Drug Development and Industrial Pharmacy, 24(10), 919–926 (1998)

RESEARCH PAPER

Evaluation of a Mucoadhesive Buccal Patch for Delivery of Peptides: In Vitro Screening of Bioadhesion

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ABSTRACT

We have assessed the bioadhesive properties of several different mucoadhesive buccal patches. The patches consisted of custom coformulations of silicone polymers and Carbopol 974P. The contact angle of water was measured for each of the test formulations, using an ophthalmic shadow scope. The corresponding work of adhesion between the water and the patches (W_1), and between the patches and freshly-excised rabbit buccal mucosa (W_2) was then calculated, using a modification of Dupre's equation. The bioadhesive strength between the patches and excised rabbit buccal mucosa was also assessed. The results of the contact-angle measurements indicated that the contact angle decreased with an increase in the amount of Carbopol in the formulation. Additionally, the calculated values of both W_1 and W_2 increased with an increase in the amount of Carbopol in the buccal-patch formulations. A correlation ($r \neq 0.9808$) was found between the measured contact angle

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and the calculated values for W_2. The direct measurement of the force required to separate a buccal patch from excised rabbit buccal mucosa with the INSTRON demonstrated that the adhesive strength increased with an increase in the amount of Carbopol. This preliminary study has shown that the measurement of contact angles alone may provide a useful technique for estimating the work of adhesion, and may serve as a convenient and rapid screening procedure to identify potential mucoadhesive buccal-patch formulations.

INTRODUCTION

Recently, considerable attention has been focussed on the development of alternative drug delivery systems for proteins and peptides. This results from the availability of larger quantities of these substances being made possible by advances in biotechnology, and from the fact that delivery of peptides and proteins has placed special demands on the route of delivery and the design of appropriate delivery systems. Routes of drug administration that were of minor importance as ports of drug delivery in the past have assumed added importance in peptide and protein delivery. These include the transdermal, buccal, rectal, nasal, vaginal, intrauterine, pulmonary, and ocular routes.

Bioadhesive systems have been used for many years in dentistry (1), as well as in ophthalmology (2) and for surgical applications (3). There has also been intense interest in the use of bioadhesive materials as controlled-release systems for the local delivery of bioactive agents (4,5), as in the case of mucoadhesive systems for buccal drug delivery. Buccal drug delivery represents a convenient route of administration for peptides. While this route of drug administration has been used for peptides for more than 10 years, it has only been recently that biocompatible and efficient mucoadhesive delivery systems have been developed. A mucoadhesive controlled-release buccal patch offers the advantage of prolonged contact of the peptide with the absorbing membrane. Presumably, this should result in a larger fraction of the applied dose reaching the systemic circulation. One added advantage of the buccal route of drug administration is the avoidance of the "first-pass" effect associated with oral delivery, and another is the inconvenience of parenteral administration. The easy accessibility of the membranes that line the oral cavity make precise localization of a buccal drug-delivery system possible. Moreover, a buccal patch may be easily removed at any time during the treatment period, and drug administration terminated. In addition, the membranes that line the oral cavity exhibit robustness and rapid cellular recovery following local irritation or stress.

To fully characterize the potential of using a mucoadhesive silicone/Carbopol buccal patch to deliver therapeutic peptides, we previously investigated the permeability characteristics of excised rabbit buccal mucosa to a representative peptide, namely oxytocin (6,7). We demonstrated that excised rabbit buccal mucosa was permeable to oxytocin, a nine-amino-acid peptide, and that oxytocin was released in vitro from the patches for more than 24 hr. Lastly, it was shown that oxytocin was delivered in rabbits following application of the buccal patch, and was not irritating to the underlying mucosa (7). The present investigation was conducted in an attempt to develop a convenient and simple test to screen silicone/Carbopol 974P formulations suitable for use in mucoadhesive buccal-patch systems. Because the bioadhesive action of a mucoadhesive device occurs at the mucus interface, it was necessary to examine and quantitatively investigate the surface properties of the buccal patch formulations. Typically, surface analysis studies may include classic preliminary tests, such as contact-angle determination (8,9), and more sophisticated spectroscopic techniques (10–13).

