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Summary of the Ph.D. thesis

DESIGN AND CHARACTERIZATION OF MUCOADHESIVE HYDROXYPROPYL CELLULOSE ORAL FILMS

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1. INTRODUCTION

Although the most popular mode of administration of medicines for patients is the oral route, the enzymes of the gastrointestinal tract cause serious disadvantages. They decompose many active substances and the first-pass effect of the liver decreases the serum level of active pharmaceutical ingredients.

However, mucoadhesive films applied to the oral mucosa eliminate these problems, and not only local effects (treatment of aphthous ulcer, gum inflammation or toothache), but also system wide effects (management of pain and angina pectoris etc.) can be achieved. Their main advantages are sustained drug delivery and chronic systemic therapy. Oral patches are welcome in paediatrics (children have the worst compliance), films are proper for elderly patients as well, who suffer from swallowing disorders or dysphagia. Buccal disks are unique medicines that can be used during travelling as a dose can be taken without water or any liquid. Patient compliance is better which improves the efficacy of the therapy and decreases the cost for both the healthcare system and the patients. Finally, the oral mucosa has high tolerance against potential allergens and has a fast healing capacity for irritation and damages.

Before their technological use, it is very important to determine the mechanical properties of mucoadhesive films because the free films are exposed to large mechanical stress during the preparation process, unpacking and sticking to the oral mucosa. These properties depend on the film-forming polymer, the excipients used and the formulation of the system.

Furthermore, the physicochemical properties of the polymer matrix not only depend on the polymer itself, but also the used excipients have marked effects on the system. These effects can be welcomed and useful, but the excipients can cause disadvantageous effects in drug delivery systems, which must therefore be tested.

In my Ph.D. work, hydroxypropyl cellulose free films were investigated as potential buccal drug delivery system. The effects of excipients on the polymer matrix were characterized in a wide range, and physicochemical properties were tested intensively. *In vitro* mucoadhesion measurement method, equipment and software developed and optimized, and accelerated stability test was evaluated.

2. EXPERIMENTAL AIMS

In my work I characterized hydroxypropyl cellulose (HPC) free films as first generation buccoadhesive polymers, as potential vehicles for oral drug delivery systems.

1. In the first part of my scientific work the film-forming polymer, the excipients were selected, the free film preparation and composition was optimized in order to prepare API loaded local and systemic drug delivery system for potential buccal administration:
    a. preformulation studies to optimize the composition;
    b. development HPC system suitable for oral use;
    c. evaluate of the excipients effects on the polymer matrix and
    d. investigate of the drug-excipients-polymer matrix compatibility and interactions via:
        i. tensile test measurements
        ii. Positron Annihilation Lifetime Spectroscopy (PALS)
        iii. Contact angle (CA) and Surface free energy (SFE) measurements
        iv. thermoanalytical studies
2. In the second part of my work I focused on the characterization of the properties of the HPC free films and on the determination of marked effects of the excipients on the system. The goals were the following:
    a. to determine the thermal decomposition and degradation of products by
        i. Thermogravimetric Analysis (TGA)
        ii. Differential Scanning Calorimetry (DSC) and
        iii. Thermogravimetric Analysis coupled with – Mass Spectrometry (TG-MS)
    b. to evaluate the crystalline/amorphous state of the matrix via X-Ray Powder Diffraction (XRPD).
    c. to investigate the possible interactions between the polymer and the incorporated excipients by Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR).
    d. to study the effect of accelerated stability test and water uptake on the polymer matrix via TGA, ATR-FTIR, XRPD and tensile test.
    e. to design, develop and optimize the *in vitro* mucoadhesion measurement protocol, software and equipment and *in vitro* mucoadhesion measurements.

3. MATERIALS AND METHODS

3.1. Materials

3.1.1. Hydroxypropyl cellulose as film-forming polymer

HPC Klucel® MF and LF (Aqualon; Hercules Inc., Wilmington, U.S.A.) was used as film-forming polymer. MF has a higher viscosity in solution and a higher molecular mass.

3.1.2. Model drugs and other excipients

Lidocaine base (Lid) (Ph. Eur., Società Italiana Medicinali Scandicci, Firenze, Italy) was chosen as the model drug in preformulation study and early characterization. Xylitol (Xyl) (Ph. Eur., Roquette, Lestrem, France) was used as taste improver. Glycerol (Gyl) (Ph. Eur., Molar Chemicals Kft., Budapest, Hungary) was used as taste coverer.

