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Title

In vitro oral cavity model for screening the disintegration behaviour of orodispersible films: a bespoke design

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Abstract

The availability of biorelevant methods for the disintegration study of pharmaceutical orodispersible dosage forms is required. The disintegration of orodispersibles should be assessed using *in vitro* methods that can combine biorelevant volumes of disintegration medium, and mechanical stresses mimicking *in vivo* conditions. This study proposes an adaptation of a mechanical oral cavity model for the disintegration study of orodispersible films. A periodic compression is applied to the sample in the presence of a biorelevant volume of artificial salivary fluid. Four orodispersible films samples (P1, C1, P2, and C2), differing in polymer type and molecular weight, and Listerine® were tested and filmed during disintegration. An image analysis program was developed for the determination of the volume reduction of the film matrix over time, as a descriptor of film disintegration behaviour. Samples P1, and Listerine® showed a volume reduction at 180s of > 90%, C1, P2, and C2 were 85%, 48%, and 37% respectively. The model was able to detect differences in the disintegration behaviour of the four samples, and results were comparable with the benchmark product. The concept of disintegration behaviour of orodispersible films was introduced for the first time as an informative method for the study of orodispersible dosage form.

Data access

The data presented in this work can be requested by emailing the author, Andrew Redfearn, a.redfearn.12@ucl.ac.uk

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1. Introduction

Orodispersible films (ODFs) are flexible, thin polymeric dosage forms offering, among other advantages, rapid disintegration in the mouth and fast release of the active pharmaceutical ingredient (API). Several ODF formulations have made their appearance on the market during the past decade, and many others have been optimised by academic research groups aiming to achieve specific therapeutic performances[1,2] and meet the needs of diverse patient groups[3]. According to the European Pharmacopoeia, pharmaceutical dosage forms are defined as "orodispersible" if their time to disintegration is faster than three minutes[4]. The assessment of the disintegration time is therefore required as a characterisation assay for ODFs and other orodispersible formulations[5]. Moreover, disintegration time was found to significantly affect the end-user acceptability of ODFs *in vivo*[6].

In vitro methodologies possessing high prediction power are required to reduce time and cost of drug development[7]. Disintegration studies are particularly important in the quality control of fast-release formulations, in order to understand the factors affecting the release of the drug[8,9]. Although a number of *in vitro* methodologies are currently available for the assessment of orally administered drug products in the early development phase, there are a limited number available for novel dosage forms such as ODFs. Brown and colleagues suggested that the assessment of the drug release should be performed using *in vitro* methods appropriate for the dosage form to be tested[10]. Similarly, Morrison and Campbell, while discussing the relationship between disintegration of the dosage form and physiological availability of the drug, highlighted the importance of assessing disintegration in an environment close to physiological conditions[11].

Despite the disintegration behaviour of dispersible formulations being a requisite for characterisation, no specific disintegration method for orodispersible preparations was defined in the European Pharmacopoeia[4]. The utilisation of high-volume USP methods was criticised in favour of lower-volume disintegration methods[12]. Methodologies such as petri dish, and drop/slide frame were proposed by several research groups[5,13,14] and extensively reviewed by others[12,15] however currently a consensus on a standard disintegration methodology for orodispersible formulations has not yet been reached. The majority of proposed methods consider only the physicochemical interaction between the sample and the disintegration medium[16]. However, disentanglement and diffusion of polymeric chains may be at the core of the ODF disintegration mechanism[17]. *In vivo* stresses applied to the dosage form are very likely the result of mechanical stimulation and surface interactions, in addition to wetting and solubilisation processes.

The effect of mechanical forces has been considered in several mathematical and *in silico* oral cavity models, however the majority of them find their applications in the field of dentistry[18,19], speech rehabilitation[20], olfaction[21], and food processing[22]. Available models provide reproducible and accurate data but are designed to accommodate relatively large amounts of food sample and mimic breakdown during mastication[23–26]. These models are unsuitable for studying ODF breakdown for several reasons; the difference in size and volume between foods and monolithic dosage forms, the

reduced or non-existing ODF requirement for mastication and the different mechanical stresses at which such dosage forms are subjected inside the oral cavity. Krampe and colleagues developed the punch & filter method to study the dissolution of ODFs under mechanical stress, however, disintegration was not specifically addressed in their study[16]. In order to study ODF disintegration during oral processing, it is proposed in this work that purposely-developed experimental equipment is required to accurately model the process. Currently available *in vitro* disintegration methods help predicting the time required for dosage forms to break down. However they have limited ability to analyse the mechanical processing of orodispersibles in the oral cavity or predict the mouthfeel perception.

