



## Chitosan-(poly)acrylic acid polyelectrolyte complexes: Enhanced mucoadhesion and sustained drug release in vaginal tablets

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### ABSTRACT

Polyelectrolyte complexes (PECs) have emerged as promising vehicles for medical applications, attributable to their non-toxicity, non-immunogenicity, and ability for controlled drug release. Notably, their inherent mucoadhesive properties are being leveraged for sustained drug delivery across mucosal barriers, including vaginal, ocular, nasal, and buccal membranes. This study delves into the formulation and effects of chitosan-(poly)acrylic acid-based PEC for vaginal tablet applications. A comparative analysis of various polymer combinations was conducted, emphasizing the differential impacts of low versus high-molecular weight chitosan. Results highlighted that PECs augmented the flowability of powder mixtures and bolstered the tablets' physical properties. Moreover, PEC-enhanced formulations exhibited a pronounced increase in swelling efficiency, with swelling index values reaching up to  $92.67\% \pm 1.90$ , ensuring structural integrity during dissolution. In *ex vivo* mucoadhesion tests, tablets from PEC mixes demonstrated extended adhesion, surpassing 48 h for certain formulations. The optimized PEC formulation successfully achieved sustained drug release while retaining tablet adhesion for the duration of the release period.

### Introduction

Polyelectrolyte complexes (PECs) are rapidly becoming a focal point in pharmaceutical research, demonstrating potential as platforms for controlled drug release (Wu et al., 2020). These complexes form when opposing polyelectrolytes, specifically polymer anions and cations, engage in electrostatic interactions. Intriguingly, while polyelectrolytes are neutral in their original state, dissolution in a compatible polar solvent leads to the dissociation of numerous ionic groups along their molecular chains, giving rise to poly-ions (Nyström et al., 2010). This dissociative process, be it partial or complete, initiates both intramolecular and intermolecular electrostatic interactions (Cazorla-Luna et al., 2021; Dakhara & Anajwala, 2010). These interactions are the foundations for PEC formation (Folchman-Wagner et al., 2017). As a result, PECs introduce a series of physicochemical modifications to drug delivery systems. These include enhanced water solubility, increased ionic conductivity, robust interchain interactions, elevated surface activity, and altered chain conformations (Schanze & Shelton, 2009). This

transformative capability empowers PECs to augment the efficacy of drug delivery systems beyond what individual polymers can achieve on their own (Meka et al., 2017).

Polysaccharides typically carry neutral or negative charges (Luo & Wang, 2014; Prezotti et al., 2014). However, chitosan stands out as the sole high-molecular-weight cationic (positively charged) polyelectrolyte. Its uniqueness arises from the protonation of amino groups along its backbone, enabling it to dissolve in acidic environments and endow it with a significant density of positive charges, a characteristic not shared by other polysaccharides (Berger et al., 2004). The formation of PECs is primarily driven by the electrostatic attraction between these cationic amino groups of chitosan and the anionic groups of another polyelectrolyte. Commonly used polyanions in this context include both natural polysaccharides like alginate, pectin, and xanthan, as well as synthetic ones such as (poly)acrylic acid. These polyanions, especially those with carboxylic groups, effectively interact with chitosan to form PECs (Berger et al., 2004; Il'ina & Varlamov, 2005).

A chief advantage of PECs lies in the structural density they attain

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through electrostatic interactions between polyelectrolytes. As these interactions unfold, a significant entanglement of the combined polymer chains occurs, resulting in a more compact and cohesive structure (Cazorla-Luna et al., 2019). This denser configuration endows PEC-based formulations with enhanced resistance to the infiltration of aqueous media. Consequently, they exhibit a moderated swelling rate, which is instrumental in prolonging drug release compared to formulations involving singular polymer chains. Additionally, once infiltrated by aqueous media, the dense structure of PECs efficiently retains large amounts of these media within their framework. This capacity further aids in decelerating the drug release process, offering a controlled and sustained delivery mechanism (Cazorla-Luna et al., 2019).

PECs significantly enhance the structural, mechanical, and thermal properties of polyelectrolytes. These enhancements are crucial in extending drug release durations, increasing tablet fracture resistance, and aiding in fiber formation (Nyström et al., 2010). The effectiveness of PECs is influenced by various factors, including concentration, molecular weight, ionic strength, hydrophobicity, charge density, the pH of the medium, and the mixing ratio of the polyelectrolytes (Hartig et al., 2007). In light of this, our study has been designed to explore the impact of PECs with varying estimated strengths on the structural, mechanical, and mucoadhesive properties of diverse vaginal tablet formulations. This investigation aims to provide a comprehensive understanding of how PECs can be optimized to enhance the performance of these pharmaceutical applications.

Traditionally, most PEC formulations have been developed through steps involving precipitation of PECs and granulation prior to tableting (Syed et al., 2014). However, this study was built on our preceding findings, where direct mixing of two polymers demonstrated improved swelling rates, suggesting the formation of PECs in the mixture (Abidin et al., 2020). From the previous study, a vaginal bilayer tablet containing both chitosan and PAA was developed as a multi-drug dosage form to be used in conjunction with the cervical cancer treatments available in low-resource countries. 5-Fluorouracil (5FU) is an antineoplastic drug and is widely used in the treatment of cancer (Major & McConville, 2017; Murphy & Middleton, 2012) was paired with a repurposed pre-existing anti-alcoholic drug (Fong & To, 2019). Thus, a significant aspect of this research is to ascertain whether PECs can spontaneously form through direct mixing and subsequently activate upon contact with vaginal fluids.

This study is primarily focused on elucidating the distinct and overlapping impacts resulting from the utilization of PECs with varying strengths, aiming to provide a detailed understanding of how these variations influence the overall efficacy and characteristics of vaginal tablet formulations. As molecular weight is one of the determining factors of the solubility of chitosan (Desai et al., 2023), a comparative analysis will be conducted between batches formulated with low-molecular-weight chitosan (CL) and high-molecular-weight chitosan (CH) was thought to add another array of information to this study. 5-Fluorouracil (5FU) is incorporated as a model drug to assess the drug delivery efficacy. While PAA, CL, and CH serve as controls due to their extensive prior study, this research predominantly focuses on the outcomes associated with the formulated PEC tablet batches. To the authors' knowledge, this is the first extensive evaluation and comparison of vaginal tablets formulated with spontaneously generated chitosan and (poly)acrylic acid-based PECs.

## Methods

### Materials

(Poly)acrylic acid (PAA) was obtained from Lubrizol Advanced Materials (Westerlo, Belgium). Low (average MW ~50,000) (CL) and high-molecular weight (average MW ~1500,000, ≥ 90 % degree of acetylation, particle size ≤ 100 mesh) chitosan (CH), 5-fluorouracil, sodium chloride, potassium hydroxide, calcium hydroxide, lactic acid, acetic

acid, glycerol, urea, glucose, bovine albumin and methanol was obtained from Glentham (Corsham, UK). Freshly excised vaginal tissues were acquired from a local farmer and butcher, Gilligan's farm (Roscommon, Ireland).