In the second part of my work the following model drugs were selected: Lidocaine hydrochloride (Lid HCl) (Ph. Eur.), Phenylephrine hydrochloride (Phe HCl) (Ph. Eur.) and Loperamide hydrochloride (Lop HCl) (Ph. Eur.). Porcine gastric mucin (for biochemistry, Carl Roth GmbH + Co. KG, Karlsruhe, Germany) was used for *in vitro* mucoadhesion tests.

3.2. Methods

3.2.1. Preparation of free films

The solvent was distilled water (Ph. Eur.) and 2 w/w% solutions were chosen for both types of HPC. Lid was ground in a mill (Retsch RM 100, Retsch GmbH, Haan, Germany) and the 100-200 μm powder fraction was incorporated. Xyl, Lid HCl, Lop HCl and Phe HCl dissolved readily and Gly compounded well in the water-polymer mixture.

At preformulation study and accelerated stability study substances were incorporated in 5, 10 or 15 w/w% of the film-forming polymer. For *in vitro* mucoadhesion test 5 w/w% was chosen for all substances.

The deaerated solution was poured onto either a glass (for surface properties) or a teflone surface (for all other measurements) and dried at room temperature (25 °C/65% RH) for 24 h through casting-solvent evaporation method. The thickness of each sample was measured with a bolt micrometer with an accuracy of 0.001 mm (Mitutoyo, Kawasaki, Japan). Measurements were taken at five different places on the free film and an average value calculated (~ 30 μm). Samples on glass slide also stored at room temperature (25 °C/65% RH) for a day and then all samples placed into climate chamber for 24 hours (40 °C/50% RH).

3.2.2. Preformulation studies

3.2.2.1. Tensile strength

The ultimate deformation force can be measured. The circular holder is situated horizontally and the jowl moves vertically. The measuring range was 0–200 N, the speed of the stamp was 20 mm/min, the sampling rate was 50 Hz, the output was 0–5 V, and the sensitivity was ±0.1 digit. The sensor comprised UNICELL force-measuring equipment, calibrated with the C9B 200 N cell; 10 parallel measurements were performed on each specimen.

3.2.2.2. Contact angle measurements

Measurements were carried out with a drop-contour analyser (Dataphysics OCA20, Dataphysics Instruments GmbH, Filderstadt, Germany), by a sessile drop method at room temperature (25 °C).

3.2.3. Positron annihilation lifetime spectroscopy (PALS)

The lifetime spectrometer applied was constructed from BaF_2 based detectors and standard ORTEC electronics. Spectra were collected in the 4096 channels of a multichannel analyser. The time/channel value was ~10 ps and the time resolution of the system was ~210 ps. As a positron source, carrier-free $^{22}NaCl$ was used, sealed between kapton foils. The activity of the source was ~5-10^5 Bq and only 5–8% of the positrons were annihilated in the source itself.

3.2.4. Thermoanalytical measurements

Mettler-Toledo TG/DSC1 and DSC 821^e instruments (Mettler Toledo, Switzerland) was used. During the DSC measurements the applied heating rate was 10 °C min^{-1} from −40 °C to 300 °C. Argon atmosphere with nitrogen drying were used. 10 ± 1 mg sample was measured into aluminium pan (40 µl). The curves were calculated from three parallel measurements and were evaluated with STARe Software.

For the TGA and the DSC measurements (with TG/DSC1 instrument coupled MS) the applied heating rate was 10 °C min^{-1} from +25 °C to 400 °C. Nitrogen atmosphere was used and 10 ± 1 mg sample was measured into aluminium pan (100 µl). The curves were calculated from three parallel measurements and were evaluated with STARe Software.

Thermal characteristics of the sample mass loss were determined with a thermal gravimetric analyzer (Mettler Toledo, model TG/DSC1) coupled with a quadrupole mass spectrometer (Pfeiffer Vacuum, model Thermostar^{TM} GSD 320), operated under N_2 atmosphere (purity = 99.999%, 70 ml min^{-1} flow rate). The connection between the TG and the mass spectrometer was done by means of a silica capillary, which was maintained at 120 °C.

3.2.5. Characterization of interaction between excipients and polymer matrix; accelerated stability study

3.2.5.1. Accelerated stability study

Samples were placed into climate chamber for 4 weeks to perform accelerated stability test (40 °C/75% RH) and stored in open Petri dishes.