An in vitro oral cavity model was previously developed to study the flow properties of non-Newtonian fluids during swallowing[27]. The model consists of a fixed acrylic plate and soft silicone body to mimic the human hard palate and tongue surfaces. During a swallow simulation the tongue surface moves upwards and undergoes a controlled compression onto the acrylic plate, this replicates *in vivo* observations, where the tongue applies a pressure wave to the hard palate, moving from anterior to posterior[28]. At the median position peak pressure applied is approximately 30 kPa for healthy adults[29].

The overall aim of the present study is to adapt the novel *in vitro* oral cavity model for the assessment of ODF disintegration under biorelevant mechanical stimulation and synthetic saliva interaction. In addition the objective of the study is to understand the effect of film-forming polymer on ODF disintegration behaviour.

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2. Materials and methods

The *in vitro* model was modified to carry out tongue-palate compression cycles on an ODF sample in a continuous manner simulating typical oral manipulation. An ODF was placed into the model oral cavity prior to testing and during compression cycles the cavity was irrigated periodically with artificial salivary fluid. Visual measurement of ODF disintegration was facilitated by the transparent acrylic palate and in order to improve on *in vitro* studies that report a single degradation time this work aims to measure degradation throughout an *in vitro* test.

2.1 Materials

PVA and CMC based ODFs were cast for use in this work and commercially available Listerine® ODFs were procured for use in this work.

Poly(vinyl) alcohol (PVOH) EMPROVE® 4-88 (m.w. 39 kDa; hydrolysis degree 85-89%) and 40-88 (m.w. 197 kDa; hydrolysis degree 85-89%) were purchased from Merck-Millipore (Darmstadt, Germany). Blanose ® carboxymethylcellulose (CMC)12M31P (m.w. 395 kDa, degree of substitution 1.2), and 7HF-PH (m.w. 725 kDa, degree of substitution 0.7) were provided by Ashland (Wilmington, Delaware, U.S.). Red food colour (anthocyanin and paprika extracts, citric acid, polysorbate 80 was purchsed from Waitrose Ltd. (Bracknell, UK).

Listerine PocketPacks® breath strips were purchased from Johnson & Johnson (New Brunswick, New Jersey, U.S.). Potassium dihydrogen phosphate, sodium chloride, calcium chloride, and sodium hydroxide were purchased from Sigma-Aldrich (St. Louis, Missouri, U.S.).

2.2 ODF preparation by solvent casting

Single-polymer placebo ODF formulations were selected on the basis of their differing disintegration times previously measured *in vivo* and *in vitro*[6]. Listerine® breath strips (Johnson & Johnson Inc., Skillman, NJ, U.S.) were also analysed. ODF samples were prepared by solvent casting method previously optimised in our research group[6]. Four solvent cast films were prepared using two grades of polyvinyl alcohol (PVOH) 5% (w/v), and two grades of carboxymethylcellulose (CMC) 1% (w/v). The polymeric grades varied in molecular weight (39 and 197 kDa, corresponding to samples P1 and P2 respectively) for PVOH (Merck-Millipore, Darmstadt, Germany), and in molecular weight and degree of substitution (395 kDa, 1.2%; and 725 kDa, 0.7%, corresponding to samples C1 and C2 respectively) for CMC (Ashland, Wilmington, Delaware, US). The formulations were modified by the addition of a 2% or 1% v/v red food colour (anthocyanin and paprika extracts, citric acid, polysorbate 80 – Waitrose Ltd., UK) to the casting solution, depending on the casting volume. All solutions were prepared in 50 mL distilled water and 6.5 mL or 15 mL, for PVOH and CMC respectively, were poured

into an 8 cm diameter casting mould, and dried at 50 °C from 1 to 2 hours. The obtained films were then peeled off and stored at 50% RH until use.

