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Editors

The Role of Microstructure in Topical Drug Product Development

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Foreword

Today, we are at the beginning of a scientific renaissance that is demystifying the ancient art of developing topical formulations and opening a new dimension of scientific understanding. The enormous practical implications of this new knowledge to our everyday work as pharmaceutical scientists is what this important book is about.

My intention in writing this foreword is not to endorse the authors or their work; many of the authors are my personal friends as well as being scientific colleagues, and I may be biased by my respect for them as individuals and as scientists. Also, readers should not infer that my foreword represents any endorsement of this book by any organization that I am or have been a part of; it does not. Instead, my intention in providing this foreword is to briefly provide some context for the significance of this work in the history of the work in this field, and to identify what makes this book unique. Readers may then judge for themselves whether they may be interested in its contents, and in participating in a remarkably democratic form of scientific collaboration that I believe this book facilitates at a crucial point in the history of this field.

Topical drug products are among the oldest medicinal dosage forms known to human civilization, and were routinely formulated as ointments, salves, and various other preparations dating back at least 5000 years, and probably much earlier. After several millennia of human experience with formulating these dosage forms, a major leap forward in topical pharmaceutics is believed to have occurred around 2000 years ago, when the Greek physician, Galen, incorporated plants that contained active medicinal (pharmaceutical) ingredients into topical formulations comprised of a carefully selected mixture of excipients. I believe that the new insights that we are currently developing represent the third major leap forward in human knowledge in this field.

This book describes complex inter-related concepts about different attributes of topical drug products in a clear and succinct manner, with well-organized topics and chapters, as well as explanations and technical descriptions that can be easily understood. Most importantly, this book focuses on practical applications that even expe-

rienced topical formulators will likely find replete with novel insights that they can utilize to enhance the quality of their work and to advance their expertise.

This book has been authored by an exceptional collection of renowned academic and industrial scientists who are not only experienced in the art of topical formulation development, but who have also been actively engaged in elucidating the scientific principles and mechanisms by which the composition, structure, and dynamic metamorphosis of topical products systematically and predictably regulate their function and therapeutic performance. In much the same manner that ontogeny recapitulates phylogeny, the structure of this book is organized in two major parts. The first part of this book focuses on understanding the dosage form, itself, which was the original focus of the most ancient human civilizations like the Babylonians and Egyptians. The next part of this book focuses on understanding the specific nature and properties of the active pharmaceutical ingredient(s) and the excipients selected for the formulation, which has been the basic focus of the art of topical formulation development in the age since Galen. The individual chapters in each part of the book describe the fundamental concepts and practical state of the art (including specific tools, techniques, tests, and tips) related to characterizing the qualities and performance of topical drug products during development.

One of the most remarkable things about this book is how quickly it is bringing cutting-edge discoveries and novel techniques in topical formulation development to readers. It's quite common that the latest research results and new advances in a field will initially be shared in the form of poster presentations at scientific meetings, which facilitates early scientific dialogue about how to interpret the results, what the implications may be, and how to develop and refine the work. Books are typically written years later, after journal articles have been peer-reviewed and published, and after review articles have collated and synthesized the information that develops scientific consensus. This process inherently relies upon thought leaders in a field to identify and collate the most relevant findings, and to describe the practical applications of the work.

The authors of this book, who are thought leaders in the field, have recognized that recent advances in our understanding of topical drug product development can be so transformative to the work performed each day in academic and industrial labs across the world, that it was critical to collate that information in a book that can serve as an accelerant for rapid and essential scientific progress in topical drug development. This book balances discussions of well-researched and established work in the field with the most impactful recent advances and describes the application of this knowledge to topical drug development tools and techniques that are often regarded as the secrets of the trade. In essence, this gives scientists in the field a rare, early opportunity to see how the big picture is coming together from a collection of inter-related scientific advances, so that the larger community of scientists in the field (not necessarily just the thought leaders) can better navigate and contribute to the ongoing research and to the collective interpretation of the results.