3.2.5.2. Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy

FTIR spectra were recorded with a Bio-Rad Digilab Division FTS- 65A/896 FTIR spectrometer (Bio-Rad Digilab Division FTS-65A/869, Philadelphia, USA) between 4000 and 400 1/cm, 128 scan size, at an optical resolution of 4 1/cm; operating conditions Harrick's Meridian SplitPea single reflection, diamond, ATR accessory. The spectra were analyzed with Spectragryph 1.0.2 (F. Menges Sofwareentwicklung, Germany) software.

3.2.5.3. X-Ray Powder Diffraction

XRPD analysis was performed with a Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) system with Cu K λI radiation (λ = 1.5406 Å). The samples were scanned at 40 kV and 40 mA from 3 deg to 40 deg 2 Θ, at a scanning speed of 0.1 deg/s and a step size of 0.010 deg.

3.2.5.4. Thermogravimetric Analysis

Please refer to subsection *3.2.4.* for TGA measurement and operation parameters.

3.2.5.5. Tensile strength

Please refer to subsection *3.2.2.1.* for Tensile strength measurement and operation parameters.

3.2.6. *In vitro* mucoadhesion

3.2.6.1. Equipment

The pressure is measured through the use of a load cell connected to a locally developed digital acquisition (DAQ) box. This is based on the Silicon Laboratories C8051F124 microcontroller kit. During the measurement, the DAQ box sends the acquired data to the PC side software via an RS232 connection. Both start and end point are controlled manually. The adhesion force measurement algorithm performs the following operations:

- At the beginning of the measurement process, the pressure jowl moves downwards and presses against the polymer film until it reaches the predefined pressure (static pressure).

- It holds its position until the desired time-out (static pressure time).
- At this time, the pressure jowl begins to move upwards until the user stops the measurement process (dynamic pressure).

The two parameters which can be set up freely in the algorithm (the static pressure and the static pressure time) have to be set before the measurement via the PC side-software. The measurement range was 0–200 N, the speed of the stamp was 20 mm/min, and the output was 0–5 V. The sensor was a Unicell force-measuring instrument, calibrated with the C9B 200 N cell.

3.2.6.2. Sample preparation

The films were stored in a climate chamber at 40 °C/50 RH% for a week.

3.2.6.3. Measurement of force of adhesion

500 mg mucin was mixed *in situ* with 5 ml distilled water. Fresh mucin gel was smeared to the bottom probe. Samples were measured at room temperature (20±5 °C). The structure of the measurement system was as follows, from top to bottom: a stainless steel holder, a bilayer adhesive tape, a film, mucin gel and a stainless steel table. Each element was measured alone, in pairs and all together. Before the adhesion test, each film was subjected to 50 N, which was held for 45s, and the holder then pulled up the film up from the mucin gel layer. At least 10 parallel measurements were performed on each specimen.

4. RESULTS AND DISCUSSION

I. OPTIMIZATION AND EARLY CHARACTERIZATION OF HPC FREE FILMS

In the first step of my work I focused to understand the mechanical and physico-chemical properties of the polymer matrix and to determine the further steps to characterize the system.

4.1. Tensile strength

When Xyl was used in the studied samples, the tensile strength of MF films was 2.5-3.5 times higher than that of empty films. This result correlates with the PALS finding (please refer to section *4.3.*), suggesting that Xyl forms H-bonds between the neighbouring polymer chains, leading to a stronger film structure. When Gly was presented in the samples, the tensile strength of the films was 2-2.5 times higher than that of the empty films. Gly causes the films to become more elastic, increasing the tensile strength through the decrease of brittleness. When the two excipients were combined the tensile strength increased eight-fold, which is a very welcome side-effect. In the case of the Klucel® MF films, the addition of Lid did not

change the effects of excipients on the films. Even when both of them were used together with Lid, the resulting tensile strength was adequate for the films.

In contrast, when the Klucel® LF film-forming polymer was investigated, we did not find any significant changes in tensile strength with variation of the excipients or their concentrations. Only when Lid was alone in the samples was the tensile strength of films slightly higher. The reason for this phenomenon is that LF has shorter polymer chains than MF.