In order to determine the bioadhesive bond strength of various bioadhesive systems, Peppas and Buri have reviewed and reported various in vitro and in vivo techniques (14). In vitro techniques primarily include those that destroy the adhesive bond by shear or peeling forces, but also involve some tensile and dynamic tests (15–18). In vivo methods presumably provide a more realistic picture of expected behavior. Several in vivo studies have been reported (19–21). However, in vitro tests are still the method generally used to assess the degree of mucoadhesion.

In the present study, an ophthalmic shadow scope was used to measure the contact angle that a water droplet made on the surface of a silicone-based mucoadhesive formulation that contained varying amounts of Carbopol 974P. The values of the thermodynamic work of adhesion calculated from contact-angle measurements were then used to calculate the theoretical work of adhesion between the mucoadhesive patch and the buccal epithelium. The resulting theoretical values for the work of adhesion were then used to supplement data acquired by directly

measuring the force required to separate the mucoadhesive buccal patch from freshly excised rabbit buccal mucosa. Results were used to determine whether a positive correlation existed between the measured contact angle and the work of adhesion calculated for the buccal patch–mucosa interface.

MATERIALS

Seven different mucoadhesive laminates were provided by Dow Corning Corporation (Midland, MI) in a blinded fashion, and were used as received. All of the formulations evaluated were non-drug-loaded laminates (1 in. × 10 in.). The formulations consisted of silicone elastomer and Carbopol 974P. The percent by weight of Carbopol 974 was 10, 15, 20, 25, 30, and 35 for the six mucoadhesive-patch laminates designated formulations #42, #41, #40, #39, #38, and #37, respectively. Formulations of the silicone/Carbopol 974P laminates have been previously described (6,22). The test laminates were stored in a desiccator in the refrigerator until the time of analysis.

The test fluid used for contact-angle measurements was distilled water (high-pressure liquid chromatography [HPLC] grade) purchased from Sigma-Aldrich (St. Louis, MO). The contact angle was measured with an ophthalmic shadow scope (URCON, Inc., Hollywood, CA). The Hamilton microsyringe (25 µl) used in the study was purchased from Fisher Scientific (Pittsburgh, PA). The bioadhesive strength between the patches and excised rabbit buccal mucosa was assessed using an INSTRON (Model 4301, Instron Co., Canton, MA).

METHODS

Work of Adhesion Experiments

The contact angles (θ_e) were measured with droplets of water (γ = 72.8 mN·m^{-1} at 25 °C) on the surface of each laminate, using the ophthalmic shadow scope. All experiments were performed at 25.0 ± 1.0 °C, since the contact angle is a function of surface tension, which is in turn related to temperature. A calibrated volume (20 µl) of water was placed on the mucoadhesive surface of each laminate by use of a microsyringe. All the droplets were released from 1 cm above the surface, to minimize the inconsistencies between each contact angle measurement. In addition, all the advancing contact angles were measured 1 min after the release of each droplet onto the surface of each formulation. The measurement of contact angles was performed by photographing the projected image of the water droplet on the screen of the shadow scope. In addition, an acetate transparency was placed on the screen and a tracing made of the projected image of the water droplet on the surface of the patch formulation. Photographs and hand-drawn transparencies were then compared, and the contact angle between the tangent line and the surface of the mucoadhesive laminate was measured with a protractor. Ten droplets of water were used for each mucoadhesive formulation, and contact angles on both the right and left sides were measured independently by two persons. The mean values for the contact angles were then used for all subsequent calculations.

Adhesive Strength of the Patch–Mucosa Bond

Rabbits (male New Zealand white, weighing 2.5–3.0 kg) were killed by intravenously injecting them with 5% pentobarbital sodium, and the buccal mucosa was immediately excised. After isolating the tissue, it was glued to a 5/8-in. × 5/8-in. stainless-steel jig, using Krazy Glue® (Columbus, OH). The mucoadhesive laminates were first cut to 5/8-in. × 5/8-in.-size pieces, and the water-impermeable backing side was fixed to the jigs, using the same glue. The jigs were allowed to stand for 45 min to obtain maximum adhesive strength between the mucosa and the jig and the laminate and the jig. The two jigs were then allowed to come into contact with one another, after first moistening the surface of the buccal mucosa with one drop of water. The maximum load required to separate the mucoadhesive laminate from the buccal mucosa was then measured with the INSTRON.