### Powder flowability evaluations

#### Characterization of powder flowability

A known mass of powder was placed in a graduated cylinder. The volume occupied is then recorded and the bulk density (BD) was calculated using Eq. (1). The graduated cylinder filled with the powder mix was then placed onto a tapped density voltmeter (Copley Scientist, Nottingham, UK) and tapped 1000 times. The volume change was then recorded, and Eq. (2) was used to calculate the tapped density (TD). The corresponding densities were then used to calculate Carr's compressibility index (CI) and Hausner ratio (HR) using Eq. (3) and (4), respectively (Shah et al., 2008). The corresponding values of CI and HR were analyzed and compared to the values indicating the different flowability as stated in Table 1. This procedure was repeated for each powder and the mixes.

$$\text{Bulk density (BD)} = \frac{\text{Mass of the powder, in grams (M)}}{\text{Volume occupied, in mL (V}_0\text{)}} \quad (1)$$

$$\text{Tapped Density (TD)} = \frac{\text{Mass of the powder, in grams (M)}}{\text{Volume occupied after tapping, in mL (V}_1\text{)}} \quad (2)$$

$$\text{Carr's Index (CI)} = \frac{\text{TD} - \text{BD}}{\text{BD}} \times 100 \quad (3)$$

$$\text{Hausner's Ratio (HR)} = \frac{\text{TD}}{\text{BD}} \quad (4)$$

#### Measurement of powder flow rate by angle of repose ( $\alpha^\circ$ )

A funnel with a wide outlet was affixed at 2 cm above the bench. A piece of paper was placed directly beneath the funnel. Each powder was carefully added while the funnel was closed. The powders were allowed to flow through and collected on the paper until a cone was formed which reached the funnel orifice. The diameter of the base of the conical pile at two opposite sides was measured using a ruler. The angle of repose ( $\alpha^\circ$ ) of the different PEC mix was calculated using Eq. (5). The height of the conical pile (H) which was fixed at 2 cm. The 4 different diameter points of the conical pile were taken, and an average diameter (D) was determined (Al-Hashemi & Al-Amoudi, 2018). The tangent of repose was given by Eq. (5), where  $\alpha$  is the repose angle. This test was done in triplicates.

$$\tan \alpha (^\circ) = \frac{2H}{D} \quad (5)$$

#### Preparation of polyelectrolyte complex (PEC) powder mixes

Each PEC powder mix was prepared by taking the mass percentage of each powder following Table 2. The weighed powders were then directly combined and mixed thoroughly for 15 min in a mortar and pestle and

**Table 1**  
Relationship of angle of repose ( $\alpha^\circ$ ), Carr's compressibility index (CI), and Hausner Ratio (HR) in characterizing the flow properties of powder (Agarwal et al., 2018).

$\alpha^\circ$	CI	HR	Flow properties
25–30	1–10	1.00–1.11	Excellent
31–35	11–15	1.12–1.18	Good
36–40	16–20	1.19–1.25	Fair
41–45	21–25	1.26–1.34	Passable
46–55	26–31	1.35–1.45	Poor
56–65	32–37	1.46–1.59	Very poor
>66	> 38	>1.60	Very very poor

**Table 2**

Percentage mass composition of the different polyelectrolyte complex (PEC) powder mix.

PEC mix	PAA* (%)	CL** (%)	CH*** (%)
PAA	100	–	–
CL	–	100	–
CH	–	–	100
Mix 1	75	25	–
Mix 2	50	50	–
Mix 3	25	75	–
Mix 4	75	–	25
Mix 5	50	–	50
Mix 6	25	–	75

\* (poly)acrylic acid (PAA)

\*\* low molecular weight chitosan (CL)

\*\*\* high molecular weight chitosan.

were put through a stainless steel sift (100  $\mu\text{m}$ ). The mix was then stored in a closed plastic container, in a dry place at room temperature, and kept out of the light until further use. The controls (PAA, CL, CH) were 100 % composed of the individual powdered materials with no added excipients.

#### Preparation of vaginal tablets

The tablets were prepared similarly to the previous study (Abidin et al., 2020). Tablet batches were made up by adding 30 % 5FU to 70 % of individual PEC mix (w/w). All combined drug and powder were mixed thoroughly using a mortar and pestle for 15 min. Then powder mix was weighed (200  $\pm$  1 mg) and compressed using a 10-mm-diameter die in a single punch tablet press machine. Each tablet was pressed with a pressure of 3 tons for 30 s.

#### Characterization of the vaginal tablets

##### Tablet uniformity

This physical variation test was carried out as per Indian Pharmacopoeia (Pharmacopoeia, 2007). Twenty randomly selected tablets were weighed individually using an electric balance (Denver Instrument M-310, New York) and the thickness was measured using a digital caliper (Mitutoyo Absolute Series 500, Japan). The deviation from the mean of both weight and thickness measurements was calculated by Eq. (6).

$$\text{Deviation (\%)} = \frac{(\text{Average value} - \text{value of individual tablet})}{\text{Average value}} \times 100 \quad (6)$$

##### Hardness

A randomly selected vaginal tablet from each batch was tested for its resistance to fracture using a Ta.XT plus Texture Analyser (Stable Micro Systems, Surrey, UK) (Abidin et al., 2023). A three-point bending base with a 5 mm depth of the groove and at a 45° angle from the horizontal line was used to hold the tablet upright. A 30 mm diameter top head was used to crush the tablets. The speed of the test was set to 2 mm/min and the pre-load function was active with 0.1 N force. The force needed to break the tablets were recorded in Newtons (N).

##### Friability

This method was carried out as per USP XXVII (Pharmacopoeia, 2015). Twenty randomly selected tablets from each batch were dusted and weighed ( $w_0$ ) together using an electric balance. The tablets were then placed into the drum of the friabilator and rotated at 25 rpm for 4 min. The tablets were collected, dusted, and re-weighed ( $w$ ). The degree of friability (brittleness) was calculated as a percentage of weight loss using Eq. (7).

$$\text{percentage loss (\%)} = \frac{w_0 - w}{w_0} \times 100 \quad (7)$$

##### Content uniformity

A randomly selected vaginal tablet from each batch was weighed, powdered, and dissolved in 100 mL of methanol. This was kept in a shaking incubator and maintained at 100 rpm and 37  $\pm$  1 °C, for 24 h. After filtration, samples (1 mL) were suitably diluted with methanol and analyzed for drug content spectroscopically (Shimadzu UV spectrophotometer, Japan) at 213 nm (Abidin et al., 2020).

##### Gel fraction (GF) study

Randomly selected tablets from each batch were submerged in simulated vaginal fluid (SVF), pH 4.2, for 30 min, 8, and 24 h. At the time intervals, the tablets were taken out and pat dry using filter paper. The weight was recorded,  $w_s$ . The tablets were then dried in the vacuum oven at 37 °C at 70 mbar for 72 h and re-weighed,  $w_d$ . Re-submerged the dried tablets in SVF (pH 4.2), this time for 48 h before drying them again in the vacuum oven for 72 h to assess the effectiveness of the cross-linking reaction (Azaman et al., 2022). The final equilibrium dry weight was recorded,  $w_{ef}$ . The gel fraction ( $GF_{SVF}$ ) of the tablets was calculated using Eq. (8).

$$GF_{SVF} = \frac{w_{ef}}{w_d} \times 100 \quad (8)$$

##### Fourier-transform infrared spectroscopy (FT-IR) analysis

Randomly selected vaginal tablet from each batch was submerged in SVF (pH 4.2) and allowed to form spontaneous complexation for 30 min, 8 and 24 h. All tablets were dried in a vacuum oven at 37 °C at 70 mbar until equilibrium weight was reached. The crosslinking interactions were analyzed using FT-IR spectroscopy on a Perkin-Elmer Spectrum One FTIR spectrometer fitted with a universal ATR sampling accessory. Drying the samples before testing can prevent the broad water peak from shadowing the significant signature peaks of the materials. The tests were run using a spectral range of 4000–400  $\text{cm}^{-1}$ . Four scans per sample cycle were utilized with a resolution of 0.5  $\text{cm}^{-1}$  at room temperature. The FT-IR spectra obtained were analyzed using the Spectragryph app version 1.2.15 (Germany).