4.2. Contact angle measurements (CA)

The CA of water (deg) and the SFEs for both HPC were measured. It was found that the CA of water in general was slightly higher for the MF samples. Only when both excipients were added at 5 w/w% was the CA appreciably higher and when Lid was incorporated at 5 or 15 w/w%, the CA was decreased. The SFE was stable or increased slightly; it decreased if both of the excipients were used in 5 w/w%. The CA of water increased in each LF free film: the average degree of the rise was 7-10°. If Lid only or both the active substance and Xyl were incorporated at 15 w/w%, the CA increased appreciably. The SFE was stable or decreased slightly in LF samples. Lower CAs were found in LF free films, and the SFE values were approximately the same. As MF has longer polymer chains, the components could enter the free holes in the polymer matrix and did not have a strong effect on the surface properties of the system. Since LF has shorter chains, the incorporated materials had fewer sites at which to enter the structure of the polymer, and Gly and Xyl present therefore exerted effects on the CA of water. These results confirmed that a macroscopically stable film structure evolved in each case. The constant SFE values indicated good bioadhesion in each case.

4.3. Positron annihilation lifetime spectroscopy (PALS)

This technique was very important for our study because it yielded information about the free volume structure of the films. It is clearly seen in *Fig. 1* that there was not much difference between the two types of Klucel® containing Xyl. As the concentration of Xyl was increased, the average size of the free volume holes decreased quite similarly in the two forms of the polymer. Gly caused different changes in the polymers. It increased the size of the free volume holes, but the effect differed in the two forms of HPC. The most relevant difference between them was that Gly caused a faster change in the LF films. This reflects the fact that LF contains shorter polymeric chains than those in MF. Thus, the plasticizer can move them apart from each other more easily than in the case of the much longer MF chains. In the end, Gly forms the same size of free volumes in both polymers.

The most interesting finding from the positron data is the opposite behaviour of Xyl and Gly. Although the two molecules have very similar structures, one of them increased the free volume in HPC whereas the other one decreased it. The explanation of this may be the size difference between the molecules. Both molecules are able to destroy the original H-bonding network in the polymers, which suggests an increase in free volume. However, the longer Xyl molecules may fill the empty spaces or be able to connect the polymeric chains through H-bonding.

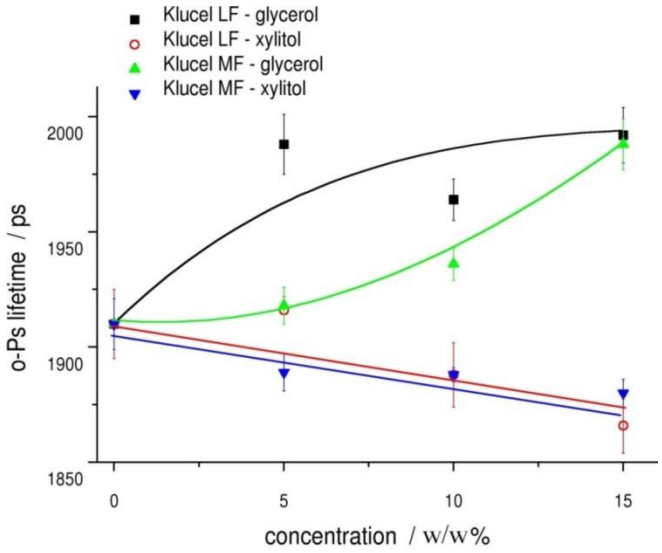

Fig. 1. *The lifetime of ortho-positronium in Klucel® films. Lines are given merely to guide the eye.*

4.4. Thermoanalytical measurements

DSC curves of the used materials are shown in *Fig. 2*. A slight endothermic baseline shift observed in both HPC between 40 and 100 °C, which can be explained with the removal of the water content. At about 340 °C signs of decomposition appear in both curves. Gly shows a definite endothermic peak between 50 and 150 °C due to the higher water content, while at about 200°C signs of decomposition can be observed until 300 °C. In case of Xyl, an onset value of 92.2 °C is followed by a peak melting point at 95.6 °C. The enthalpy change of the process is 217.4 J g^{-1}. Xyl has much greater thermal stability as the baseline change and the decomposition process start only at about 280 °C and end over 380 °C (see *Fig. 2*). Lid has a lower melting point because the onset value is 67.2 °C and the peak of the melting point appears at 68.6 °C. The enthalpy change of the process is 59.1 J g^{-1}. The baseline change appears over 180 °C, and then the decomposition process is accelerated over 200 °C and finishes at about 330 °C.

It was found during the analysis of the TG results (see *Fig. 3.*) that the two HPC are thermally stable, a mass loss of only 1-1.5% can be detected until 100 °C (removal of water), the decomposition process starts over 300 °C, and mass loss is 85% for Klucel® LF and 87% for Klucel® MF until 400 °C.