Data Analysis

The thermodynamic work of adhesion (W_A) is defined as the reversible work per unit area required to separate two phases initially in contact at an interface at equilibrium. Dupre's equation (23) states that W_A is defined as the energy required to break the attraction between the unlike molecules, and is related to interfacial tensions through Equation (1)

$$W_A = \gamma^{LV} + \gamma^{SV} - \gamma^{SL} \quad (1)$$

where, γ^{LV} and γ^{SV} are the interfacial tensions of phase 1 and phase 2 in contact with air, respectively, and γ^{SL} is the interfacial tension across the interface between phases 1 and 2.

A relationship for evaluating the interfacial tension of solid surfaces can be related to the equilibrium surface forces of a liquid droplet resting on a solid surface (24). The relationship in which the droplet forms an equilibrium contact angle at the solid surface (θ_e) is expressed through Young's equation, given as Equation (2):

$$\gamma^{SV} - \gamma^{SL} = \gamma^{LV} \cdot \cos \theta_e \quad (2)$$

where γ^{SV}, γ^{LV}, and γ^{SL} are the solid/vapor, liquid/vapor, and solid/liquid interfacial tensions, respectively. Combining equations (1) and (2) results in the work of adhesion between the liquid and the mucoadhesive as shown in equation (3)

$$W_1 = \gamma^{LV} \cdot (1 + \cos \theta_e) \quad (3)$$

Interfacial tensions can also be related by an empirical equation developed by Neumann et al. (25) and given as equation (4), where variables are defined as in equation (2):

$$\gamma^{SL} = \frac{(\sqrt{\gamma^{SV}} - \sqrt{\gamma^{LV}})^2}{1 - 0.015\sqrt{\gamma^{SV} \cdot \gamma^{LV}}} \quad (4)$$

Equation (4) was found to be internally consistent and to accurately predict interfacial tensions for surfaces and liquids with interfacial tensions as high as 72.8 $mN \cdot m^{-1}$ (25). Because γ^{LV} and θ_e are easily measured, one can obtain the value of γ^{SV} and γ^{SL} by using equations (2) and (4). Combining equations (2) and (4) results in a cubic equation [equation (5)]:

$$0.015\, x^3 - (2 + 0.015\, \gamma^{LV} \cdot \cos \theta_e) \cdot \gamma^{LV} x + (\gamma^{LV})^2 \cdot (1 + \cos \theta_e) = 0 \quad (5)$$

where $x = \sqrt{\gamma^{SV} \cdot \gamma^{LV}}$.

In order to obtain the precise roots of equation (5), a computer program in C language was compiled to provide an initial estimated root range. A numerical solution expressed graphically on standard cartesian coordinates yields three values on the x-axis where $f(x) = 0$. The negative value is nonpractical, while the other two, positive values are the roots required. Based on the estimated root range calculated from the above computer program, an additional computer program was written in FORTRAN language to compute the precise values of γ^{SV} and γ^{SL}. The work of adhesion between the mucoadhesive laminate and the buccal mucosa (W_2) was then estimated with equation (1) as modified by Adamson (26) and shown as equation (6),

$$W_2 = \gamma^{SV} \cdot (2 + \beta \cdot \gamma_c) - \beta \cdot (\gamma^{SV})^2 \quad (6)$$

where β is a constant with a value of approximately 0.04 for low-energy surfaces like Teflon, and γ_c is the critical surface tension of a given solid. The buccal epithelium may be assumed to represent a low-energy surface (24) with an approximate value of γ_c similar to that of Teflon (18 $mN \cdot m^{-1}$).

In the present study, equations (2) and (4) were used to calculate γ^{SV} (mucoadhesive laminate – air) and γ^{SL} (mucoadhesive laminate – water). The work of adhesion between water and the mucoadhesive laminate (W_1) was calculated with equation (3). Equation (6) was used to calculate the equilibrium work of adhesion (W_2) of the mucoadhesive laminate on the surface of buccal epithelium in the presence of air.