##### Swelling study

Randomly selected tablets from each batch were submerged in 10 mL of SVF (pH 4.2) and maintained at 37  $\pm$  1 °C. The weight of each tablet before swelling was taken,  $w_d$ . The individual tablets were taken out according to the time intervals of 15 and 30 mins, 1, 2, 4, 6, 8, 24, and 48 h. When taken out, excess water was pat dry and the re-weighed,  $w_s$ . Any weight gained indicates some hydration (water uptake, WU) of the tablets which is associated with the swelling ability (swelling index, SI) and calculated using Eqs. (9) and (10), respectively.

$$\text{water uptake (WU) \%} = \frac{(w_s - w_d)}{w_d} \times 100 \quad (9)$$

$$\text{swelling index (\%)} = \frac{w_s}{w_d} \times 100 \quad (10)$$

##### Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was performed to evaluate and compare the surface morphology of dry and after-swelling vaginal tablets. Randomly selected tablets from a batch were submerged in 10 mL of SVF (pH 4.2) and maintained at 37  $\pm$  1 °C, for 24 h. The swollen tablets were taken out and immediately freeze-dried for 24 h. The tablets were then submerged in liquid nitrogen for 10 min and cut cross-sectionally.

The samples were then placed on an aluminum stub and were gold coated using Baltec SCD 005 sputter coater (BAL-TEC GmbH, Pfäffikon, Switzerland) for 110 s at 0.1 mBar vacuum before observation on a Tescan Mira SEM (Oxford Instruments, Abingdon, UK) using a range of magnifications.

#### *In vitro* release study

The drug release study was performed in SVF prepared according to Owen and Katz (1999), by mixing NaCl (3.51 g), KOH (1.40 g), Ca(OH)<sub>2</sub> (0.222 g), albumin (0.18 g), acetic acid (1.00 g), lactic acid (2.0 g), glycerol (0.16 g), urea (0.4 g), glucose (5.0 g) in 1 L of water (Owen & Katz, 1999). The mixture was stirred well until completely dissolved and the pH was adjusted to 4.2 with acetic acid. Randomly selected vaginal tablets from each batch were individually weighed and placed in a borosilicate glass flask containing 100 mL of SVF (pH 4.2) and placed in an orbital incubator and maintained at 37 ± 1 °C and 100 rpm. Samples (5 mL) were withdrawn at 15, 30, 60-min intervals, then at 2, 4, 6, 8, 24, 48, and 72-hr intervals. An equal amount of fresh SVF kept at the same temperature was replaced after every sample withdrawal to maintain sink conditions. Samples were diluted appropriately and assayed using a Shimadzu (Kyoto, Japan) UV spectrophotometer at 213 nm.

#### Mucoadhesion test

Freshly excised sheep vaginal mucosa was cut into fragments of approximately 72 × 25 mm and fixed on glass slides with cyanoacrylate adhesive. Randomly selected tablets from each batch were then individually placed in the centre of the mucosa and pressed with fingertip contact force for 30 s. The slides were positioned at an angle of 60° and immersed in 200 mL of SVF and incubated at 37 ± 1 °C and 100 rpm, until total detachment. The adhesion time was determined by visual observation of the samples. Samples were observed every hour for the first 8 h (Abidin et al., 2020; Pacheco-Quito et al., 2020).

#### Forced detachment test

Randomly selected tablets from each PEC mix batch were individually dipped into SVF and pressed with a fingertip force for 30 s onto a fragment of sheep vaginal mucosa tissue. Both top and bottom clamps were fixed onto the TA.XT plus Texture Analyser (Stable Micro Systems, Surrey, UK). The tablet and tissue sample are clamped at the bottom and the top was clamped onto the tablet. The test was conducted by pulling apart the clamps until detachment of the tablet from the vaginal tissue (Abidin et al., 2023). The speed of the test was set to 2 mm/min and the pre-load function was active with 0.1 N force. The force required to detach the tablet was recorded in Newtons (N).

## Results and discussion

#### Characterization of powder flowability

Understanding the physical behavior of powders is pivotal in the formulation and processing of solid dosage forms. The flow characteristics of powders, or flowability, play a critical role in various pharmaceutical processes, including mixing, blending, tablet compression, and capsule filling, as well as during transportation (Dubey, 2017; Sarraguca et al., 2010). Optimal powder flow is essential for ensuring the quality of the final product, characterized by acceptable content uniformity, minimal weight variation, and consistent physicochemical properties (Aguilar-López & Villafuerte-Robles, 2016; Sandler et al., 2010; Sarraguca et al., 2010). Assessing the flowability of each powder type is fundamental, as it determines the necessity, type, and quantity of glidants or lubricants required to enhance the quality of the mix and facilitate the mixing process (Aguilar-López & Villafuerte-Robles, 2016; Dubey, 2017). However, in our study, we intentionally refrained from

adding glidants or lubricants to the powder mixes. This approach was adopted to accurately report the inherent properties and performance of the various PEC powder mixes, as detailed in Table 3.

The Carr's compressibility index (CI) and the Hausner ratio (HR) are instrumental in evaluating the flowability of powders and their propensity for compression and the powder flow rate can be further evaluated using the angle of repose ( $\alpha^\circ$ ). These parameters are intricately linked to the interparticle attractions governed by intermolecular forces. A high degree of these attractions usually indicates a cohesive nature, rendering the powder less free flowing (Abidin et al., 2020). Lower values of all CI, HR, and  $\alpha^\circ$  are indicative of a more free flowing powder (Agarwal et al., 2018).

Badwan et al. (2015) have reported that chitosan has a more fibrous structure, which facilitates entanglements between particles, in addition to its cohesive nature resulting in adverse mechanical interlocking of powders with irregular shapes, consequently, poor flow properties are displayed (Badwan et al., 2015). Therefore, it is not surprising that the powder flowability gets poorer in the PEC mixtures with higher chitosan content, and it is true for both CL (Mix 2–3) and CH (Mix 5–6). A similar observation of  $\alpha^\circ$  was reported for Mix 2,3, 5, and 6. CH mixes in particular have higher  $\alpha^\circ$ , which coincides with the study reported by Sun et al. (2009) that stated as the molecular weight of chitosan increases, the  $\alpha^\circ$  increases (Sun et al., 2009).

The CI values appear to be reduced in most of the PEC mixes as compared to the powders of individual polymers on their own. Referring to the poor flowability of PAA and both chitosan, it can be hypothesized that when mixed the particles can become entangled with one another resulting in bigger particle sizes. Badwan et al. (2015) also stated that the bigger the particle size the better flowability of chitosan (Badwan et al., 2015). Nonetheless, this finding strongly recommends incorporating a glidant or lubricant, particularly in formulations with high chitosan content or when using high-molecular-weight chitosan, to improve the flowability and processing efficiency.

#### Characterization of the vaginal tablets

Physical characterization and measurements are to evaluate the uniformity of tablets in a particular batch (Abidin et al., 2023). Characterization data of vaginal tablets of all the batches is displayed in Table 4.

The uniformity of tablets is a critical factor in ensuring the consistency of their physical attributes and dosage efficiency (Abidin et al.,

**Table 3**

Recorded bulk (BD) and tapped (TD) densities and calculated values of Carr's compressibility index (CI), Hausner ratio (HR), and angle of repose ( $\alpha^\circ$ ) indicating the flow properties of each powder following values listed in Table 1.

Batch	BD	TD	CI*	HR*	$\alpha^\circ$ **
PAA	0.24	0.34	27.54 (poor)	1.38 (poor)	41 ± 2.09 (passable)
CL	0.25	0.38	35.48 (very poor)	1.55 (very poor)	41 ± 2.69 (passable)
CH	0.21	0.33	36.25 (very poor)	1.57 (very poor)	37 ± 4.40 (fair)
Mix 1	0.29	0.37	21.43 (passable)	1.27 (passable)	38 ± 1.45 (fair)
Mix 2	0.30	0.38	22.00 (passable)	1.28 (passable)	41 ± 1.57 (passable)
Mix 3	0.26	0.35	27.69 (poor)	1.38 (poor)	45 ± 1.43 (passable)
Mix 4	0.28	0.42	34.43 (very poor)	1.53 (very poor)	38 ± 2.03 (fair)
Mix 5	0.26	0.36	27.35 (poor)	1.38 (poor)	43 ± 2.79 (passable)
Mix 6	0.24	0.33	26.40 (poor)	1.36 (poor)	46 ± 0.99 (poor)

\* These values are stated as calculated values (flow property of the powder).