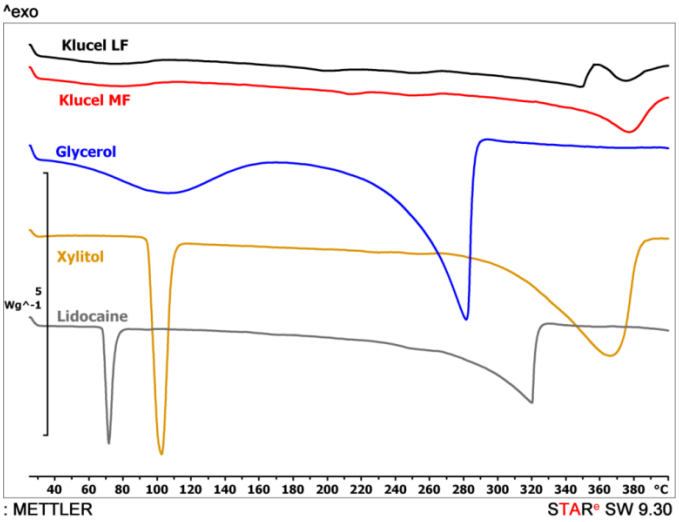

Fig. 2 *Thermal properties of Klucel® film-forming materials, active ingredient and excipients as shown by the DSC curves.*

Klucel® LF products were chosen for early characterization via the examination of their thermal stability. It was found that although the decomposition process changes with the increase in the concentration of the excipients, when heated up to 400 °C mass loss does not differ significantly compared to Klucel® LF films without excipients. However, over 180-200 °C, the decomposition processes start, the TG curves open up more, which is probably due to the fact that the molecules built-in among the polymer chains loosen the structure, which in turn is decomposed more easily.

Lid loaded films illustrated in *Fig. 3*. It is remarkable that while a smaller mass loss was observed for the 5 and 10% films, the mass loss of the loosening effect of Gly and Lid on the polymer structure. TG results of films with Lid and without Lid were also evaluated. It was concluded that in the case of the 5% and 10% systems, the presence of Lid practically did not result in a significant difference in thermal stability, while in the concentration of 15%, the films which contained Lid were decomposed more easily. This can probably be explained by the fact that the plasticizer, when used in a lower concentration, can be incorporated in the film structure. However, when it is applied in higher concentrations, the stability of the film structure deteriorates.

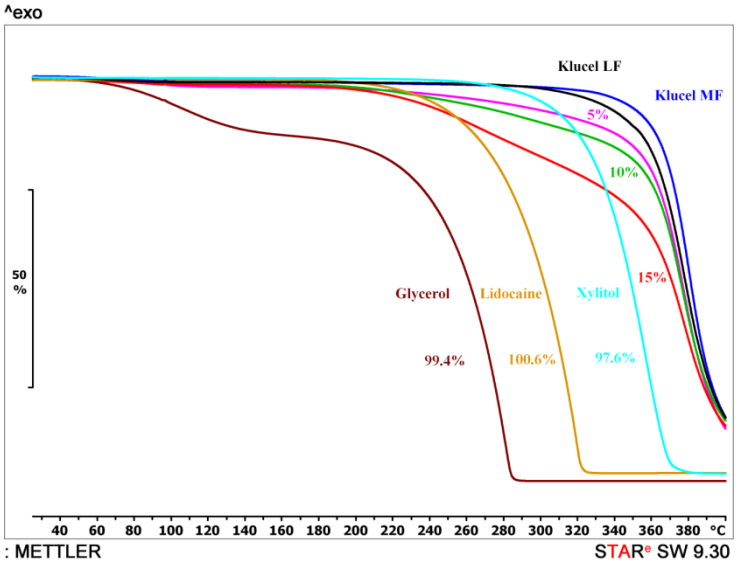

Fig. 3 *Thermal properties of films made from Klucel® LF film-forming material containing Lid as well as Xyl and Gly as shown by the TG curves.*

The TG-MS results of 15% Gly loaded films are presented in *Fig. 4*. The peak intensity of the fragments depicted decreased in the following order: m/z = 44–43–42–41–58–45.