The information in this book positions readers to conduct research at a more advanced level, and to innovate and refine the tools and techniques discussed in ways that effectively crowdsource the greatest thinking of all the minds that can be

brought into the endeavor. I think that is the most impactful aspect of this book, because it allows a large number of scientists in the field to begin applying the insights to their daily work and to engage in the evolving conversations at an early point, improving the quality of their science and of the dialogue that those experienced scientists will have with each other over the exciting next few years.

The successful outcome of this work should be that the preliminary conclusions, concepts, proposed nomenclature, current best practices, and other aspects of what is discussed will change, evolve, and be refined, and that this will happen at an accelerated pace based upon the zeal of the many minds that become engaged in the work. Indeed, there are already other world experts in topical drug product development across academia, industry, and government institutions who have been leading much of the most groundbreaking work that has contributed to the recent renaissance in this field, and the results of their research will continue to be published and discussed. The insights gained from this book should allow its readers to contribute meaningfully to that discussion, and empower readers to develop their own practical inventions that will collectively define the best practices for the new age of topical drug development.

Sam Raney, PhD

Acknowledgments

On May 24, 2016, a Workshop co-hosted by the Center for Dermal Research and BASF entitled "Topical Semi-Solid Microstructure and its Significance in Formulation Performance and Efficacy" was held on the Rutgers campus. About 4 months later, speakers from the Workshop gathered for dinner during the September 2016 Innovations in Dermatological Sciences Symposium organized by Professor Bozena Michniak-Kohn, Center for Dermatological Sciences. The dinner was organized by Norm Richardson and Nigel Langley from the Technical Services and Scientific Affairs group of BASF Corporation. The topic discussed was the formation of an Industrial Working Group to draft "White Papers" concerning the concept of "Microstructure" in the development of topical pharmaceutical products. This original nucleus of development scientists created the Q3 Working Group, expanded the membership of the group, adopted a Charter and Bylaws, narrowed the topics to the five chapters contained in this book, and selected Q3 Committee Chairs to organize drafting of the five chapters. The members of the Q3 Working Group had three primary functions: 1) to serve as chairs or co-chairs on each of the five Q3 Committees; 2) to arrange for their companies to provide funding to cover the costs of teleconferences, face-to-face meetings, and copyright permission fees; and 3) to provide a critical technical review of the finished chapters. The Q3 Working Group membership was evenly distributed between development scientists completing ANDAs, NDAs, and excipient/contract service providers. Despite the employers of the Q3 Working Group membership being commercial competitors, the Q3 Working Group membership accomplished this publication through cooperation and a shared desire to advance topical product development science. The Q3 Working Group membership is listed below:

Padam C. Bansal
Debra Dow (Chapter 3 Reviewer)
Jean-Pierre ETCHEGARAY
Amber Fradkin
Michael H. Fowler (Chapter 4 Reviewer)
Michael Kimball (Chapter 1 Reviewer)
Louli Kourkounakis (Secretary)
Nigel A. Langley
Michael Lowenborg
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Narasimha Murthy (Chapter 5 Reviewer)
Vijendra Nalamothu (Chapter 2 Reviewer)
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David W. Osborne (Chair)
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Part I
Critical Quality Attributes

Rheological Characterization in the Development of Topical Drug Products

Amit Rawat, Simerdeep Singh Gupta, Haripriya Kalluri, Michael Lowenborg, Kuljit Bhatia, and Kevin Warner

Abstract This chapter presents an overview of utilizing rheological properties to develop topical semisolid products. A review of theoretical concepts and practical applications is described to show that rheological properties are an important attribute in the development of topical drug products.