2.3 Mechanical properties characterisation

The assessment of ODF tensile strength, Young's modulus, and elongation at break was performed using an Instron Universal Tester 5567 (Instron Ltd, Wycombe, UK), with a 500 kg load cell, and 1 kN grips. ODF samples were cut into a dumbbell shape specimen (type 3: overall length 50 mm; length of the narrow portion 16 mm; width of the wide ends 8.5 mm; width of the narrow portion 4 mm)[30–32]. The experiment was carried out at a crosshead speed of 50 mm/min[32]. Results were analysed using Bluehill software v. 3 (Instron Ltd., Wycombe, UK). Tensile strength, elongation at break, and Young's modulus were calculated according to equations 1, 2, and 3, respectively[33].

$$\sigma_B = \frac{F_{max}}{A} \tag{1}$$

Where σ_B corresponds to tensile strength, F_{max} is the maximum load applied, and A is the cross-sectional area.

$$\varepsilon_B = \frac{\Delta L}{L_0} \times 100 \tag{2}$$

Where ε_B corresponds to % elongation at break, ΔL is the difference between the sample length at break and the original length of the sample, L_0.

$$E = \frac{F}{A\varepsilon} \tag{3}$$

Where E corresponds to Young's modulus, F is the force applied at corresponding strain, and ε is the strain. Mechanical properties data were analysed using one-way ANOVA followed by Tukey's post hoc test (Prism 7, GraphPad Software Inc., La Jolla, US.).

2.4 Experimental conditions for disintegration time measurement

During a compression cycle the model tongue applied continuous pressure reaching a maximum of 30 kPa at the median section of the palate[29]. A simulated salivary fluid was prepared according to the formulation reported by Gittings and colleagues[34], the composition is summarised in table 1.

--- TABLE 1 ---

This solution was sprayed into the artificial oral cavity using an atomiser spray bottle once every two compression cycles. This spray rate resulted in a typical saliva flow rate of 1.5 mL/min[35] based on calibration measurements of volume ejected per spray. A compression cycle consisted of a full compression and retraction, lasting 0.7 s and then a pause for 2 s. The oral cavity volume is 12 ml prior to a compression and is 0 ml at full compression. A video camera (Sony RX100 M4) recording at 25 fps was positioned above the acrylic plate facing downwards, and controlled lighting conditions were used to illuminate the oral cavity. An ODF sample was placed on the silicone tongue surface, at the median position, and the compression sequence was initiated (Figure 1). Recording was stopped upon complete film disintegration.

--- FIGURE 1 ---

A video data processing program was developed using MATLAB (MathWorks, Natick, MA, USA). From the original video file one frame was extracted at every compression sequence during the 'open' (prior to compression) phase. The background area was selected by a crop function from the first extracted image, and the sample area was selected using a second crop function. For each pixel; red, green and blue signal intensity was recorded, and the two highest values extracted. Exclusion of pixels belonging to the background area was achieved by a manual thresholding function. Subsequently, the two highest signal values were summed, and the result subtracted from the background signal intensity in each frame. Signal intensity was normalised by the mean film thickness, measured at twelve locations across the film sample prior to testing using a micrometer. A higher signal intensity corresponded to a thick film area, and lower signal intensity to a thin film area. The resulting signal intensity for each frame was plotted against time, smoothed, and normalised for the intensity value of the first extracted frame. The resulting disintegration curves represented the film volume (thickness x area) compared to the first extracted frame, when the film had not yet started its disintegration process. Tests were carried out in triplicate and the mean and standard deviation volumes for each film over time were calculated using built in MATLAB functions.

3. Results and discussion

3.1 Assessment of mechanical properties

The mechanical properties of the four ODF samples, and Listerine® are summarised in Figure 2.

--- FIGURE 2 ---

The tensile strength corresponds to the tensile stress at which a sample breaks. The highest tensile strength (61.7 ± 1.8 MPa) was shown by sample C1, followed by sample C2 (49.8 ± 2.9 MPa), P2 (27.7 ± 3.0 MPa), P1 (21.0 ± 1.9 MPa), and Listerine® (20.7 ± 0.7 MPa). Significant differences were observed between Listerine® and C1, and C2 ($p<0.0001$). The elongation at break indicates the ability of the sample to deform before breaking. The maximum elongation of sample P2 (9.5 ± 5.5 %) was higher than Listerine® (2.8 ± 0.5 %) but not statistically significant, whereas the elongation of all the other samples was similar. The Young's modulus represents the stiffness of the sample: the stress required to cause a deformation, in this case elongation. In comparison with Listerine® (1,900 ± 55 MPa), the following samples were significantly stiffer: P1 (5,550 ± 6 MPa; $p<0.001$), P2 (4,730 ± 655 MPa; $p<0.01$), and sample C2 (3,600 ± 77 MPa; $p<0.05$). Higher entanglement density generated by high molecular weight chains has been linked to the higher tensile strength of a polymer[36] . The lower Young's modulus, and higher tensile strength exhibited by the two CMC-based samples compared to PVOH-based samples might depend on the presence of β 1-4 linked glucose rings that limit the rotation around the C-O-C bonds[37], potentially reducing the chain mobility and conferring higher resistance to load.