RESULTS

Contact Angle (θ_e) and Work of Adhesion

Figure 1 represents a plot of the mean values of the measured contact angle of water on the mucoadhesive patch laminates versus the percent weight of Carbopol 974P in the formulation. It can be noted in Fig. 1 that the contact angle decreased with an increase in the amount of Carbopol 974P in the formulation. Figure 2 illustrates the trends associated with the mean values of the calculated work of adhesion between water and the buccal patch (W_1) and between the buccal patch and rabbit buccal mu-

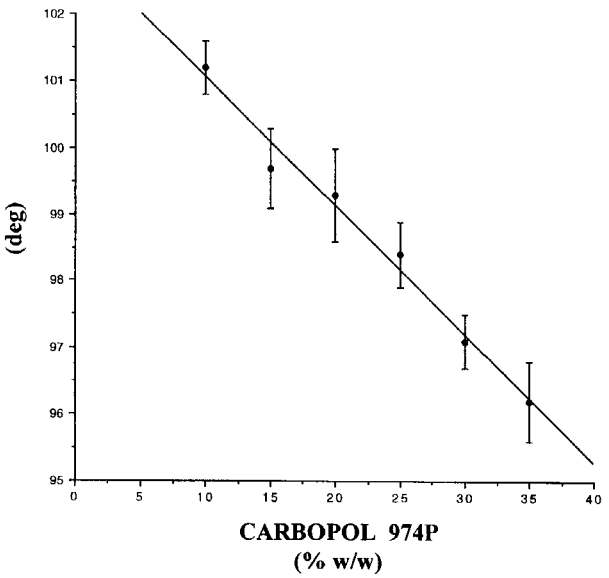

Figure 1. Effect of increasing amounts of Carbopol 974P on the measured contact angle of water on the surface of silicone/Carbopol 974P buccal patches. Each symbol represents the mean value ± SD of three measurements. The line through the mean values is included to visualize the trend, and does not represent a linear regression through the data points.

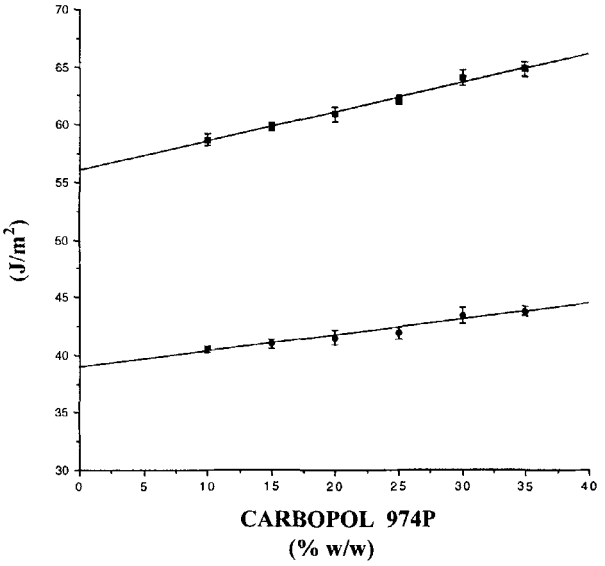

Figure 2. Effect of increasing amounts of Carbopol 974P on the theoretically calculated work of adhesion between either water and the mucoadhesive silicone/Carbopol 974P buccal patch (-●-) or between the patch and buccal mucosa (-■-). Each symbol represents the mean value ± SD of three individual calculations, using the data obtained from the contact-angle measurements and described in Methods. The line through the mean values is included to visualize the trend, and does not represent a linear regression through the data points.

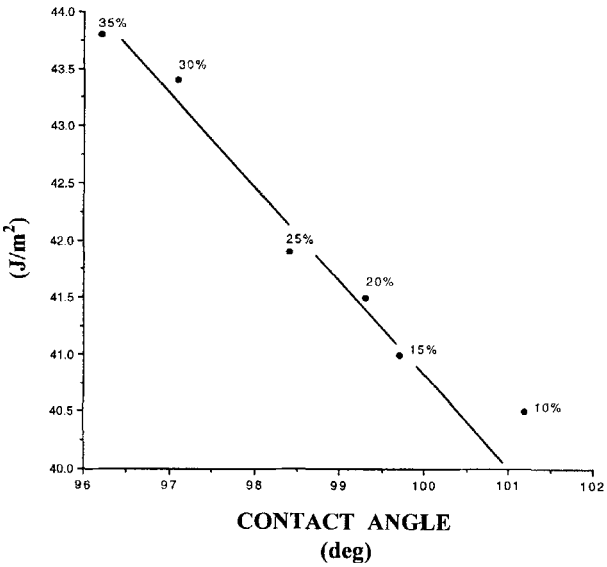

Figure 3. Correlation of the mean values of the measured contact angle of water on the patch surface and the theoretically calculated work of adhesion at the buccal patch–mucosa interface. The weight percent of Carbopol 974P in the patch formulation is indicated. The correlation coefficient (r) associated with a linear regression was −0.9808.