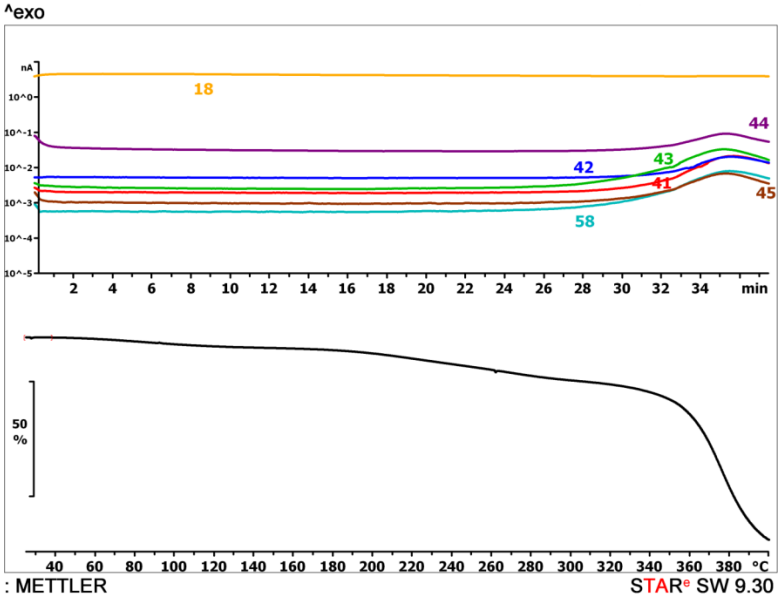

Fig. 4 *Thermal properties of films made from Klucel® LF film-forming material containing 15% Gly as shown by the TG-MS curves.*

All these indicate that carbon dioxide is formed in the greatest concentration, which is confirmed by the increase of m/z = 44. m/z = 43, 45 may indicate the development of acetic acid and/or isopropyl alcohol, while m/z = 43, 58 may be indicative of the formation of acetone. With regard to the good workability of the free films and the pharmaceutical technology requirements, Klucel® MF was chosen as film-forming polymer. Lid and the

excipients Gly and Xyl should be used in a concentration of 5 w/w% (in accelerated stability study the excipients were used at 5-10-15 w/w% because I would like to investigate their effects on the polymer matrix in higher concentrations also).

II. CHARATERIZATION OF HPC FREE FILMS

In this part of my work I focused on the characterization of the system: incorporation of excipients, their effects on the polymer matrix, stability of the HPC free films and *in vitro* mucoadhesion studies were evaluated.

4.5. Interaction between excipients and the polymer matrix, accelerated stability study

4.5.1. Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy

Marks of intermolecular hydrogen bonds were found in all types of samples. Peaks between 3200-3550 1/cm suggest that the used excipients incorporated into the polymer matrix and confirmed the hydrogen bonds between the –OH groups of the HPC and used excipients. Xyl only in 5 w/w% incorporated completely into the HPC film meanwhile, Gly incorporated in all concentrations. FTIR analysis revealed the so-called 'synergic' effect of Gly, which helps the bonding of Xyl into the polymer matrix. 10 w/w% of Gly is effective for entering Xyl into the polymer chains. Both Xyl and Gly facilitated the water sorption into the tested systems. Xyl is commonly not used as a plasticizer in the field of pharmacy, but our results suggest that Xyl also can act as a plasticizer in any formulation. This result initiates a novel application of Xyl in pharmaceutical technology and the excipient is welcomed in manufacturing, due to both financial and health-care considerations. Furthermore, if Gly and Xyl incorporated into HPC films, less water sorption and migration were found. It confirms that the most stable film structure is formed if both excipients are used together which suggests the so-called 'synergic' effect of the two excipients.

4.5.2. X-Ray Powder Diffraction

It was found that Xyl bonds entirely into the HPC polymer matrix because marks of crystallinity were not found. Water uptake was detected during the storage – the changes in MFG 15% patterns summarised in *Fig. 5* – XRPD showed that films containing Gly and/or Xyl, linked water during accelerated stability study. The shape and the high angle halo displayed a shoulder resembling the halo for bound water. This phenomenon did not have effect to the bonded Xyl, because crystallinity was not found after water uptake, the polymer

system stayed amorphous. In case of Gly at 15 w/w% the increase of diffraction at about 8.5 and 20 deg (2 Θ) in the spectra indicated that water sorption proceed (clearly seen in *Fig. 5*).

