# Texture Profile Analysis of Bioadhesive Polymeric Semisolids: Mechanical Characterization and Investigation of Interactions Between Formulation Components

DAVID S. JONES,* A. DAVID WOOLFSON, and JASMINA DJOKIC

The Pharmaceutical Devices Group, School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97, Lisburn Road, Belfast BT9 7BL, Northern Ireland, United Kingdom

SYNOPSIS

This study reports the use of texture profile analysis (TPA) to mechanically characterize polymeric, pharmaceutical semisolids containing at least one bioadhesive polymer and to determine interactions between formulation components. The hardness, adhesiveness, force per unit time required for compression (compressibility), and elasticity of polymeric, pharmaceutical semisolids containing polycarbophil (1 or 5% w/w), polyvinylpyrrolidone (3 or 5% w/w), and hydroxyethylcellulose (3, 5, or 10% w/w) in phosphate buffer (pH 6.8) were determined using a texture analyzer in the TPA mode (compression depth 15 mm, compression rate 8 mm $s^{-1}$, 15 s delay period). Increasing concentrations of polycarbophil, polyvinylpyrrolidone, and hydroxyethylcellulose significantly increased product hardness, adhesiveness, and compressibility but decreased product elasticity. Statistically, interactions between polymeric formulation components were observed within the experimental design and were probably due to relative differences in the physical states of polyvinylpyrrolidone and polycarbophil in the formulations, i.e., dispersed/dissolved and unswollen/swollen, respectively. Increased product hardness and compressibility were possibly due to the effects of hydroxyethylcellulose, polyvinylpyrrolidone, and polycarbophil on the viscosity of the formulations. Increased adhesiveness was related to the concentration and, more importantly, to the physical state of polycarbophil. Decreased product elasticity was due to the increased semisolid nature of the product. TPA is a rapid, straightforward analytical technique that may be applied to the mechanical characterization of polymeric, pharmaceutical semisolids. It provides a convenient means to rapidly identify physicochemical interactions between formulation components. © 1996 John Wiley & Sons, Inc.

## INTRODUCTION

Texture profile analysis (TPA) is a technique that has been extensively employed to mechanically and geometrically characterize food materials,[1,2] including various fruit materials,[2] whipped toppings, commercially available gelatin dessert gels, carrageenan gels,[3] pudding desserts, cheeses,[4] and instant mashed potato.[5] In TPA, two passes of a solid probe are made into the product with a predefined pause allowed between each pass. From the resultant force–time curve, the textural properties of the product may be calculated. The parameters that may be derived from TPA are hardness (force required to attain a given deformation), elasticity (the rate at which the deformed sample returns to its undeformed condition after the removal of the deforming force), adhesiveness (a quantity that simulates the work required to overcome the attractive forces between the surface of the sample and the surface of the probe with which the sample comes into contact), and compressibility (the force per unit time required to deform the product during the first compression cycle of the probe).[1]

In the development of polymeric, pharmaceutical semisolid preparations for topical application, sev-

* To whom correspondence should be addressed.

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eral desirable product characteristics may be defined. These include ease of expression of the product from the container, spreadibility of the product on the substrate (skin or mucosal epithelium), and, notably, adhesion of the product when the substrate is a mucosal surface. Such properties contribute to the ultimate clinical efficacy of the product.[6-8] Consequently, a knowledge of comparative mechanical characteristics is important in the formulation chemistry of semisolid preparations. Thus, the present study reports the use of TPA as a convenient method for the mechanical characterization of model pharmaceutical semisolid preparations with bioadhesive properties.

## EXPERIMENTAL

### Materials

Hydroxyethylcellulose (HEC, Natrosol 250M-Pharm) was a gift from Aqualon, Ltd., Warrington, UK. Polyvinylpyrrolidone (PVP) K90 (Povidone USP) was obtained from BASF, Ludwigshafen, Germany. Polycarbophil (PC, Carbopol Noveon AA-1) was a gift from B. F. Goodrich Co., Cleveland, OH. All other chemicals were purchased from BDH Laboratory Supplies, Poole, UK, and were of AnalaR or equivalent quality.