In a study published by Borges[38] the following mechanical properties were identified as acceptable: Tensile strength 15 to 35 MPa, elongation at break between 5 and 40%, and Young's modulus 500 to 1,500 MPa. Visser[33] suggested slightly different values: tensile strength higher than 2 MPa, elongation at break bigger than 10%, and Young's moduli lower than 550 MPa. In this respect, none of the samples analysed would fall within the acceptable range for all the three parameters. This was not surprising in the case of single-polymer ODF, as they were not optimised formulations and the lack of other excipients such as the plasticiser might have resulted in the relatively high Young's modulus. However it is notable that the elongation at break and Young's modulus of Listerine® also fell outside these previously-published "acceptable" ranges, suggesting that such ranges might be overly-restrictive. In summary, the four single-polymer ODF samples showed some mechanical properties outside published acceptable ranges, however the parameters are similar to those of Listerine®.

3.2 Assessment of disintegration behaviour

Volume reduction throughout a simulation is illustrated by the characteristic degradation curves given in Figure 3. Table 1 shows the mean ODF volumes at 180 s along with respective standard deviations (n=3) for the tested ODFs in the oral model; both P1 and Listerine® samples were fully degraded by 180 s, defined as having a volume less than 10 %. The time to disintegration was suggested to be a function of the polymeric chain length of the film-forming polymer [39,40], possibly due to the higher link density among molecules. Therefore lower molecular weight films were expected to disintegrate faster than their high molecular weight counterparts within the same polymeric species.

--- TABLE 2 ---

--- FIGURE 3 ---

The methodology proposed and tested in this work was able to measure film volume (relative to initial volume) for a range of different ODF formulations, including a commercial film, during mechanical and chemical degradation in a model oral cavity. The results presented in Figure 3 illustrate clear differences between characteristic volume reduction curves for each ODF tested. Essential to this being a useful method for measuring ODF breakdown, the volume of film at 180 s could be measured and used as a comparator between ODF formulations. During dissolution each ODF adhered to the acrylic palate after the first compression cycle. It is not uncommon for ODF to exhibit adhesive properties *in vivo*, and therefore adhere to the palate of a patient[6].

A marked difference in ODF breakdown behaviour was observed between PVOH-based and CMC-based films. Extracted frames of the disintegrating ODF are presented in Figure 4. PVOH films exhibited the tendency to break into pieces, whereas CMC films formed a thickened fluid instead. CMC is widely used as a thickener in many food and pharmaceutical preparations due to its excellent water retention properties. Carboxylic groups are responsible for the high solubility of CMC[41], as opposed to PVOH, which does not contain such substitution groups, thus potentially explaining the different breakdown behaviour observed between the two polymeric species.

The breakdown behaviour of Listerine® was similar to that of the CMC-based films, although its disintegration time was much faster. Listerine® ODFs do not contain CMC, however they do contain other polysaccharides such as pullulan, carrageenan, locust bean gum, and xanthan gum. The specific characteristics of the polymers used in Listerine® are not specified, so it is difficult to relate attributes such as molecular weight to disintegration time and behaviour. Similarities in the molecular structures such as the presence of repeated monosaccharide units might have determined the similarity observed in the breakdown behaviour between CMC and Listerine® samples.

--- FIGURE 4 ---

Only P1 and Listerine® completely disintegrated in less than 3 minutes, thus confirming the capability of the method to correctly identify a marketed product meeting the requirements of the European