Keywords Rheology · Viscosity · Topical formulations · Stability

1 Introduction

Rheology is the science of how a material deforms and flows under the influence of external forces (Martin 1993). The flow behavior of materials as related to their viscosity, elasticity, and plasticity under physical deformations has tremendous implications on how the material behaves during manufacturing, packaging, storage, dispensing, and application at the site of administration by the end user. An understanding of the rheological properties of topical semisolid formulations is particularly critical as these formulations typically display shear-thinning or shear-thickening phenomenon in the presence of stress (i.e., non-Newtonian behavior). For example, an ointment may flow from a tube under pressure, but

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regains its structure once the stress is removed, thereby preventing further flow (Park and Song 2010). This differs from a Newtonian material where the viscous stresses arising from its flow, at every point, are linearly proportional to the local strain rate, the rate of change of its deformation over time (Martin 1993).

Rheological characterization serves as an important tool for developing topical drug products in a Quality by Design approach. For example, this tool helps us understand why different products with similar viscosities behave differently upon application, why products settle or separate over shelf life, and why some formulations flow while others retain structure under shear. Rheology can also impact the sensory and in vivo product performance. Rheology therefore is a valuable tool in topical product development that can guide development of robust formulations and shorten product development cycles.

2 Definitions of Key Rheological Terms

Rheological behavior of most topical semisolid formulations possesses a combination of elastic and viscous behaviors and is characterized as viscoelastic.

Viscosity (η): measure of the internal resistance of a substance to flow when subjected to force. Deformation is elastic if the substance recovers its original shape after the force has been withdrawn or plastic, if deformation remains. It is defined as the shear stress divided by the rate of shear strain and is expressed as centipoise (cP) or milli-pascal second (mPa.s).

Shear flow: deformation of a material in the presence of an external force.

Shear rate (γ): velocity ($d\nu$) of an upper plane passing over an adjacent plane divided by the distance between the two planes (dh), indicating the rate at which a material flows when a specified force is applied ($d\nu/dh$). Unit of shear rate is "1/s" or "s^{-1}."

Shear stress (σ): force applied per unit area (dynes/cm^2) and can be defined as viscosity times shear rate.

Shear thinning (pseudoplastic): behavior of materials in which the viscosity decreases in the presence of shear (Figs. 1 and 5).

Shear thickening (dilatant) : upon application of stress, a material may experience rearrangement of its microstructure such that the resistance to flow increases with shear rate (Figs. 2 and 5).

Thixotropy: property of a progressive decrease in viscosity with time for a constant applied shear stress, followed by a gradual recovery when the stress is removed (Fig. 3a). This behavior when plotted for stress vs. shear rate, as depicted in Fig. 3, is known as a hysteresis loop.

Rheopexy: rheopectic materials exhibit an increase in viscosity under constant shear stress (Fig. 3b).

Yield stress: critical threshold level for shear stress above which a material deforms and flows (Fig. 4).

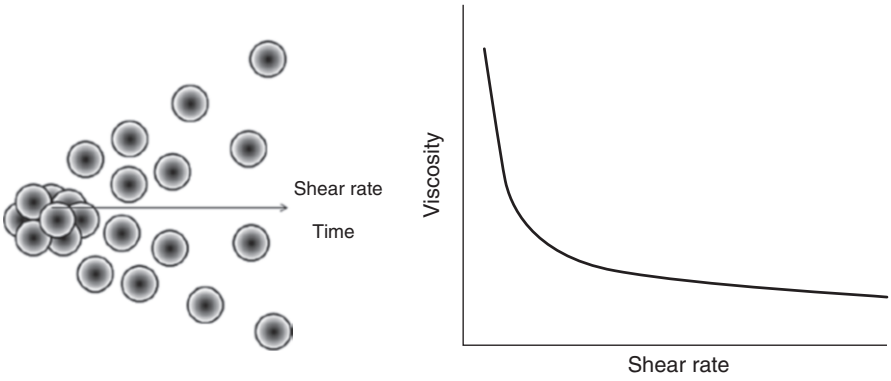

Fig. 1 Shear-thinning effect. (Reproduced from Mastropietro et al. 2013 and Kulkarni and Shaw 2015)