### Manufacture of Pharmaceutical Polymeric Semisolids

HEC was dissolved in the required volume of phosphate-buffered saline (PBS, 0.03*M*, pH 6.8) using a high-speed mixer. Following complete dissolution, the gel thus formed was transferred to an ointment slab. PVP K90, and PC were incorporated into the gel manually with thorough mixing. Following removal of air under a vacuum, all formulations were transferred to amber ointment jars and stored at 4°C.

### Texture Profile Analysis of Pharmaceutical Polymeric Semisolids

Evaluation of the mechanical properties of the preparations was performed using an STS Stable Micro Systems texture analyzer (Model TA-XT2) in the TPA mode. Formulations were transferred into a 10 mL beaker and packed to a fixed height, taking care to avoid the introduction of air into the samples. The analytical probe (10 mm diameter) was compressed twice into each sample to a depth of 15 mm at a rate of 8.0 mm $s^{-1}$. A delay period of 15 s was allowed between the end of the first and the beginning of the second compression. All tests were performed at least in quadruplicate on samples at ambient temperature.

### Statistical Analysis

A factorial design was used ($2 \times 2 \times 3$). The effects of formulation changes on hardness, adhesiveness, elasticity, and compressibility were evaluated using a three-way analysis of variance (ANOVA, $P < 0.05$ denoting significance). Post-hoc statistical analyses of the means of individual groups were performed using Fischer's PLSD test ($P < 0.05$ denoting significance).

## RESULTS AND DISCUSSION

The semisolid formulations examined exhibited a wide range of mechanical properties dependent on the formulation design. Typical observed ranges of hardness, adhesiveness, compressibility, and elasticity were, respectively, 0.22 ± 0.01 to 5.17 ± 0.19 N, 0.09 ± 0.02 to 9.30 ± 0.18 N $s^{-1}$, 0.27 ± 0.01 to 23.74 ± 1.50 N $s^{-1}$, and 0.55 ± 0.01 to 0.95 ± 0.01.

The effects of changing the concentrations of HEC, PVP, and PC on product hardness, adhesiveness, compressibility, and elasticity are shown in

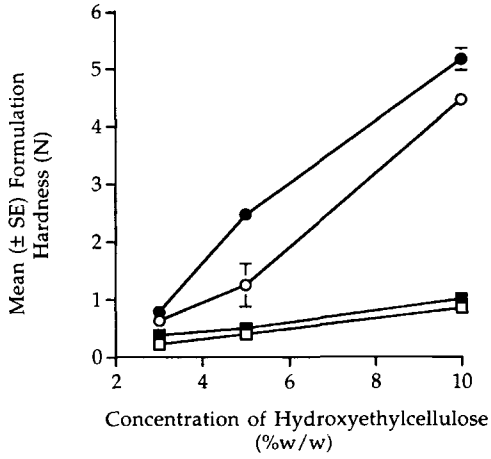


**Figure 1** The effect of HEC concentration (3, 5, 10% w/w) on the hardness of formulations containing PC and PVP: (□) 1% w/w PC/3% w/w PVP; (■) 1% w/w PC/5% w/w PVP; (○) 5% w/w PC/3% w/w PVP; (●) 5% w/w PC/5% w/w PVP. Each datum point point represents the mean ± standard error of four replicate samples.

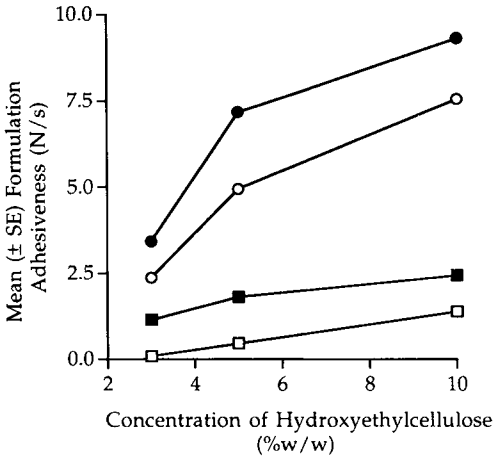


**Figure 2** The effect of HEC concentration (3, 5, 10% w/w) on the adhesiveness of formulations containing PC and PVP: (□) 1% w/w PC/3% w/w PVP; (■) 1% w/w PC/5% w/w PVP; (○) 5% w/w PC/3% w/w PVP; (●) 5% w/w PC/5% w/w PVP. Each datum point point represents the mean ± standard error of four replicate samples.

