A MEDISCA TECHNICAL REPORT

NovaFilm™

Rheological and Clinical Evaluation of a Novel Concentrated Mucoadhesive Gel Base

PATENT PENDING

INTRODUCTION

In order to overcome side effects linked to the delivery of medication through the oral routes, several efforts have been made to develop innovative mucosal drug delivery systems. These systems are known and preferred due to their ability to bypass first-pass metabolism, avoid gastrointestinal degradation and achieve more rapid onset of action. Within the human body, several mucosae are advantageous as drug delivery sites due to their high vascularisation and their low level of enzymatic activity however challenging due to its near constant mobility and self-cleansing action. Recognition of this issue had led to the development of mucoadhesive polymers that can adhere to the mucosal surface and prolong residence time. NovaFilm™ is a proprietary concentrated gel base designed to improve mucoadhesion, coating properties and prolong retention of medications at applications sites within the targeted mucosae.

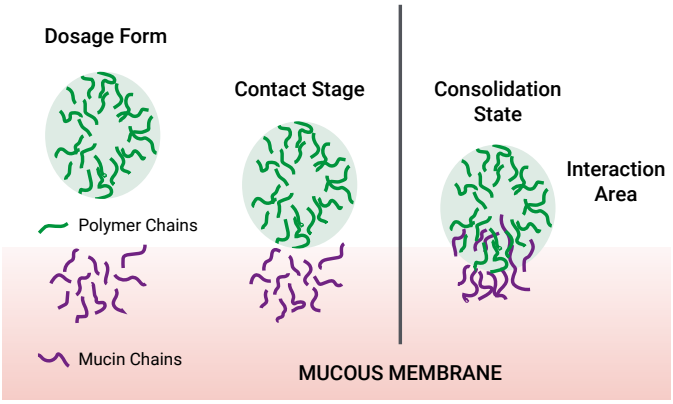

Figure 1: Mechanism of mucoadhesion.

One of the main advantages of mucosal administration is the improvement of therapeutic effect due to the permeation of API directly through the mucosal absorption membrane. The absorption membrane relies mostly on the mucosal layer and the epithelial tissue. In order to overcome barriers, drug delivery systems have to exhibit various functions and features, such as mucoadhesive and protective activity, solubility improving, permeation and uptake enhancing, and drug release controlling properties. It is therefore imperative to find a suitable vehicle that will not only provide means for the drug to permeate beyond the mucosal layer, but that will also allow the active ingredient to reach the targeted site.

MEDISCA, dedicated to developing and providing innovative solutions for compounding pharmacists, demonstrated the superior properties of NovaFilm™ Gel Base by conducting two *in Vitro* mucoadhesive comparative studies and a clinical case study. The aim of the *in Vitro* studies was to showcase the superior mucoadhesive properties of NovaFilm™ Gel Base by comparing it to another vehicle using standard rheological methods. The aim of the case study was to showcase the film-forming, improved retention capabilities, and mucoadhesive properties of NovaFilm™ Gel Base when applied on the vaginal mucosa in a clinical setting. Prior our testings, NovaFilm™ Gel Base toxicity and safety was evaluated using industry standard testing and showed no irritation and shown to be well tolerated.

METHOD

The *in Vitro* evaluation of mucoadhesive properties of NovaFilm™ Gel Base and a competitor product was performed in collaboration with Intertek and the Rheology Lab. Both laboratories performed a thorough evaluation of the rheological characterization of both products using standard methodologies (Hägerström et al. 2001; Jones et al. 1997).

STUDY 1: Evaluation of Mucin Interaction

The aim of the analysis performed on both samples was to characterize the rheological metrics most relevant to the behaviour of the samples and to identify the degree of variation in these rheological properties. As a concentrated base, NovaFilm™ Gel Base possesses higher viscosity properties. To avoid any bias, NovaFilm™ Gel Base was diluted using water to achieve a viscosity that was comparable to that of the competitor product.

Mucin solutions were made using deionized water and porcine gastric mucin (II) purchased from Sigma Aldrich. Each solution was made to a concentration of 10%, the pH adjusted to 6.2 using 0.5M NaOH solution before being diluted with deionized water to a final concentration of 6% before use. Using 3g of the prepared mucin solution, this was mixed with an equal weight of the sample under test, giving a final mucin concentration of 3% (w/w).