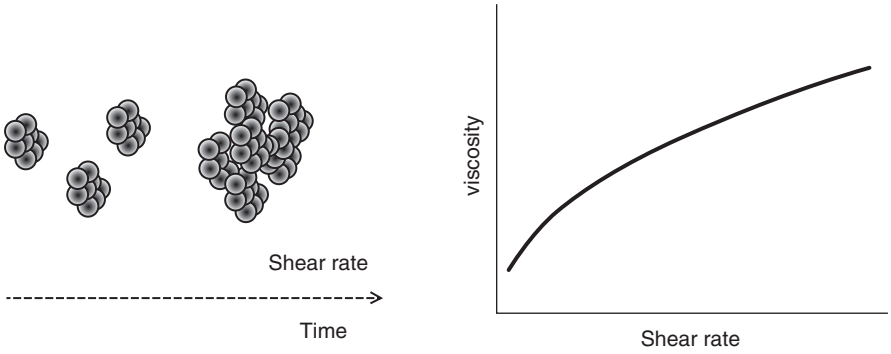

Fig. 2 Shear-thickening effect. (Reproduced from Mastropietro et al. 2013 and Kulkarni and Shaw 2015)

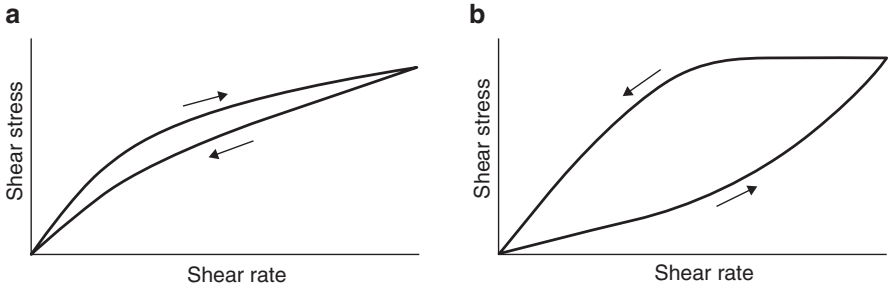

Fig. 3 Flow curves of (**a**) thixotropic and (**b**) rheopectic materials. (Reproduced from Kulkarni and Shaw 2015)

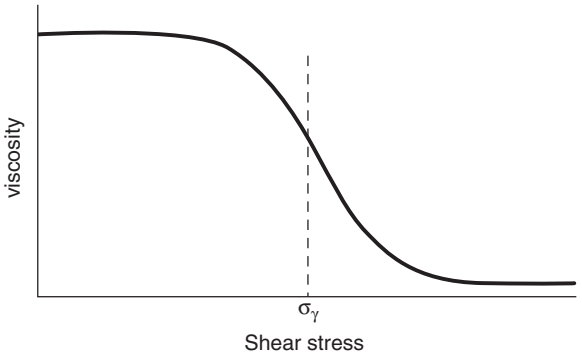

Fig. 4 Yield stress (σy) on a plot of viscosity vs. shear stress. (Reproduced from Kulkarni and Shaw 2015)

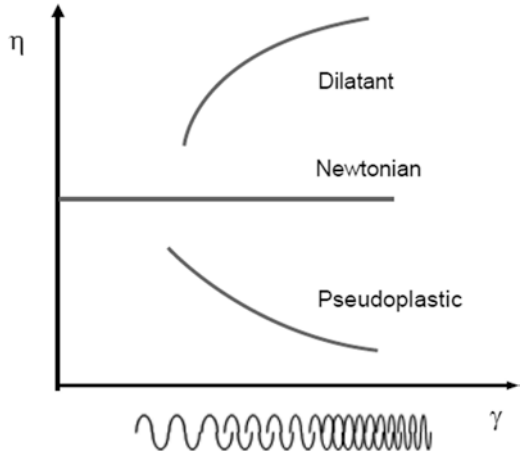

Fig. 5 Change in viscosity (η) as a function of shear rate (γ) for shear-thickening, Newtonian, and shear-thinning systems. (Reproduced from Mastropietro et al. 2013)