Pharmacopoeia for orodispersible formulations[4]. The lower molecular weight films of each polymeric species disintegrated faster than their high molecular weight counterparts as would be expected. The molecular weight of PVOH should not influence its solubility at low hydrolysation degree[42], however, the disintegration of thin polymeric films might be mediated by other mechanisms such as chain entanglement, and swelling properties. Film volume decreased linearly in P1 and Listerine®, whereas it decreased in a non-linear way for the high-molecular weight films. The two non-linear regions in the volume reduction of high-molecular weight films, as well as the increasing time to disintegration in accordance with molecular weight, could be related to the disentanglement of the polymeric chains in liquid media. The phenomenon could be also dependent on the type and number of specific substitution groups. According to Linossier and colleagues[43] dissolution of polymeric films is regulated by hydrogen bonds forming with the substitution groups of the polymeric chains. Stronger hydrogen bonding could have been formed between the liquid solution and carboxyl substitution groups in comparison with hydroxyl groups. At pH 7.4 carboxyl groups are ionised, whereas hydroxyl groups are not. Therefore, as CMC has carboxyl substitution groups, we can expect it to exhibit negative charges that can favour dissolution. The presence of a delay in the onset of the linear phase of high molecular weight films could be explained by a longer initial hydration period, this was also reported by Linossier. The non-linear region at the end of the disintegration curves may be due to interaction between polymeric chains and the acrylic (PMMA) rigid surface. Film adhesion may have temporarily limited chain mobility, and therefore slowed the availability of new hydrogen bonding sites on the opposite surface of the film, thus delaying disintegration. Adsorption and potential bonding between PVOH and PMMA were previously reported in the literature[44,45]. During dissolution, polymeric films tend to swell before releasing their chains from the matrix[46]. The periodic mechanical compression of the film against the acrylic palate might have favoured the elimination from the oral cavity of detached polymeric chains in solution.

Different polymer species have been previously found to exhibit characteristic mechanical properties and disintegration time[47], hence a difference in the disintegration behaviour of the tested polymer ODF samples was expected here. Higher polymeric molecular weights likely exhibit a high entanglement density. The intrinsic molecular structure of different polymer species, and the degree of substitution within the same species might also contribute to the ability of the polymeric chain to form intermolecular bonds. In turn, this is likely to influence the resistance of the polymeric matrix to mechanical stresses. Therefore the difference in both the tensile strength and disintegration behaviour that was observed among the test ODF samples might find explanation in such polymeric attributes.

The disintegration times of the films tested in the present study are longer compared to the same samples assessed by other *in vitro* methods[48], and *in vivo*[6], however, proportionality was maintained. In this respect, a direct comparison with other *in vitro* techniques for the measurement of disintegration time might not be appropriate, as the measurement end-points differ considerably[12]. Regarding the comparison with available *in vivo* data, a direct correlation of sample disintegration

time might also not be appropriate[6]. The disintegration time reported by panellists may be shorter due to limitations in perceptual sensitivity; subjects may be reporting absence of the film when there is a still a measurable presence on the simulator. However, comfort/discomfort scores assigned by panellists over the acceptability of perceived disintegration time might provide useful information to interpret the data obtained by oral cavity model. Samples that showed a non-linear volume reduction were also evaluated less acceptable than samples exhibiting linear disintegration behaviour[6]. A key advantage of the *in vitro* methodology presented here is the opportunity to obtain a disintegration behaviour profiling of the film samples by evaluating film volume reduction during simulated oral processing.

4. Conclusions

An artificial oral cavity model was adapted for the *in vitro* evaluation of the disintegration behaviour profiling of ODFs. Four single-polymer ODFs, and one benchmark product, were characterised by mechanical properties and then tested for disintegration. The mechanical characteristics differed among the four samples. To assess ODF disintegration, the detection of the film volume reduction vs. time was achieved via processing images using a bespoke video analysis technique, developed using MATLAB. The proposed methodology was able to detect differences determined by the polymeric type, molecular weight, and degree of substitution. Samples P1, and Listerine® underwent complete disintegration in less than 3 min, therefore confirming the discriminative power of the developed method. The oral cavity model and image analysis method developed in this work have potential for implementation as a decision-supporting tool in the early drug design process for ODF disintegration behaviour and acceptability. Further adaptations of the method might involve the visualisation of the loaded drug in order to study the drug release properties of the film, and the addition of different mechanical stress types in order to mimic more closely the physiology of the human oral cavity.

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Table 1: Composition of simulated salivary solution from Gittings and colleagues[34].

Component	Concentration
Potassium dihydrogen phosphate	12 mM
Sodium chloride	40 mM
Calcium chloride	1.5 mM
Sodium hydroxide	To pH 7.4
Demineralised water	To 1 L

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Table 2: Volume percentage (units: 0-1) of ODF samples remaining at 180 s.