\*\* These values are stated as calculated values ± SD (n = 3) (flow property of the powder).



**Table 4**  
Physico-chemical evaluations for characterization of vaginal tablet batches.

Batch <sup>c</sup>	*Weight (mg) <sup>a</sup>	Weight deviation (%) <sup>a</sup>	*Thickness (mm) <sup>a</sup>	Thickness deviation (%) <sup>a</sup>	Hardness (N) <sup>b</sup>	Friability (%) <sup>a</sup>	*Drug content
PAA	200.20 ± 1.09	-1.38 to 1.06	1.92 ± 0.016	-2.60 to 1.04	361.88 ± 34.03	0.88 ± 0.100	108.53 ± 5.77
CL	202.35 ± 1.44	-1.66 to 0.78	1.92 ± 0.012	-1.04 to 1.56	259.31 ± 26.41	0.22 ± 0.002	103.66 ± 8.76
CH	201.04 ± 2.45	-1.91 to 1.97	1.89 ± 0.022	-1.59 to 2.65	289.03 ± 20.19	0.13 ± 0.001	101.84 ± 8.41
Mix 1	200.40 ± 1.02	-1.00 to 1.17	1.89 ± 0.016	-1.59 to 1.59	469.44 ± 0.14	0.12 ± 0.006	94.68 ± 4.91
Mix 2	201.30 ± 0.80	-0.84 to 0.75	1.89 ± 0.017	-1.59 to 1.06	469.31 ± 0.33	0.08 ± 0.004	99.60 ± 3.14
Mix 3	200.46 ± 2.14	-1.29 to 3.45	1.87 ± 0.025	-2.14 to 3.74	469.43 ± 0.17	0.08 ± 0.003	103.07 ± 11.22
Mix 4	200.61 ± 1.53	-0.83 to 1.99	1.90 ± 0.017	-1.58 to 2.63	469.06 ± 0.20	0.12 ± 0.014	92.23 ± 5.57
Mix 5	201.07 ± 0.68	-0.59 to 0.70	1.86 ± 0.020	-2.15 to 2.15	469.39 ± 0.46	0.06 ± 0.004	97.98 ± 7.45
Mix 6	201.59 ± 0.72	-0.69 to 0.60	1.86 ± 0.017	-2.15 to 1.61	469.55 ± 0.15	0.03 ± 0.004	100.77 ± 3.97

\* Each value is reported as mean ± SD (standard deviation).

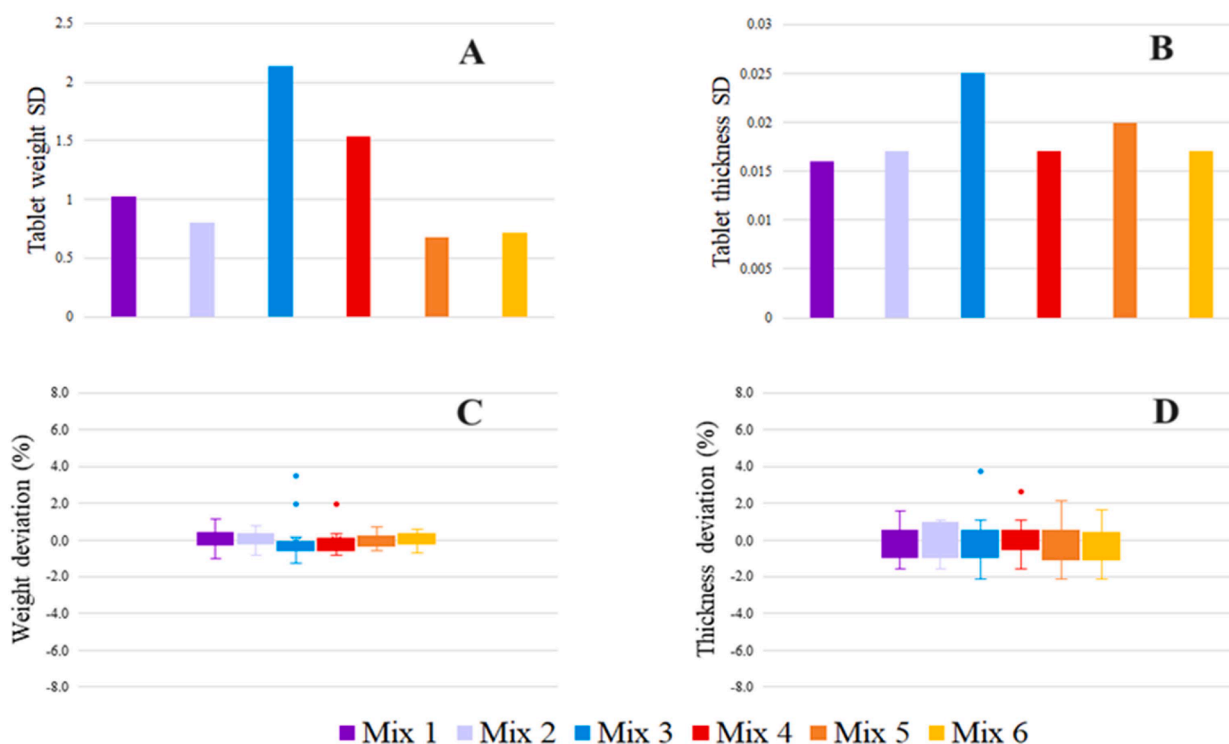
<sup>a</sup> n = 20.

<sup>b</sup> n = 3.

<sup>c</sup> n = 3.

2023). Variations in weight and thickness are key indicators of uniformity, with the standard deviations (SD) of these measurements providing a clear gauge. This is further complemented by the percentage deviation from the mean, as illustrated in Fig. 1. A smaller SD value signifies less variability, suggesting a higher likelihood of tablet consistency and uniformity. Conversely, a larger SD indicates greater variability, which could compromise consistency and reproducibility. Interestingly, the SD values for thickness across all batches are negligible, as shown in Fig. 1B. Thus, the weight measurements may offer a more discerning characterization for comparing different batches.

According to Fig. 1A, Mix 3 and Mix 4 exhibit the highest and second-highest SD values in weight, respectively. This indicates greater variability in these mixes, aligning with their previously reported poor powder flowability. Focusing on CL and CH, tablets from Mix 3 and Mix 6, which share the same polymer ratio (25 % PAA and 75 % CL or CH), are particularly noteworthy. Despite similar compositions, the weight SD values for tablets made with CH are noticeably smaller compared to those with CL (Mix 1–3). This suggests that, despite CH's poor flowability, tablets formulated with CH demonstrate superior consistency, reproducibility, and uniformity compared to their CL counterparts.



**Fig. 1.** Characterization of tablet uniformity by standard deviations of tablet's weight (A) and thickness (B) and deviation percentages from the mean weight (C) and thickness (D).

The deviation percentage is an essential metric for evaluating the extent of variation from the mean weight or thickness of individual tablets within a batch. This is visually represented in Fig. 1C and D, where each dot corresponds to an individual tablet, depicting its deviation from the batch mean. Fig. 1C corroborates the large standard deviation (SD) values noted in Fig. 1A, illustrating noticeable isolated deviations in certain batches. However, it's important to note that tablets from all batches are deemed uniform within the context of pharmacopeial standards (Bhat & Shivakumar, 2010). The observed deviations fall within the acceptable pharmacopeial limit of  $\pm 7.5\%$  for tablets weighing 200 mg (Pharmacopeia, 2015). This demonstrates that, despite some variability, the batches maintain a level of uniformity that is compliant with established pharmaceutical guidelines.