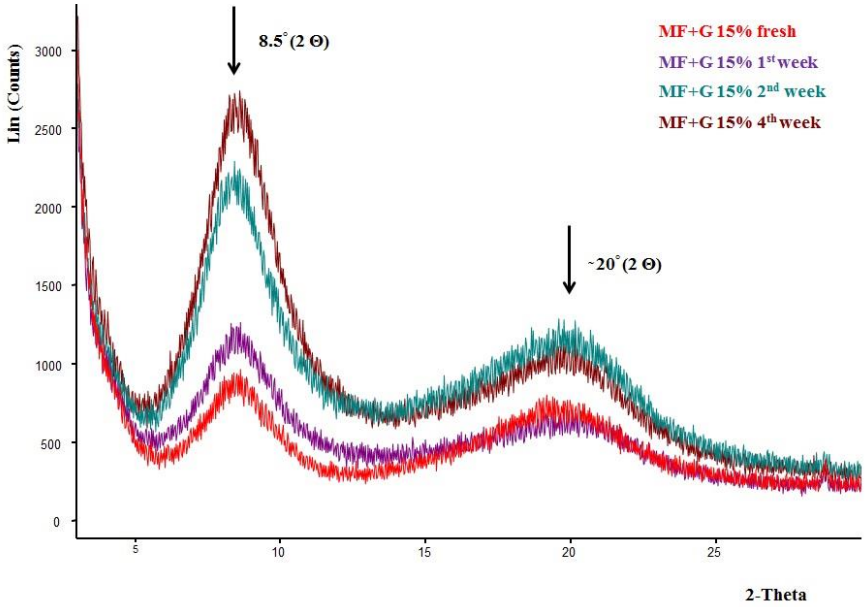

Fig. 5 *summarizes the water sorption and migration of glycerol plasticized HPC films in XRPD spectra.*

4.5.3. Thermogravimetric Analysis

Water vapour was detected at 60 to 100 °C in all type of samples. The one-week-old films decomposition was the fastest, during one week storage the films absorbed higher amount of water which were migrating in the system and had marked effect on their physical decomposition. It was hypostatised that after two weeks the excess water was evaporating from the system and a local equilibrium was formed. The four-week-old MFXG plasticized films at 15w/w% were the most stable. In case of using Gly and Xyl together stabilizing effect was found.

4.5.4. Tensile strength

Because of the highly hygroscopic behaviour of Gly, films plasticized at 15 w/w% with Gly were chosen to investigate the effect of accelerated stability conditions into the mechanical properties of samples and the results were compared to HPC films without any plasticizer. After one week of storage the tensile strength of films decreased by 83%. The polymer structure was destroyed via the water-Gly plasticizing duo. After two weeks of storage the excess amount of water was evaporating from the system and after four weeks of storage the initial tensile strength force was measured. After one week of storage the tensile strength of HPC films increased with 2-fold, not decreased as in case of Gly plasticized ones. The

entering water forms H-bounds between the polymer chains and caused a plasticizing effect which phenomenon was detected via the increase in tensile strength.

4.6. *In vitro* mucoadhesion

The force of adhesion measurement is involved the total deformation process, also. The curves are observed to comprise three sections. During pressing, the bilayer adhesive tape, the mucin and the film undergoes a deformation: section 1. The almost horizontal parts of the curves (section 2) relate to the period when contact with the bottom at 50 N is maintained for 45 s. After the 45 s holding time, the motor is reversed and starts to pull up the film. This is shown by the vertical line, followed by a 2-s pause. The peaks in the last part of the curves (section 3) relate to the force of adhesion (43.5 N), which covers the elastic recovery of the sample (the bilayer adhesive tape, the mucin and the film together). Finally, correction of three-layered adhesion force by subtraction of the forces of adhesion of the tape and mucin leads to the force of adhesion of the sample: *18.1 N*.

The pure films had higher adhesive force (the movable hydroxypropyl chains of the empty film easily form adhesive bonds with the chains of mucin) than the excipient loaded samples. Contrarily, both of the excipients decreased the force of adhesion (*Table 1*.).

Table 1. *In vitro* force of adhesion

Sample	**Force of adhesion** (N ± *SD)*	**Difference from pure film (N)**	**Difference from pure film (%)**
Pure film[1]	23.26 ± *6.21*	—	—
Gly	12.43 ± *4.35*	-10.83	-46.56
Xyl	8.58 ± *2.18*	-14.68	-63.11
Gly+Xyl	15.28 ± *1.82*	-7.98	-34.26
Phe HCl+Gly+Xyl	20.70 ± *6.00*	-2.56	-11.01
Lid+Gly+Xyl	11.55 ± *4.50*	-11.71	-50.34
Lid HCl+Gly+Xyl	34.57 ± *6.18*	+11.31	+48.62
Lop HCl+Gly+Xyl	25.53 ± *6.88*	+2.27	+9.76

[1]Pure film means the empty samples (without drug substance and/or excipients).