Sample name	Volume at 180 s (units: 0-1)	Standard deviation (units: 0-1)
P1	< 0.10	-
P2	0.52	0.03
C1	0.15	0.10
C2	0.63	0.08
Listerine ®	< 0.10	-

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Figure 1:
Diagram of compression sequence steps: a) oral cavity is ‘open’ and salivary fluid is sprayed inside, b) dynamic compression of ODF, c) full compression position. This sequence is repeated until the ODF has dissolved.

Figure 2:
Tensile strength, % elongation at break and Young’s modulus of single-polymer ODF samples and Listerine (n=3). Asterisks refer to statistically significant difference with Listerine.

Figure 3:
Volume percentage (0-1) of ODFs during disintegration (n=3). Standard deviation is represented by the dashed lines.

Figure 4:
Extracted frames from videos showing ODF samples during disintegration.

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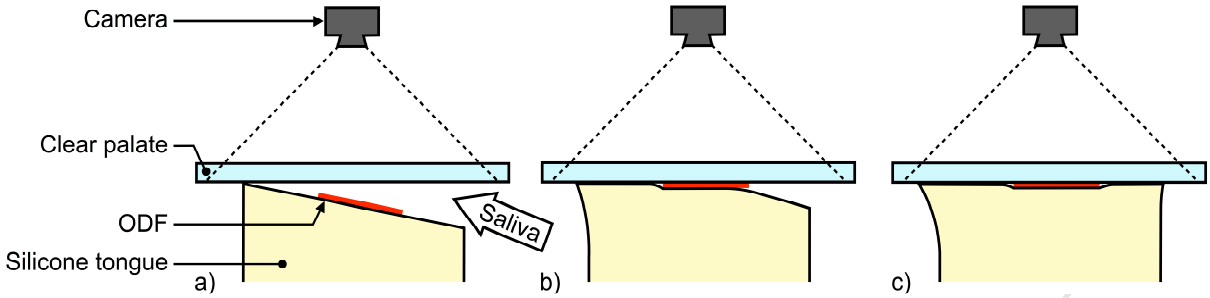

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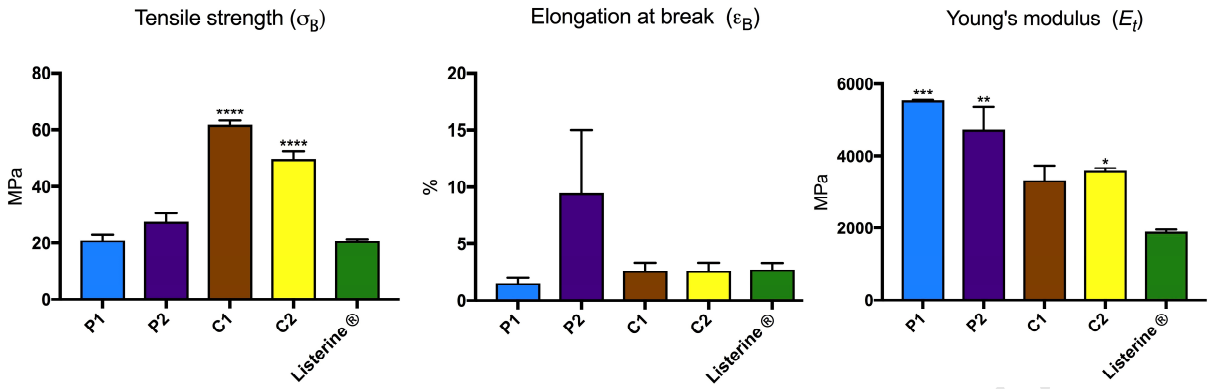