The hardness and friability of tablets are critical parameters reflecting their ability to withstand the rigors of manufacturing, handling, and transportation. The beneficial impact of polyelectrolyte complexes (PECs) on these physical attributes is evident from the data presented in Fig. 2. Tablets derived from PEC mix batches exhibit a notable enhancement in physical strength compared to those composed of single polymers (PAA, CL, CH). As illustrated in Fig. 2A, tablets from all PEC mix batches demonstrate a higher resistance to fracture under force, irrespective of the varying PEC strengths across batches. The maximum force endured by the tablets is significantly higher for PEC mixes compared to the controls. This was similar to the findings by Nyström et al. (2010) which reported an increase in tablet fracture resistance and aiding in fiber formation (Nyström et al., 2010). While this assessment is not designed to pinpoint the optimal tablet formulation, it serves as a useful indicator of the maximum force or pressure that the tablets can withstand during various stages of production and transportation.

The incorporation of PECs into our formulations significantly bolstered tablet strength, rendering them less friable (brittle), as evidenced by reduced weight loss percentages, as shown in Fig. 2B. Notably, the friability of all PEC mix batches was below 1%, thereby meeting the pharmacopeial standards for tablet strength (Bhat & Shivakumar, 2010; Pharmacopeia, 2015). Although the friability of the PEC mixes was generally lower than that of the controls, Mixes 1 and 4 exhibited a slightly higher weight loss compared to other mixes. This can be attributed to the inherent brittleness of PAA tablets, which tend to chip easily, as reflected by their high friability weight loss. Consequently, a higher proportion of PAA in a formulation, as in Mixes 1 and 4, adversely impacts the tablet's physical properties. The hardness tests revealed minimal differences between tablets made with CL or CH. However, the friability test indicates that CH-based tablets (Mixes 5 and 6) exhibit less brittleness compared to CL-based tablets (Mixes 2 and 3). This suggests that while both CL and CH contribute to tablet hardness, CH may be more effective in reducing tablet brittleness.

### Crosslinking of PEC

The integration of PECs within the vaginal tablet formulations was assessed through gel fraction (GF) studies, complemented by Fourier-transform infrared (FT-IR) spectroscopy to confirm the chemical interactions between PAA and CHN. According to Azaman et al. (2022), in the absence of crosslinking, swollen samples are likely to dissolve. The GF represents the proportion of polymer components that do not dissolve, indicative of their participation in crosslinking interactions. Consequently, a higher GF value can be interpreted as a signifier of increased crosslinking within the tablet matrix. This assessment not only underscores the physical integrity of the tablets but also provides insights into the chemical stability and interaction dynamics between the constituent polymers.

Fig. 3 offers a comparative analysis of the gel fraction in swollen vaginal fluid (GFSVF) across various PEC mix batches. Notably, Mixes 2, 3, 5, and 6 exhibit higher GFSVF compared to Mixes 1 and 4. Mixes 2 and 5, both formulated with a 50:50 ratio of PAA to CL and CH respectively, and Mixes 3 and 6, containing 75% CL and CH respectively, demonstrate this trend. The enhanced gel fraction in these mixes may be attributed to the heightened ionization of CHN at pH 4.2, facilitating more pronounced chemical interactions, especially in comparison to Mixes 1 and 4, which contain higher proportions of PAA. Interestingly, as time progresses, formulations with a greater PAA content, particularly Mix 1 followed by Mix 4, exhibit the highest GF values. This observation aligns with the expectation that over time, CHN will gradually dissolve as the tablet swells. These findings suggest that the rapid ionization of chitosan in simulated vaginal fluid (SVF) can be moderated by incorporating as little as 25% PAA, thereby forming a stable complex that preserves the tablet structure and enhances gelling, without an overly rapid loss of CHN in the fluid. When comparing the molecular weights of CHN, CH appears to dissolve slightly more than CL at the 30 min mark. However, over time, the GF of CH increases, indicative of ongoing complex formation. This differential behavior underscores the nuanced impact of molecular weight on the stability and performance of CHN within these formulations.

Crosslinked networks are known for their ability to absorb substantial quantities of water while maintaining their structural configuration, a property crucial for the stability of dosage forms (Suhail et al., 2022). Consequently, a decrease in gel fraction (GF) often correlates with a loss of structural integrity in tablets, potentially leading to handling difficulties. This relationship is evident in Fig. 4, which illustrates the impact of PEC on tablet structure. Notably, all tablets from the PEC mix batches retained their structural integrity even after 24 h of swelling, in stark contrast to the CHN controls. The CHN control tablets dissolved over time, failing to maintain their structural integrity. In comparison, the PAA tablets remained structurally intact. While there were observable changes in color and size—indicative of the formulation's partial dissolution over time—no signs of erosion, fragmentation, or total

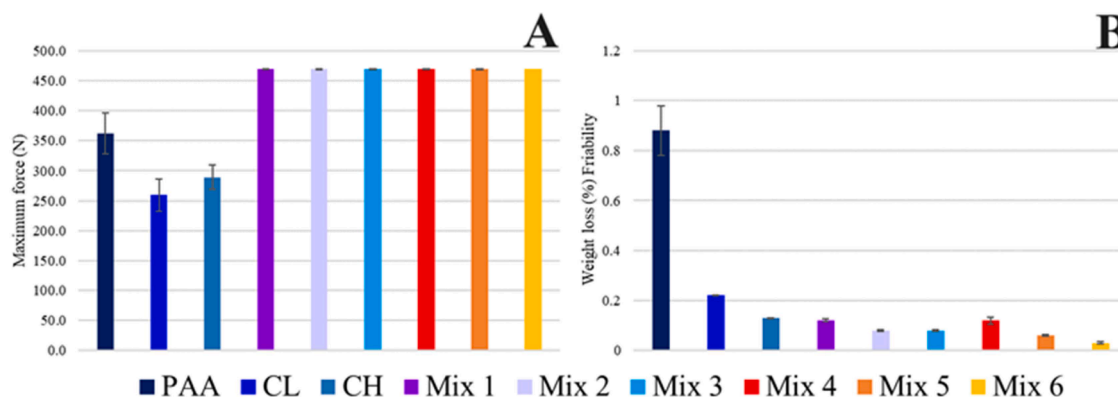


Fig. 2. Tablet's hardness (A) and friability weight loss (B) of different batches.

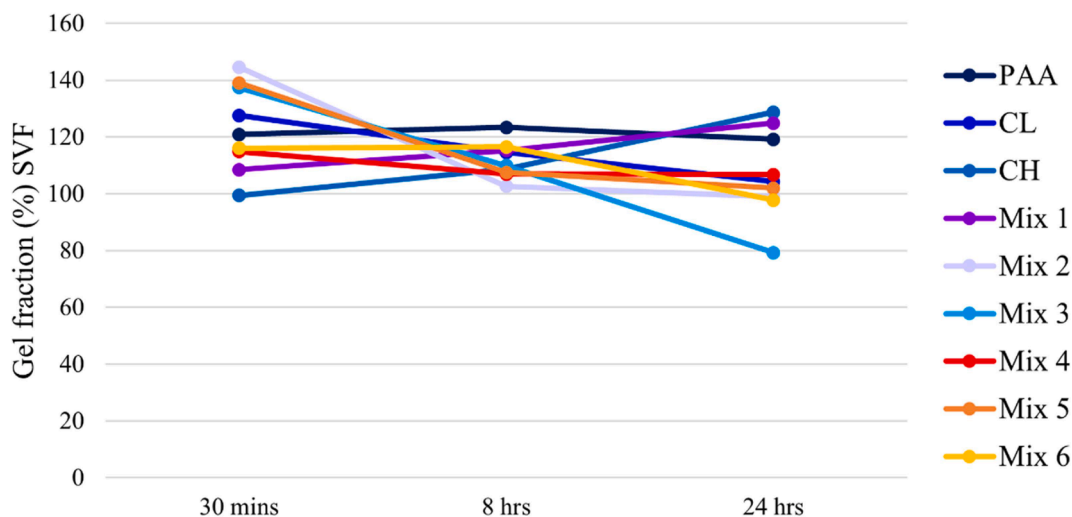


Fig. 3. Gel fraction (GF<sub>SVF</sub>%) of tablets from each batch at 30 min, 8- and 24 h swelling intervals in simulated vaginal fluid (pH 4.2).

