* performance are multivariate. Recent work in this field has gone some way to address this complexity through the development of a multivariate objective function constructed using gel properties, computations of flow behavior of the gel and the performance criteria for defined flow phenotypes [77].

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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