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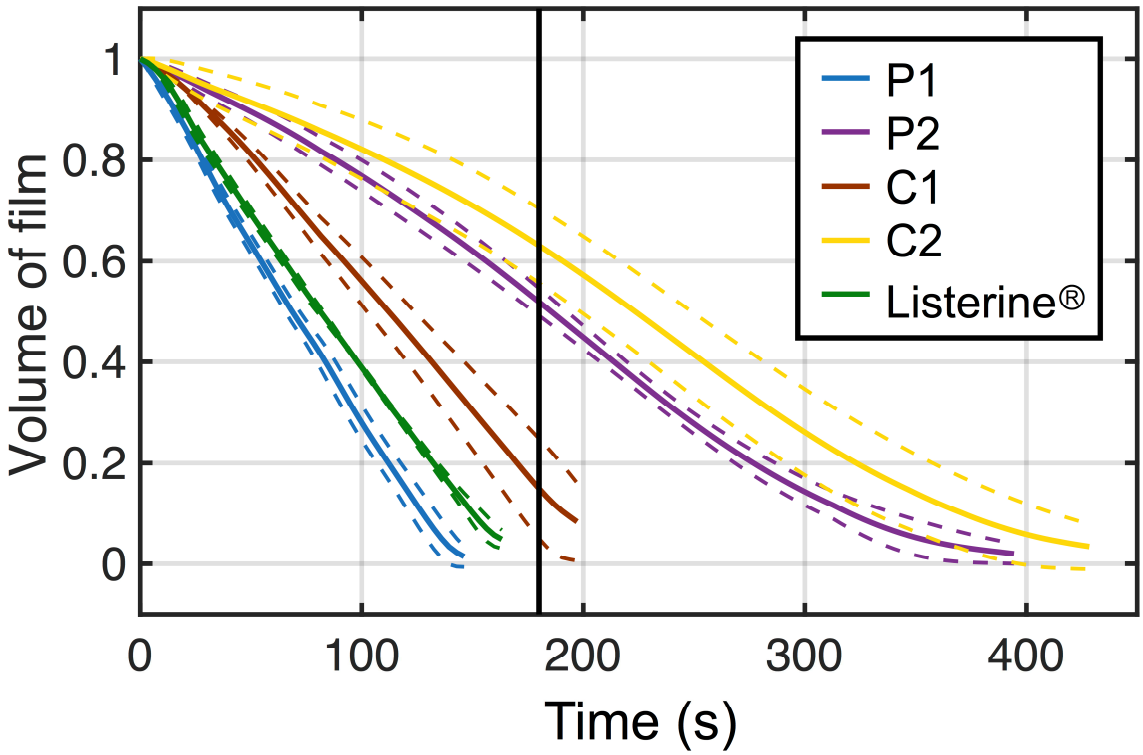

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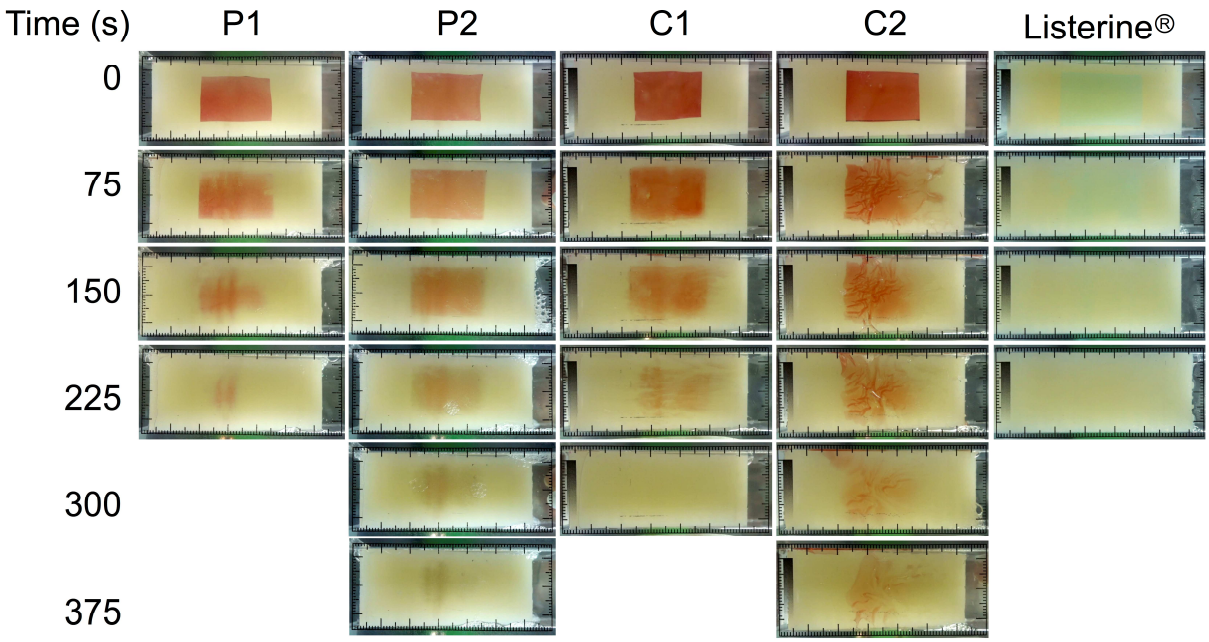

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