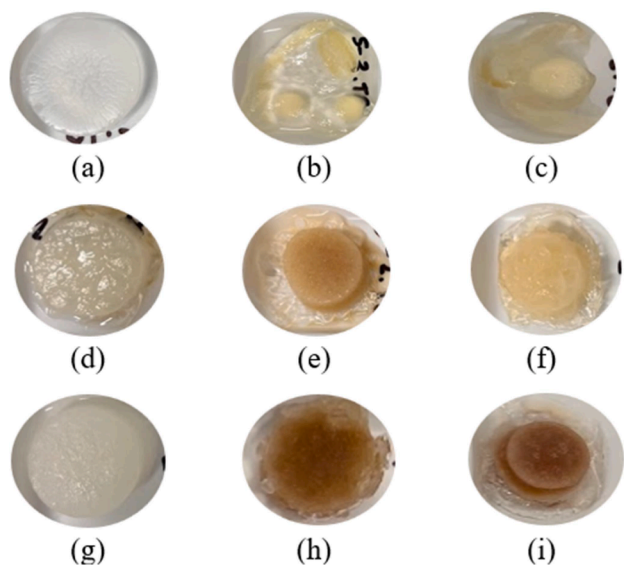


Fig. 4. Condition of the tablets after 24 h of swelling in SVF. Tablet (a) PAA, (b) CL, (c) CH, (d) Mix 1, (e) Mix 2, (f) Mix 3, (g) Mix 4, (h) Mix 5, (i) Mix 6.

gelling were noted. This resilience underlines the robust nature of the complex formed between PAA and CHN, affirming its capability to preserve the tablet structure throughout the dissolution process. This finding is particularly significant as it highlights the potential of PECs in enhancing the stability and efficacy of pharmaceutical tablet formulations under physiological conditions.

#### Confirmation of PEC interactions

The utilization of FT-IR spectroscopy to analyze the interaction between PAA and CHN in PEC tablet mixes offers insights into the chemical dynamics of these polyelectrolyte polymers. The formation of cross-linking networks, indicative of complex formation, involves temporary covalent bonds between the ionized polymers. Analyzing the IR spectra of each PEC tablet mix (Mixes 1–6) alongside the controls (PAA, CL, and CH) can reveal potential electrostatic interactions characteristic of polyelectrolyte complexes. Four specific IR absorption peaks are instrumental in indicating successful chemical interactions between

PAA and CHN. According to studies by He et al. (2018) and Radwan et al. (2021), a peak around 1500 cm<sup>-1</sup> corresponds to the amide group (NH<sub>2</sub>) in CHN, suggesting interaction at this site (He et al., 2018; Radwan et al., 2021). Additionally, Radwan et al. (2021) observed the broadening of the O–H and N–H peaks above 3000 cm<sup>-1</sup>, attributed to increased hydrogen bonding during polymer interaction (Laksanawati & Trisanti, 2019; Radwan et al., 2021). Furthermore, Liew et al. (2016) reported a decrease in the intensity of the C=O peak (1690–1710 cm<sup>-1</sup>) from PAA's carboxyl group, inferring interaction between the carboxylate anion (COO<sup>-</sup>) and CHN's cations (NH<sub>3</sub><sup>+</sup>) (Liew et al., 2016). Another indicator is the emergence of a new peak between 1630 and 1650 cm<sup>-1</sup>, associated with a different type of C=O stretching vibration, further suggesting network interaction (Laksanawati & Trisanti, 2019; Queiroz et al., 2014). The presence of these four characteristic peaks in the IR spectra of the PEC mix tablets, as depicted in Fig. 5, confirms the chemical interactions between PAA and CHN. When compared to the controls, these peaks not only confirm the occurrence of chemical interactions but also allow us to gauge the extent of PEC formation through the intensity of these peaks.

The IR spectra of all tablet formulations were analyzed after 8 h of swelling in SVF (pH 4.2), focusing specifically on the four characteristic peaks indicative of chemical interactions between PAA and CHN. The findings, summarized in Table 5, reveal a noteworthy trend: tablets with a higher proportion of CHN (Mixes 2, 3, 5, and 6) exhibit markedly less chemical interaction compared to those with a higher content of PAA (Mixes 1 and 4). This observation is in line with the gel fraction results in SVF, as presented in Fig. 4 (Section 'Crosslinking of PEC'), which demonstrates that Mixes 1 and 4 maintain higher GF values after 24 h of swelling compared to the other formulations. Furthermore, the FT-IR spectra for tablet mixes containing CL and CH displayed similar patterns, suggesting no significant difference in chemical interaction between the two chitosan variants. This similarity leads us to infer that the molecular weight of chitosan (CL versus CH) does not substantially affect the chemical interaction within the PEC matrix under these conditions. Consequently, our findings suggest that tablets with a higher PAA content may offer enhanced performance in vaginal pH environments, as they maintain significant chemical interactions even after prolonged exposure to SVF. This highlights the potential of PAA-rich formulations for sustained efficacy in vaginal drug delivery applications.

#### Swelling characteristics

The swelling behavior of polymers is intrinsically linked to their mucoadhesive capabilities, a crucial aspect of effective drug delivery