cosa (W_2) as the percent by weight of Carbopol 974P was incrementally increased. Mean values for W_1 and W_2 increased from 58.7 ± 0.52 × 10^3 J·m^{-2} to 64.8 ± 0.67 × 10^3 J·m^{-2}, and from 40.5 ± 0.34 × 10^3 J·m^{-2} to 43.8 ± 0.47 × 10^3 J·m^{-2}, respectively, as the concentration of Carbopol 974P was increased from 10% to 35%. Figure 3 demonstrates the correlation (r = −0.9808) observed between the mean values of the measured contact angles and the calculated work of adhesion for the mucoadhesive patch–mucosal interface. As shown in Fig. 3, as the measured contact angle increased from 96.2 ± 0.61 degrees to 101.2 ± 0.43 degrees for formulations that contained 35% w/w to 10% w/w Carbopol 974P, respectively, the calculated mean values for W_2 decreased from 43.8 ± 0.47 × 10^3 J·m^{-2} to 40.5 ± 0.34 × 10^3 J·m^{-2}.

Bioadhesion Between Patches and Rabbit Buccal Mucosa

Adhesive strength between excised buccal mucosa and the mucoadhesive formulations is summarized in Table 1; all data are expressed as the mean ± SD (N = 3). The results indicate that the force required to separate the mucoadhesive patch from excised rabbit buccal mucosa (i.e., the bioadhesive strength) increased with an increase in the weight percent of Carbopol 974P contained in the formulation. However, when the amount of Carbopol 974 reached 25% by weight of the total formulation, the force required to separate the mucoadhesive laminate from the

Table 1

Effect of Carbopol 974P Concentration on Maximum Load Required to Separate a Silicone/Carbopol 974P Mucoadhesive Buccal Patch from Freshly Excised Rabbit Buccal Mucosa

Formulation No.	Percent Carbopol 974P	Maximum Load at Yield (g)
37	35	>2000[a]
38	30	>2000[a]
39	25	>2000[a]
40	20	813 ± 178[b]
41	15	378 ± 101
42	10	107 ± 30.4

[a] Indicates failure between the mucosa and jig rather than separation of buccal mucosa and the mucoadhesive patch.
[b] Mean value ± SD.

underlying buccal mucosa was so great that the buccal mucosa separated from the stainless steel jig; that is, the adhesive strength between the patch and buccal mucosa exceeded the force required to separate the buccal mucosa or the mucoadhesive laminate from the faceplate of their respective jigs.

DISCUSSION

The selection and characterization of an appropriate mucoadhesive polymer is the initial step for the development of a controlled-release buccal patch for the administration of drug substances such as therapeutic peptides. In addition, the bioadhesive strength of a mucoadhesive polymer selected for this purpose must be assessed. In the present study, both a surface property and the bioadhesive strength of the mucoadhesive buccal formulations were evaluated. It would appear reasonable to assume that mucoadhesive formulations that result in a smaller contact angle with water and yield greater values for the calculated work of adhesion should have greater bioadhesive strength. Results in the present study showed that when the amount of Carbopol 974P included in the formulation was increased, the corresponding calculated values for the work of adhesion increased, as did the bioadhesive strength, although we have limited data on the latter. Moreover, a strong correlation was observed ($r = -0.9808$) between the measured contact angle of a drop of water on the patch surface and the theoretically calculated work of adhesion at the patch–mucosa interface (see Fig. 3).

Adhesion is the state in which two surfaces are held together by interfacial forces. Bioadhesion has been used to describe phenomena related to the ability of some synthetic and biologic macromolecules and hydrocolloids to adhere to biologic tissues (27,28). Leung and Robinson (29,30) discussed the possible mechanisms for mucoadhesive interaction, which included electronic interactions, hydrogen bonding, hydrophobic interactions, and diffusion and interpenetration of macromolecules. In agreement with earlier findings by of Smart et al. (18) and Ponchel et al. (31), Leung and Robinson concluded that interpenetration should be the prime mechanism of mucoadhesion, and that all molecular features of a candidate polymer favoring entanglement with mucus (e.g., flexible chains, expanded network structure, secondary interactions) should increase its mucoadhesiveness. Although the occurrence of interpenetration is accepted as a mechanism for adhesion between polymers, it is still poorly understood in terms of whether it is the predominant process relevant to the formation of the mucoadhesive interface.