Xyl had the strongest effect on adhesion; a change of more than 60.0% was detected. Gly also indicated a considerable change in adhesion force. In case of both excipients the force decreased by a third. Xyl occupied the empty volumes in the polymer matrix and bonded the movable polymer chains. This phenomenon caused the high decrease in adhesion force; the occupied chains could not form adhesive bonds with the chains of mucin. The smaller Gly molecules let more polymer chains form adhesive bonds and it indicates less decrease in adhesiveness. When both excipients were used, the negative change was smaller.

Lid and Phe HCl decreased meanwhile Lid HCl and Lop HCl increased the force of adhesion. The effect of Phe HCl (approx. -10.0%) and Lop HCl (approx. +10.0%) was slight compared to Lid (approx. -50.0%) and Lid HCl (approx. +50.0%). Lid was in a suspended form in the polymer matrix, while on the other hand the HCl salts were absolutely dissolved. The homogenous distribution of HCls indicates higher adhesiveness. It clearly shows that adhesiveness was absolutely based on the formulation and determined not only by the used film-forming polymer.

5. SUMMARY

Mucoadhesive free films offer innovative drug delivery systems for both local and systemic target. It is very important to deeply study and understand the evaluated system.

Based on the preformulation study and early characterization the following can be summarised as main findings:

- Tensile strength suggested that Xyl forms hydrogen bonds and the strongest structure is resulted if both excipients were used together.
- CA measurements demonstrated that macroscopically stable film structures were achieved at all compositions and constant SFEs suggest good bioadhesion.
- PALS suggested that Xyl forms hydrogen bonds and Gly increases while Xyl decrease the free volumes of the HC films.
- Thermal study suggested that excipients in low concentration incorporated into the system. Carbon dioxide, acetic acid and/or isopropyl alcohol formed during TG-MS study. The tested systems were thermally stable, below 100°C only water loss was detected.

From the accelerated stability study and the incorporation tests of free films the main findings are listed below:

- FTIR confirmed that both excipients incorporated to the polymer system via hydrogen bonds. It highlighted the so-called ‘synergic’ effect of Gly and Xyl used together. Water uptake and migration were detected. Xyl was found to be a potential plasticizer which finding offers a new indication for Xyl in the field of pharmacy.
- XRPD also confirmed the incorporation of the excipients used, the system remained amorphous. Water uptake and migration were detected and confirmed via the changes of shape and angle halo of patterns.
- TGA confirmed the presence of bulk water.

- Tensile strength highlighted the softening behaviour of water and the over plasticization effect of it with Gly.

The *in vitro* mucoadhesive study showed that this equipment with the new software is suitable for studying the deformation of a mucoadhesive film and for the determination of the force of adhesion. The results demonstrate that the characterization of mucoadhesive films is possible. The findings were utilized to create a theoretical model suitable for the prediction of the optimum film composition.

The novelties of my work are as followins:

- PALS demonstrated that Gly increases and Xyl decreases the free vacancies of the HPC films via moving the polymer changes.
- Tensile strength measurement and FTIR highlighted the so-called ‘synergic’ effect of Gly and Xyl used together. Samples with the two excipients showed the best mechanical, physico-chemical properties and these were the most stable in each case.
- Xyl is commonly not used as a plasticizer in the field of pharmacy, but our results suggest that Xyl also can act as a plasticizer in any formulation. FTIR highlighted the potential novel application of Xyl in pharmaceutical technology and this finding is welcomed in manufacturing, financial and also health-care considerations.
- The novel *in vitro* adhesion measurement protocol, the developed equipment and software offer a great tool to study and evaluate both the deformation of the tested system and the adhesion of free films.

ARTICLES RELATED TO THE PH.D. THESIS

I. András Kelemen, **Mihály Gottnek**, Géza Regdon jr, Klára Pintye-Hódi: New equipment for measurement of the force of adhesion of mucoadhesive films *J Adhes Sci Technol* 29:(13) pp. 1360-1367. (2015)

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II. **Mihály Gottnek**, Klára Pintye-Hódi, Géza Regdon jr: Tracking of the behaviour of lidocaine base containing hydroxypropylcellulose free films with thermoanalytical method *J Therm Anal Calorim* 120: pp. 201-208. (2015)

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IV. **Gottnek Mihály**, Hódi Klára, ifj Regdon Géza: Szájnyálkahártyán alkalmazható mukoadhezív filmek.: I. rész: A szájnyálkahártya és a nyál anatómiai, élettani áttekintése *Gyógyszerészet* 57:(1) pp. 24-31. (2013)

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