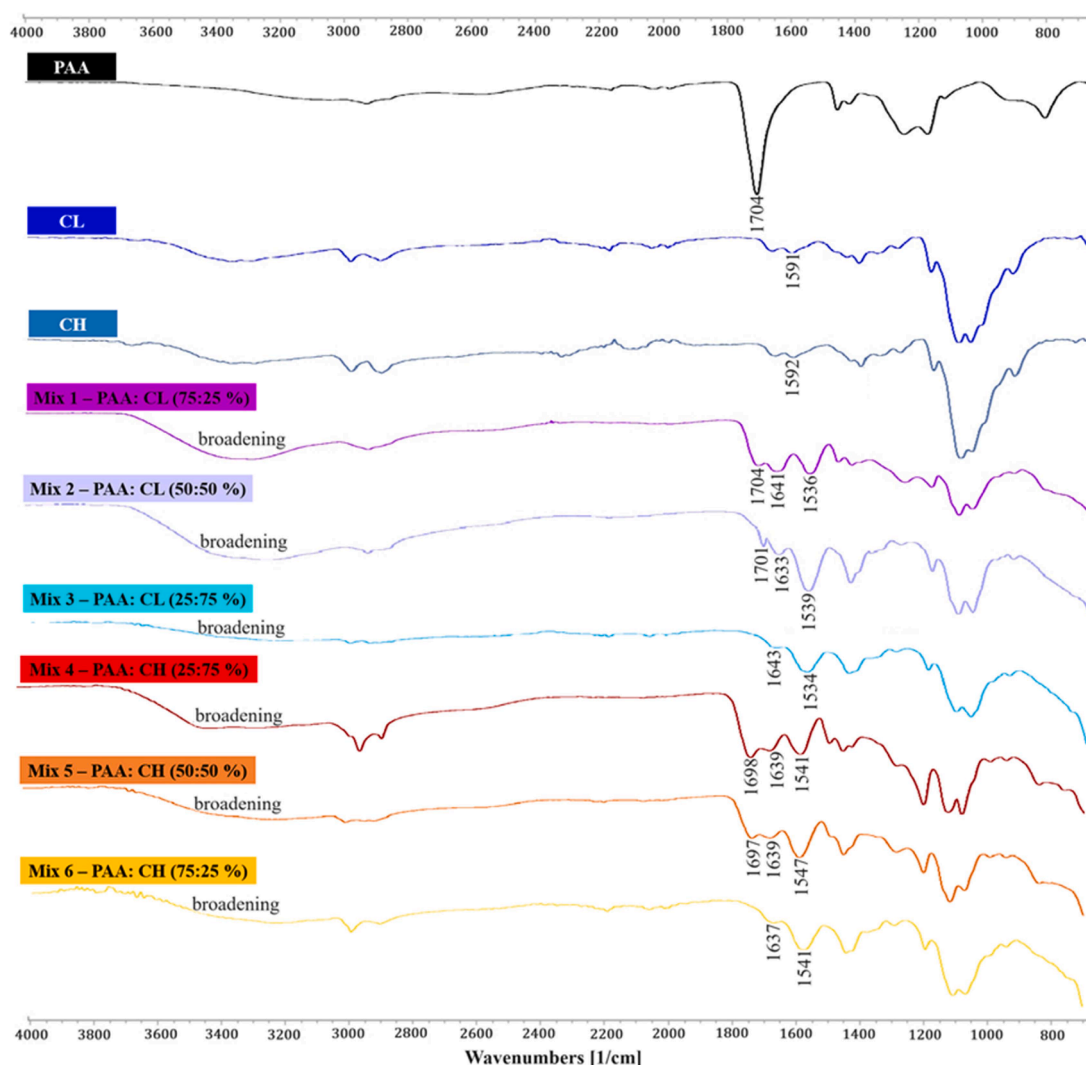


Fig. 5. The FT-IR spectra of all the tablets after 30 min of swelling in SVF (pH 4.2). It shows the presence of the 4 characteristic peaks to confirm the chemical interactions between PAA and CHN.

Table 5

Presence and intensity of the IR characteristic peaks, in all PEC mix tablets at 8 h of swelling in SVF (pH 4.2).

IR characteristic bands	Mix 1	Mix 2	Mix 3	Mix 4	Mix 5	Mix 6
Peaks at 1500–1590 $\text{cm}^{-1}$	√√	√	√	√	√	√
Broadening of peak >3000 $\text{cm}^{-1}$	√√√√√	√	√	√√√√√	√	√
C=O peak at 1700 $\text{cm}^{-1}$	-	√	√	-	√	√
Peaks at 1630–1650 $\text{cm}^{-1}$	√	-	-	√√	-	-

\*Note: The number of √ indicates the intensity of the peaks observed.

systems targeting the vaginal mucosa. Rapid and optimal hydration of mucoadhesive polymers is essential for successful adhesion in the aqueous environment of the vaginal tract (Abidin et al., 2023). However, excessive hydration might diminish adhesion efficiency due to competitive interactions between water molecules and the active sites on mucin chains, which otherwise would bind to the polymer’s functional groups (Abidin et al., 2023). To evaluate this dynamic, we conducted a swelling study to assess the hydration rate and potential adhesive properties of tablets from each PEC mix batch. The study

involved measuring the water uptake (WU) and swelling index (SI) of the tablets over predetermined time intervals, with the results presented in Fig. 6. According to Fig. 6A, a consistent increase in WU over time was observed for all tablet formulations. A notable disparity was evident between the control and PEC mix tablets, particularly in the early stages. Within the first 15 min, PEC mix tablets exhibited a significantly higher rate of WU, underscoring the enhanced hydration capacity conferred by the PEC. This trend continued for up to 48 h, with the PEC mix tablets showing a steep, ongoing increase in WU—indicative of their sustained structural integrity and water absorption capability. In contrast, the control tablets either dissolved or reached their maximum swelling capacity. Among the PEC mix batches, Mixes 2 and 5, both having a 50:50 polymer ratio, initially displayed a marginally higher WU rate. Over time, however, the PEC mixes involving PAA and CL (Mixes 1, 2, and 3) demonstrated a more consistent increment in WU, whereas those with CH (Mixes 4, 5, and 6) exhibited somewhat erratic hydration patterns. This differentiation suggests that the specific polymer combinations within the PEC mix influence the swelling and hydration behaviors, which are critical for their potential application in mucoadhesive vaginal drug delivery systems.

WU is a crucial measure of the moisture content in a tablet, directly influencing its degree of swelling at specific time intervals. This parameter effectively delineates the swelling efficiency, as reflected by the SI of different tablet batches over time (Fig. 6). Results depicted in



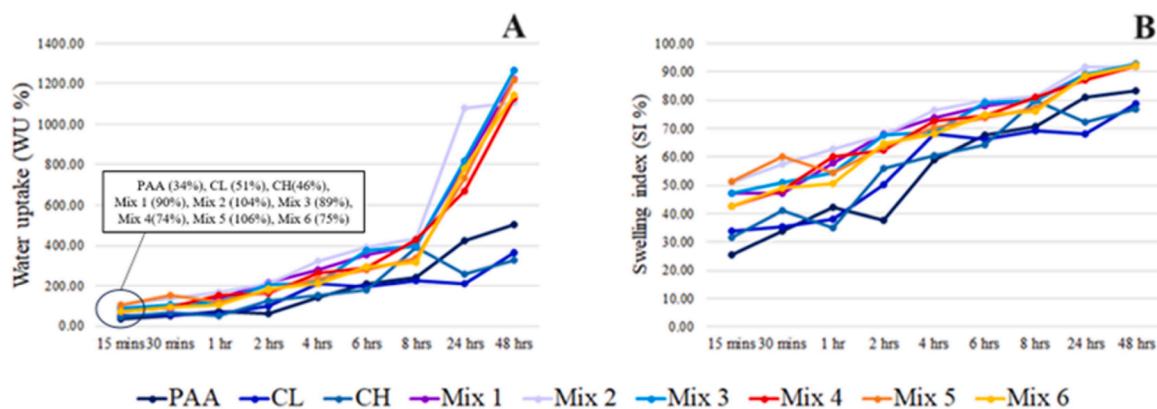


Fig. 6. Evaluation of the (a) water uptake (WU%) and (b) swelling index (SI%) of tablets from each PEC mix compared to the controls, at different time intervals in SVF (pH 4.2).

Fig. 6B, demonstrate that the PEC mix batch tablets exhibit exceptional water absorption capabilities, approaching nearly 100 % water content. The high SI values observed in the PEC mix batches underscore their superior swelling efficiency. This capacity to absorb and retain significant amounts of water suggests that these formulations are highly efficient in swelling, which is a desirable trait for mucoadhesive drug delivery systems. Such high swelling efficiency not only reflects the physical robustness of the tablets in an aqueous environment but also has implications for their sustained drug release and adhesion properties.

The enhanced swelling efficiency observed in the PEC mix batches not only confirms the effectiveness of the PEC formulation but also suggests potential improvements in the tablets' mucoadhesive properties (Abidin et al., 2023). Among the various formulations, Mix 3 stands out, demonstrating the highest swelling index and, thus, the most efficient swelling behavior. The ability of these tablets to rapidly and significantly swell suggests they could offer improved contact and adhesion to mucosal surfaces, a key factor for effective drug delivery (El-Enin et al., 2020).