Newtonian vs. non-Newtonian systems: the relation between viscosity and shear rate reveals the nature of the rheological behavior of a material which can be Newtonian or non-Newtonian. Newtonian systems have no change in viscosity as a function of shear rate (Fig. 5). The flow behavior of Newtonian fluids can therefore be described with a simple linear relation between shear stress [mPa] and shear rate [1/s]. This relationship is now known as Newton's law of viscosity, where the proportionality constant η is the viscosity [mPa-s] of the fluid:

$$\sigma = \gamma\eta$$

where σ is shear stress, η is viscosity [mPa-s], and γ is shear rate [1/s].

This equation suggests viscosity of Newtonian fluids will remain constant no matter how rigorous the conditions are during compounding, filling, dispensing, and application.

Most semisolids are non-Newtonian, meaning the viscosity is dependent on shear rate (Fig. 5), and exhibit shear-thinning (pseudoplastic), shear-thickening (rheo-

pexy). or thixotropic (decrease in viscosity with time under shear stress followed by a recovery of viscosity when the shearing is stopped) properties in the presence of stress above the yield value. This is related to the structural reorganization of the particulate matter due to flow because of stress (depicted in Figs. 1 and 2).

3 Rheological Testing and Practical Applications

The most commonly used instruments to report single point viscosity measurements are rotational viscometers where a spindle is immersed in the material and rotated at a constant speed (see USP 42- NF 37 chapters 911–913 (USP 2018)). The torque required to rotate the spindle in the medium gives a measure of the viscosity of the material. Typical spindles are disk, cylindrical, and T bar. The shear rates are dependent on the size and geometry of the spindle and the rotation speed. Release and shelf viscosity data on topical semisolid products are typically generated in QC labs using a rotational viscometer because they are amenable to fast, repetitive testing.

Rotational rheometers are commonly used as a standard tool to study the rheological behavior of topical formulations during development. Tests such as time sweep, stress sweep, frequency sweep, temperature sweep, and creep recovery are routinely performed on formulations during development. These tests enable characterizing the rheological profile of a formulation, and provide insight on the impact of external forces the formulation may experience during manufacturing, dispensing from the container closure system, application on the skin surface, and the effect of skin surface temperature.

4 Applications of Rheology to Topical Products

Even though the active and inactive ingredients of two Q1 (qualitatively the same) and Q2 (quantitatively the same) products may be identical, their physicochemical attributes (Q3) could be very different. It takes much more for two products to be similar than just the fact that their components are the same. Polymorphism, agglomeration, processing conditions, and storage may play a major role in obtaining similar structural properties. Differences in physicochemical attributes (Q3) between dosage forms that are qualitatively and quantitatively similar may result in differences of quality and performance attributes. Rheological characterization is one attribute that can determine differences between formulations. Rheology is not only the determination of viscosity but also investigates the impact of shear and frequency on the products. This information could provide useful information on the quality and performance attributes such as processing, spreadability (application on the skin), and patient compliance. Bhuse et al. published classification of topical products where they used various analytical techniques, including rheology

to determine viscosity and shear rate versus stress (Buhse et al. 2005). From these studies, a decision tree was constructed classifying commercially available OTC and prescription cream, lotion, gel, and ointment products based on thermal, viscoelastic, and physical properties. Based on the factors from the decision tree, viscosity was the dominant factor in distinguishing products, especially lotions and creams, and not specific gravity, % water content or surface tension. Bhuse et al. concluded that even though there may be an overlap of several hundred thousand cP in viscosity, there was a general trend where lotions had the least viscosity, followed by creams and then ointments. Viscosity by itself can be used as a useful classification and in our case a comparative tool for test versus RLD products.