For control samples, the mucin solutions and samples under investigation were diluted to 50% (w/w) of their initial concentration using deionized water. To remove changes in pH as a possible influence the dilutions were also adjusted to pH 6.2. All prepared samples were allowed to equilibrate overnight at 5°C before any analysis was conducted.

STUDY 2: Evaluation of Maximum Compressive and Adhesive Force

The aim of the analysis performed on both samples was to measure the compressive and adhesive properties of NovaFilm™ Gel Base in comparison to the competitor sample using a Texture Analyzer. This additional testing would provide better understanding of the behaviour of the product once submitted to external stress. The investigation was focused on the measurement of the maximum compressive and adhesive forces for both samples.

The compressive and adhesive properties of both liquids/gels were measured using a Stable Micro Systems TA-XT2i HR. Each gel was scooped into a ~39 mm diameter plastic cup until a depth of about 20 mm was reached. Testing was performed at ambient temperature and humidity and was accomplished using a ½" diameter stainless steel probe with a 1" radius of curvature. Five trials were performed for both materials.

STUDY 3: Urogenital Atrophy Clinical Case Study

In recent years, a vast quantity of clinical data has been accumulated on the pathophysiology of symptomatic vulvovaginal atrophy (VVA) syndrome of menopause in postmenopausal women and on the treatment options for these conditions. Guidelines from several societies have recently been updated in favor of VVA vaginal therapy with the lowest possible doses of estrogens.

MEDISCA conducted a case study to assess the effectiveness of a compounded preparation using NovaFilm™ Gel Base and low dose of estriol in the alleviation of the symptoms associated with urogenital atrophy. The study was performed in collaboration with Dr. Kristy Prouse MD, OB/GYN (Chief Medical Officer and founder of The Institute for Hormonal Health) and Miranda Tawfik R.Ph, ABAAHP (Compounding pharmacist and co-owner of Origins Pharmacy). The investigator recruited a female patient aged between 50-79 y/o , with amenorrhea and a recurrent issue with moderate to severe urogenital atrophy symptoms. The treatment was compounded by Miranda Tawfik R.Ph, ABAAHP using NovaFilm™ Gel Base and estriol (supplied by MEDISCA) to reach a final concentration of 0.05% Estriol. For 12 weeks, the patient applied the preparation daily at bedtime for 2 weeks followed by twice a week thereafter. Gynecological evaluation and dried urine spot hormone evaluation were monitored at the beginning of the study, at 4 weeks and at the end of the study (12 weeks) to evaluate the patient's hormone level at each time point.

During the checkup, the investigator had the patient fill a qualitative evaluation using two questionnaires: vaginal symptoms score (VSS) and profile of female sexual function (PFSF). In addition to these questionnaires, the investigator evaluated the overall health of the vaginal mucosa using a vaginal health index (VHI), evaluated the endometrial thickness and had the patient perform dried urine spot hormone testing.

Figure 2: Dilution of NovaFilm™ Gel Base using a magnetic stirrer.

RESULTS

STUDY 1: Evaluation of Mucin Interaction

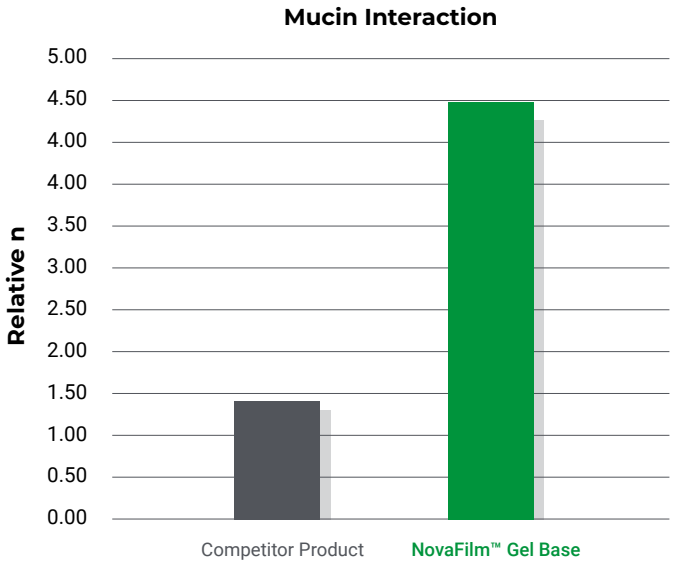

Figure 3: Mean rheology results for Study 1 with gel and mucin mixes.