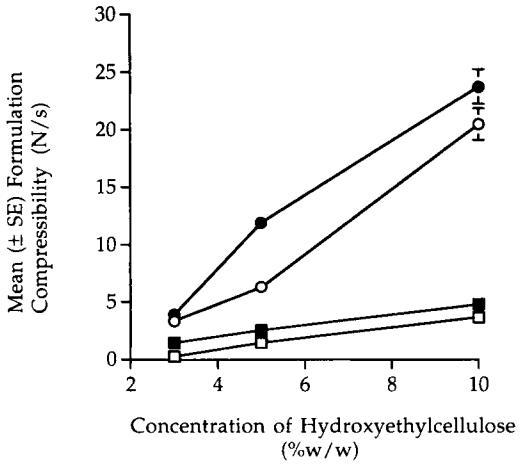


**Figure 3** The effect of HEC concentration (3, 5, 10% w/w) on the compressibility of formulations containing PC and PVP: (□) 1% w/w PC/3% w/w PVP; (■) 1% w/w PC/5% w/w PVP; (○) 5% w/w PC/3% w/w PVP; (●) 5% w/w PC/5% w/w PVP. Each datum point point represents the mean ± standard error of four replicate samples.

Figures 1–4, respectively. Increasing the concentration of PC, HEC, and PVP significantly increased hardness, adhesiveness, numerical values of elasticity, and the force per unit time required for compression (compressibility). A summary of the statistical analyses is presented in Table I.

In addition to the significant effects of the primary variables on the physical properties under investigation, several statistical interactions between the contributions of these primary variables (concentrations of each polymer constituent) to each of the various mechanical parameters were observed. With respect to product hardness and force per unit time required for product compression (compressibility), PVP and HEC (especially at 5% and 10% w/w, respectively) had more pronounced effects in the presence of 5% w/w compared to 1% w/w PC. Statistically significant interactions were observed between PC and PVP and between PC and HEC with respect to product adhesiveness. Again, these interactions reflect the statistically greater effects of HEC and PVP on adhesiveness in the presence of a higher concentration of PC (5% w/w). Therefore, increased product hardness, compressibility, and adhesiveness following increases in HEC concentration (from 3 to 5% w/w and from 5 to 10% w/w) or PVP concentration (from 3 to 5% w/w) is statistically enhanced in the presence of 5% w/w PC.

Two other interaction terms involving product elasticity can be observed from Table I between PC and HEC and between PC and PVP. Thus, in the presence of 5% w/w PC, increasing the concentrations of either PVP (from 3 to 5% w/w) or HEC (from 3 to 5% w/w or from 5 to 10% w/w) resulted in minimal alterations to product elasticity. However, such increases in concentration in the presence

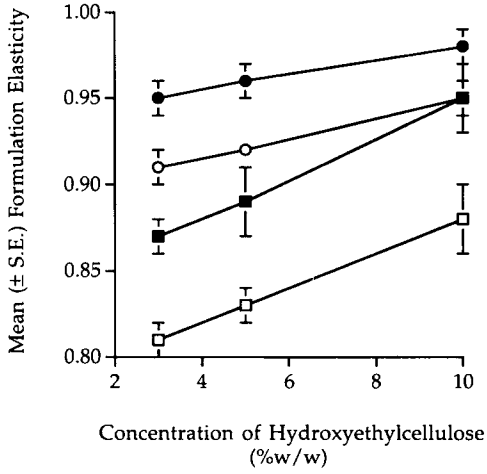


**Figure 4** The effect of HEC concentration (3, 5, 10% w/w) on the numerical values of elasticity of formulations containing PC and PVP: (□) 1% w/w PC/3% w/w PVP; (■) 1% w/w PC/5% w/w PVP; (○) 5% w/w PC/3% w/w PVP; (●) 5% w/w PC/5% w/w PVP. Each datum point point represents the mean ± standard error of four replicate samples.