4.1 Creams

As per FDA, cream is an emulsion based semisolid dosage form, usually containing >20% water and volatiles and/or <50% hydrocarbons, waxes, or polyols as the vehicle, and they are intended for external application to the skin or mucous membranes. The cream products consist of oil-in-water emulsions (less frequently water-in-oil emulsions) or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable (Drug Nomenclature Monographs – Dosage Forms). Creams, ideally, are not free flowing and conform to their container. They are more viscous than lotions, with typical values ranging from about 30,000 to 70,000 cP. They are usually processed at high temperatures, stored at room temperature, and applied to skin which has a surface temparature of approximately 31.5 °C. Rheological properties of creams at each of those stages could be different and could affect product performance and stability. Korhonen and coworkers investigated a cream product with different surfactants using dynamic and static rheological tests (Korhonen et al. 2001). The aim of this study was to understand the effect of storage time and conditions on the rheology of creams. They concluded that higher elasticity creams were more stable. The creams which had polyethylene glycol 10 soya sterol and sorbitan trioleate were more elastic, and they performed better over time than the ones which had polyethylene glycol 25 soya sterol. Kwak et al. also investigated the importance of rheology of creams in terms of application to human skin (Kwak et al. 2015). In this manuscript, they compared creams to lotions by strain-controlled rheology to evaluate the steady shear flow and linear viscoelastic properties. Additionally, they also tested the temperature dependency on the application of those products. In conclusion, they showed that both creams and lotions had finite magnitude of yield stress, which correlated to the breaking point of the product in terms of viscosity. They also showed that both products exhibited shear thinning, which reflected to their ability to spread on the surface of the skin during application. The linear viscoelastic region (LVR) of both products was dominated by the storage modulus, which showed that they could better hold onto their structure during storage. The viscous and elastic properties of both products decreased gradually with an increase in temperature, thus showing that there will not be any drastic change in properties during or after application.

4.2 Lotions

Lotions are semisolid dosage forms with some viscosity intended for external application to the skin (Drug Nomenclature Monographs – Dosage Forms). They could be similar to creams in composition, but due to their free flowing nature, they are classified differently. Yao and Patel highlighted important tests to characterize body lotions, such as measurement of viscosity vs. stress, stress vs. shear rate, storage and loss moduli vs. angular frequency, and viscosity vs. temperature (Yao and Patel 2001). The recommended tests are predictive of drug product properties such as processing behavior, temperature sensitivity, stability during storage, and applicabilion on the skin. Lotions should ideally have some viscosity or internal structure to prevent flow from the application site once dispensed, but thin enough to spread evenly when little shear is applied.

4.3 Ointments

Ointments are semisolid preparations intended for external application to the skin or mucus membrane (Drug Nomenclature Monographs – Dosage Forms). Ointments usually contain <20% water and volatiles, and >50% hydrocarbons, waxes, or polyols as the vehicle. As the definition suggests, ointment products are waxy or oily and have higher viscosity and lower spreadability than creams. The viscosity measurement of eight commercially available ointments was in the range of 450,000 and 1.7 million cP, significantly higher than that of creams (Lionberger 2003). Pena et al. studied the structure of a model ointment consisting of white petrolatum, mineral oil and microcrystalline wax (Pena et al. 1994). In their formulation-based rheology study, they observed that the rheology of ointment was controlled by white petrolatum and mineral oil primarily, whereas the wax helped to build up the structure. Similar observations can be made in most ointments, where the oil components act as vehicle and/or to give the required smooth application consistency to the ointment. The wax components are responsible for the solid-like behavior, the storage modulus, of the ointments. The wax components ensure structural integrity of the product even at body temperatures.

4.4 Gels

Gel, as per FDA, is a semisolid dosage form that contains a gelling agent to provide stiffness to a solution or a colloidal dispersion (Drug Nomenclature Monographs – Dosage Forms). Gels could either be suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels, in general, are two- or three-component formulations as compared to more complicated semisolid