After analyzing the mucoadhesive properties for both samples, the study showed that NovaFilm™ Gel Base had superior results in comparison to a competitor product. For drug delivery purposes, the term mucoadhesion implies attachment of a drug carrier system to the mucus coat on the surface of a tissue *(Carvalho et al. 2010)*. In our case, when applying NovaFilm™ Gel Base preparation on the mucosal surface, the interaction will be between a mucin surface and the polymers within the formulation. Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. The American Society of Testing and Materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both. Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug.

The results of the investigation of the mucin interactions with both samples indicated that both showed some mucin interaction, however NovaFilm™ Gel Base has a greater degree of mucin interactivity than the competitor product. This is thought to indicate a greater degree of mucoadhesion.

STUDY 2: Evaluation of Maximum Compressive and Adhesive Force

The investigation performed on the rheological metrics for both samples has demonstrated the superiority of NovaFilm™ Gel Base in comparison to a competitor sample. When analysing the rheological metrics of a mucoadhesive product, it is important to consider two parameters: the maximum compressive force (MCF) and the maximum adhesive force (MAF). The latter are hypothetical indicators of the overall performance of the product once applied on the mucosal surface.

MCF can be defined as the load applied just before the crushing of a material. In our case, we can correlate it to the strength with which the material resists to external compressive force. Based on the results, we can see that the force needed to compress NovaFilm™ Gel Base is greater than that of the competitor product. This suggests that NovaFilm™ Gel Base is more resistant to load and stress than the competitor product. Upon application, NovaFilm™ Gel Base will more likely maintain its shape compared to the competitor product.

MAF can be defined in terms of tackiness as tack results from adhesive/ cohesive forces between two materials in contact. For pressure sensitive adhesives such as NovaFilm™ Gel Base, tack can be defined as the ability to form an adhesive bond to a mucosal surface/ substrate under slight pressure and brief contact. The results show that the NovaFilm™ Gel Base shows greater results in terms of adhesion when compared to the competitor product.

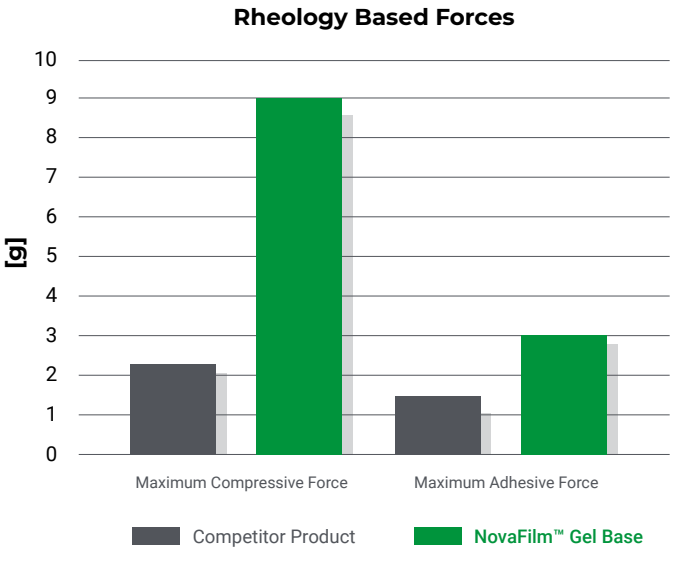

Figure 4: Average Maximum Compressive and Maximum Adhesive Force Data for Study 2.

STUDY 3: Urogenital Atrophy Clinical Case Study

In the last two decades, mucoadhesion has shown renewed interest for prolonging the residence time of mucoadhesive dosage forms through various mucosal routes in drug delivery applications. Mucoadhesive-based systems have shown enhanced bioavailability. It has been demonstrated that hormone treatment can aid in establishing and maintaining a healthy vaginal ecosystem. Knowing this, MEDISCA has hypothesized that a mucoadhesive preparation compounded with a low-dose concentration of estriol (E3) will have beneficial results in post-menopausal women suffering from UGA.