**Table I A Summary of the Statistical Analyses of the Effects of Increasing Concentrations of Polycarbophil (PC), Polyvinylpyrrolidone (PVP), and Hydroxyethylcellulose (HEC) on Formulation Hardness, Adhesiveness, Elasticity, and Compressibility**

| Variables | Mechanical Properties of Formulations | | | |
|---|---|---|---|---|
| | Hardness | Adhesiveness | Elasticity[a] | Compressibility[b] |
| PC (1–5% w/w) | Significant increase | Significant increase | Significant decrease[a] | Significant increase |
| PVP (3–5% w/w) | Significant increase | Significant increase | Significant decrease[a] | Significant increase |
| HEC (3–5% w/w) | Significant increase | Significant increase | No effect | Significant increase |
| HEC (5–10% w/w) | Significant increase | Significant increase | Significant decrease[a] | Significant increase |
| PC × PVP | Significant | Significant | Significant | Significant |
| PC × HEC | Significant | Significant | Significant | Significant |
| PVP × HEC | No effect | No effect | No effect | No effect |
| PVP × HEC × PVP | No effect | No effect | No effect | No effect |

Statistical design was a 2 × 2 × 3 factorial. Results were analyzed using a three-way analysis of variance ($P < 0.05$ denoting significance); individual differences between mean values of groups were statistically evaluated using Fischer's PLSD test ($P < 0.05$ denoting significance).

[a] Lower numerical values (dimensionless) as determined by TPA in the elasticity mode indicate greater product elasticity.

[b] Force per unit time required for product compression.

of 1% w/w PC resulted in significant increases in the numerical values of product elasticity (as recorded by the texture analyzer). Finally, while HEC concentration was observed to exhibit a significant primary effect on product elasticity, post-hoc statistical investigations revealed that increasing the concentration of HEC from 3 to 10% w/w and from 5 to 10% w/w statistically increased elasticity, whereas an increase from 3 to 5% w/w was insignificant.

Physical characterization of pharmaceutical semisolids has been performed using a variety of techniques, including conventional rheometry[9,10]; dielectric spectroscopy, oscillating rheometry,[11] FTIR,[12] and gel strength determination.[6] A knowledge of the physical properties of such products is of value for the predictive performance of the product under a variety of conditions, particularly during product filling,[13] spreadibility over and bioadhesion to mucosal or nonmucosal sites,[14] perceived "feel" of the product,[7] and ease of product removal from the final packaging system. Consequently, a knowledge of such properties will be of value in both preformulation and formulation studies of polymeric semisolid dosage forms.

TPA has been employed in the food industry to physically characterize food materials. However, there are few studies in which TPA has been applied to pharmaceutical products. This study therefore represents one of the first applications of this technique to the characterization of pharmaceutical semisolids, which may be compared to food products in the sense that there is a subjective element to their feel and appearance.

It is of interest to describe the individual contributions of the polymeric constituents of each model formulation to the physical form of the final product. In all formulations, HEC was dissolved to form a gel into which PVP was then dissolved until its saturation solubility in the formulation was reached. Beyond this point, PVP was present as a suspended solid. Even at the lowest concentration of PVP, its total dissolution was not observed in any formulation. Thus, in formulations containing 5% w/w PVP, there is a greater amount of undissolved polymer in comparison to formulations containing a lower concentration (3% w/w). Finally, PC, due to its crosslinked structure, did not dissolve in any formulation but rather exhibited swelling. Formulations containing PC (5% w/w) had a greater percentage of this polymer present as a suspended, unswollen, solid than did their counterparts containing 1% w/w polycarbophil, due to the limited amount of water available in the formulation for this process. Hence, the model formulations studied are described as semisolids.