In the present study, the relationship between interfacial tension and bioadhesive strength suggests that interfacial tension may also contribute to the bioadhesion between mucoadhesive buccal patches and mucosa. In contrast to the theory of interpenetration, interfacial tensions are general thermodynamic parameters for adhesion. The advantage of the thermodynamic approach is that it deals only with properties at the interface, thus eliminating contributions from the chemical nature of the adhesive or the structure of the mucosa. In addition, the thermodynamically defined work of adhesion, as an equilibrium property of the mucosa and mucoadhesives, is independent of the particular conditions under which a dynamic measurement may be made and subsequently used to characterize the adhesiveness of patches. Lehr et al. (32) measured contact angles of air–octane bubbles in isotonic saline, artificial gastric fluid, and artificial intestinal fluid, and suggested that in addition to interpenetration, interfacial energies between the respective substrate and adhesive (Polycarbophil; Carbopol EX-55 resin) play an important role in mucoadhesion. Guo (33,34) reported that the average peel strength of buccal patches from a polymeric test surface (a hydrated polyvinylpyrrolidone/cellulose acetate hydrogel) did not necessarily follow the general rule that a low substrate surface energy, as in the case of buccal epithelium or teflon, should correspond to increased bioadhesive strength of an applied mucoadhesive patch.

Mucoadhesion is believed to involve a two-step process. The first adsorptive contact is governed primarily by surface-energy effects and spreading processes. In a later phase of mucoadhesion, polymer chains might interdiffuse across the interface and hence enhance the final bond. The results of the present study and the studies by Guo (33,34) suggest that the bioadhesive strength of mucoadhesive buccal patches cannot be predicted by surface properties alone. However, since it is much easier to measure the contact angle of a drop of test fluid on the surface of a mucoadhesive patches than to measure bioadhesive strength between buccal mucosa and a mucoadhesive patch, the contact-angle-measurement method for estimating the work of adhesion may be a more convenient and useful screening technique for the identification of promising mucoadhesive buccal-patch formulations. The present study would also corroborate the findings of Lehr et al. (32) regarding the benefits of contact-angle measurements for rapidly assessing the relative degree of hydrophilicity/hydrophobicity of solid mucoadhesive surfaces.

The foregoing findings are important in view of the intense interest in using mucoadhesive drug-delivery systems for oral and buccal delivery of therapeutic peptides. In examples of the former, Lehr et al. (35) and Junginger et al. (36) have used polycarbophil-based mucoadhesives to increase the transport of the model peptide 9-desglycinamide-8-arginine vasopressin across rat intestinal tissue in vitro, as well as having used tomato-lectin-coated polystyrene microspheres to specifically bind to porcine enterocytes in vitro (37). More recently, Lueßen et al. (38) demonstrated that carbomer (Carbopol® 934P) and polycarbophil are potent inhibitors of the intestinal proteolytic enzyme trypsin. While the present study did not evaluate the potential for Carbopol 974P to inhibit proteolytic enzymes such as trypsin, it would appear reasonable to assume that Carbopol 974P may exert a similar inhibitory effect. Lastly, Luessen et al. (39) have recently demonstrated that Carbopol 934P and chitosan hydrochloride were able to enhance the intestinal absorption of buserelin in rats. The results of the present study with Carbopol 974P/silicone elastomers, as well as of previous studies of the buccal delivery of several therapeutic peptides (6,7,22,40), would suggest that silicone elastomer containing 15% w/w Carbopol 974P would appear to represent the most suitable mucoadhesive buccal patch for the sustained delivery of biologically active macromolecules. Moreover, the potential may exist for inhibition of proteolytic enzymes in the oral cavity by Carbopol 974P.

ACKNOWLEDGEMENTS

This work was supported in full by the Dow Corning Corporation, Midland, Michigan, through a grant awarded to T.P. Johnston.

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