This hypothesis was confirmed by the results of the combination of NovaFilm™ Gel Base and low-dose E3 as the treatment regimen was able to considerably improve the clinical signs and symptoms as well as the quality of life of menopausal women suffering from vaginal atrophy. When evaluating the Estriol levels in the patient, the values were compared to the luteal range for Estriol of 5-18 ng/mg which is described as the premenopausal range. For the case study, the patient's level at onset, was below the luteal range at 2.9 ng/mg while at the 12 week mark it increased to 7.7 ng/mg bringing it within the luteal range.

When reviewing the vaginal health index, the total initial score was 10 out of a possible 25, while the 12 week check-in increased to 18 with significant improvements seen in elasticity, epithelial integrity and moisture coating.

The hypothesis for the study was that Estriol compounded in a mucoadhesive preparation would increase the retention time of the API to achieve promising local efficacy. It was seen that this therapy is well tolerated with no incidence of side-effects and high E3 bioavailability.

VAGINAL HEALTH INDEX - INITIAL

	1	2	3	4	5
Elasticity	None	Poor	**Fair**	Good	Excellent
Fluid volume (pooling of secretions)	None	**Scant amount, vault not entirely covered**	Superficial amount, vault entirely covered	Moderate amount of dryness (small areas of dryness on cotton-tip applicator)	Normal amount (fully saturates on cotton-tip applicator)
pH	>= 6.1	**5.6 - 6.0**	5.1 - 5.5	4.7 - 5.0	<4.6
Epithelial integrity	**Petechiae noted before contact**	Bleeds with light contact	Bleeds with scraping	Not friable, thin epithelium	Normal
Moisture (coating)	None, surface inflamed	**None, surface not inflamed**	Minimal	Moderate	Normal

VAGINAL HEALTH INDEX – 12 WEEKS

	1	2	3	4	5
Elasticity	None	Poor	Fair	Good	**Excellent**
Fluid volume (pooling of secretions)	None	Scant amount, vault not entirely covered	**Superficial amount, vault entirely covered**	Moderate amount of dryness (small areas of dryness on cotton-tip applicator)	Normal amount (fully saturates on cotton-tip applicator
pH	>= 6.1	**5.6 - 6.0**	5.1 - 5.5	4.7 - 5.0	<4.6
Epithelial integrity	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	**Not friable, thin epithelium**	Normal
Moisture (coating)	None, surface inflamed	None, surface not inflamed	Minimal	**Moderate**	Normal

Tables 1 & 2: Vaginal Health Index completed by study physician at Week 1 and 12 respectively, with green representing the physician's selection.

CONCLUSION

The aim of the scientific studies performed using NovaFilm™ was to showcase the mucoadhesive properties of this novel concentrated base. The superior mucin interaction results can be translated as NovaFilm™ Gel Base aiding in prolonging the residence time of compounded mucosal preparations in comparison to a competitor product. Moreover, the results from the compressive and adhesive force study demonstrate that when applying NovaFilm™ Gel Base to a mucosal surface, it will better resist the near constant mobility and self-cleansing action of the mucosa.

This superior mucin interaction combined with higher resistance to compressive force can be interpreted as NovaFilm™ having an improved coating effect on the mucosa, thus allowing the Active Pharmaceutical Ingredient to have longer contact time with the mucosa. This increase in contact time can potentially facilitate reduced drug dosing frequency in turn resulting in an improved patient compliance and experience.

Lastly, the positive patient outcome from the clinical case study demonstrated the applicability of using NovaFilm™ as a mucoadhesive drug delivery vehicle in vivo. Based on recent scientific evidence and current treatment guidelines, the Estriol 0.05% compounded in NovaFilm™ can be considered a promising candidate for compounded vaginal preparations for women's health.

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> *"NovaFilm™ (mucoadhesive base) for vaginal administration of estriol had an appreciable impact on vaginal restoration as rated using a comparative vaginal health index (VHI) as well as patient reporting. I will continue using this base as part of my hormone protocols."*
>
> **– Dr. Kristy Prouse, Gynecologist (OBGYN)**