Few studies have addressed the effects of formulation chemistry on product hardness and product compressibility. However, it was reported that the hardness of polysaccharide gels was increased as their degree of crosslinking was increased,[12] whereas Ferrari et al.[6] reported that the gel strengths and viscosities of hydroxypropylcellulose gels were increased as their concentrations were increased. In

the present study, increased formulation hardness associated with increased concentrations of PVP, PC, and HEC is due to the concomitant increase in viscosity of these products, producing an increased resistive force to product deformation.

Product compressibility was found to be dependent on the concentrations of PC, PVP, and HEC. Thus, increased concentrations of these components increased the force/unit time required for compression. The relative order of contributions of these polymers to product compressibility was similar to their ranked contributions to product hardness. Consequently, increased force/unit time required for compression (and increased hardness) is related to the increased viscosity of the products resulting from the dissolution, swelling, or dispersion of PC, PVP, and HEC within the formulation. The statistical interactions observed between PVP and PC and between HEC and PC on product hardness and compressibility are probably due to the significantly enhanced viscosities in products containing 5% w/w PC as a result of the greater mass of suspended solids present in these formulations.

The model formulations examined in this study exhibited a wide range of adhesiveness that was again dependent on the concentrations of polymeric components present. The polymers used in this study were described as bioadhesive[14-16] and subsequently can form adhesive interactions with an appropriate substrate. The relative contributions of PC, PVP, and HEC to product adhesiveness reflected their reported adhesion bond strength.[15] Consequently, PC, a well-known mucoadhesive,[14] was the greatest contributor to the adhesiveness of the various formulations, whereas HEC and PVP, polymers with limited bioadhesive character, exhibited lower contributions to product adhesiveness. The significant effect of PC concentration on adhesiveness is due to the greater amount of undissolved polymer in formulations containing 5% w/w. In the unswollen state, polymeric chains can be mobilized by moisture, leading to more effective interpenetration of the polymer with the substrate.[17] In addition, since a greater percentage of PC is in the swollen state when the lower concentration of PC (1% w/w) is employed, a greater percentage of polymer is also in the neutralized state at the formulation pH (6.8). Consequently, PC adhesiveness, which is related to the number of free carboxylic acid groups present on the polymer chains, is reduced.[14] However, in formulations containing 5% w/w PC, a major proportion of PC will exist as unswollen particles whose surface charge is therefore relatively unaffected by the formulation pH. This occurs because of competition from HEC and, in particular, PVP, for the relatively small amount of available water in the formulation. PVP and HEC therefore increase the adhesiveness of formulations containing 5% w/w PC to a greater extent than do formulations containing 1% w/w PC. Hence, the observed statistical interactions.

Product elasticity represents the rate at which the deformed sample returns to the undeformed condition.[1] Lower numerical values (dimensionless) as determined by TPA in the elasticity mode indicate greater product elasticity. In this study, PC (principally) and PVP were the major determinants of elasticity. Formulation effects on elasticity are related to the pharmaceutical form of the product. Consequently, decreased product elasticity due to increased concentrations of PVP and PC reflects the greater times required for structural reformation associated with products that contain a higher percentage of suspended solids. However, the situation is complicated by the viscoelastic nature of the model formulations. At higher solution concentrations of HEC (the most soluble of the polymeric components), the increase in product viscosity may affect overall viscoelastic behavior, with the viscosity component becoming a more significant determinant of overall elastic behavior, a trend seen in Figure 4.

In conclusion, this study reports the use of TPA for the mechanical characterization of model pharmaceutical semisolids with bioadhesive properties. By manipulation of the formulation chemistry, products exhibiting a wide range of mechanical properties were obtained. TPA proved to be a convenient and rapid method for the mechanical characterization of these semisolid products. Together, with the use of an appropriate experimental design, TPA may be used to identify interactions between formulation components that can affect the final mechanical properties of the formulated product.

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