#### Scanning electron microscopy (SEM) analysis

An examination of the surface morphology of the dry tablets, as depicted in Fig. 7, reveals a notable presence of larger pores and, in some instances, a flaky texture. Particularly, mixes 2 and 4 (Fig. 7V and VIII, respectively), which contain a 50:50 ratio of PAA and chitosan, exhibit a less porous texture. This observation suggests that the 50:50 ratio effectively reduces porosity, presumably by filling in the gaps within the powder matrix during the tablet pressing process.

The impact of swelling on tablet morphology is evident in Fig. 8. Post-swelling, the tablets display a markedly smoother surface with significantly reduced porosity. The micrographs of swollen PEC mix tablets (Fig. 8d–i) show this transformation, with surfaces becoming smoother and pores ranging from markedly smaller to almost non-existent in some formulations. According to Notario-Pérez et al. (2018), polymers with robust swelling capabilities tend to result in a narrow pore distribution, an attribute observable in most of the PEC mix tablets. This feature likely contributes to the tablets' structural integrity and their ability to sustain drug release.

Furthermore, the surface morphology of the swollen PEC mix tablets

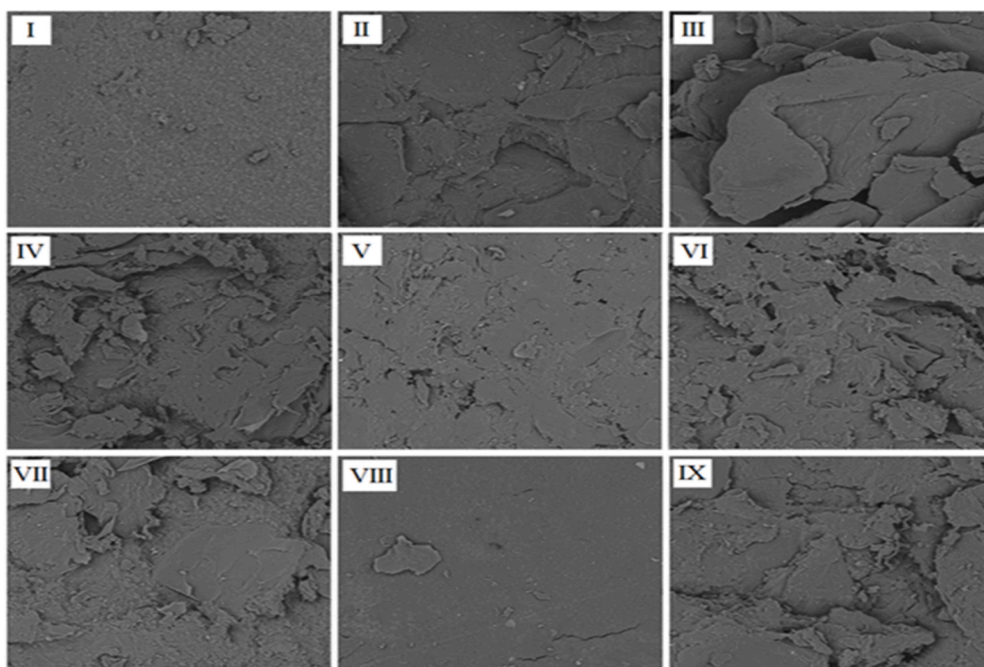
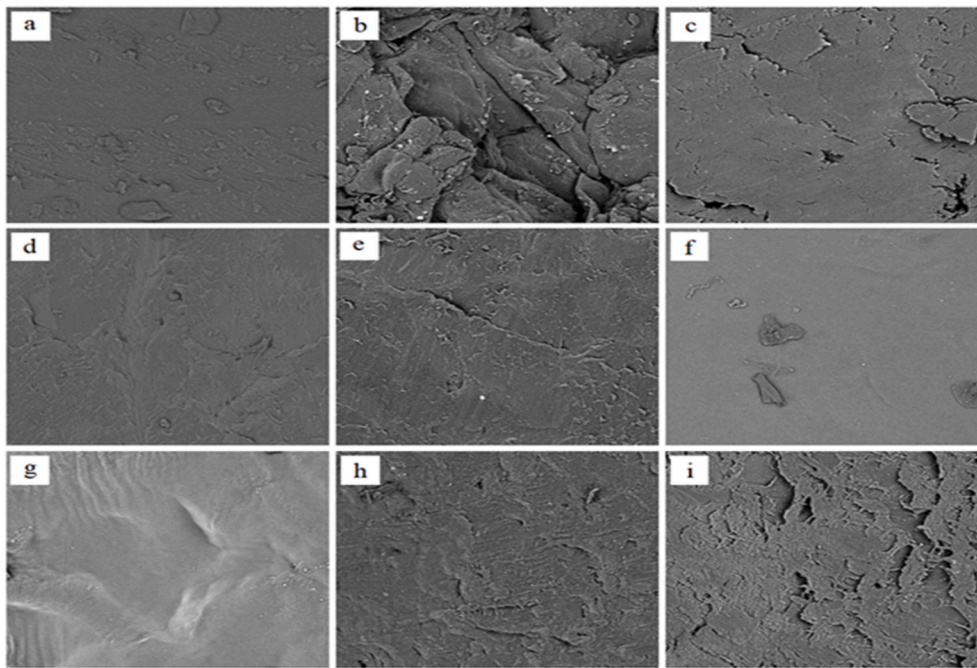


Fig. 7. SEM micrographs of tablets (I) PAA, (II) CL, (III) CH, (IV) Mix 1, (V) Mix 2, (VI) Mix 3, (VII) Mix 4, (VIII) Mix 5 and (IX) Mix 6, before swelling at 1000 × magnification.



**Fig. 8.** SEM micrographs of tablets (a) PAA, (b) CL, (c) CH, (d) Mix 1, (e) Mix 2, (f) Mix 3, (g) Mix 4, (h) Mix 5 and (i) Mix 6, after 24 h of swelling in SVF (pH 4.2) at 1000 × magnification.

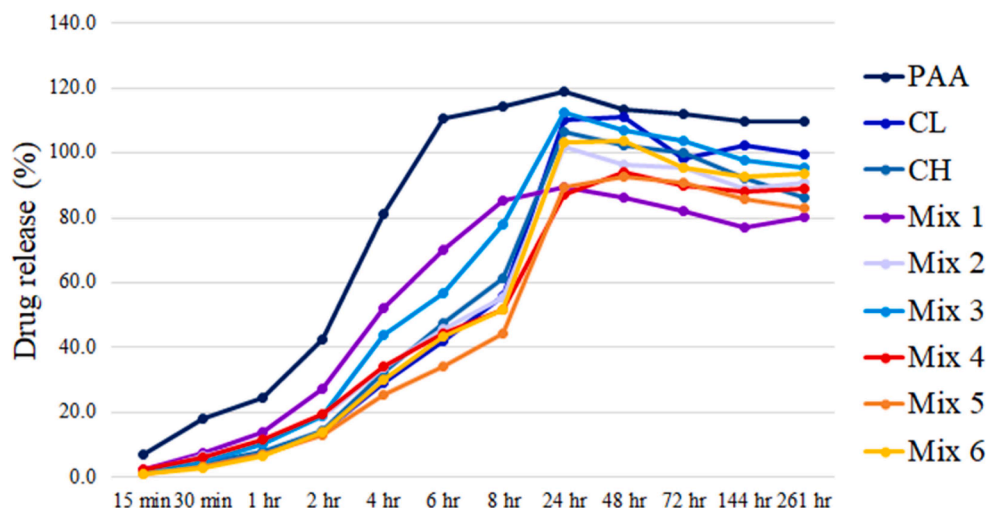
correlates well with the previously reported swelling index percentages. Tablets from Mix 1 (8d), Mix 3 (8f), and Mix 4 (8g) exhibit smoother surfaces, reflecting higher swelling efficiencies as indicated by their elevated SI percentages. This contrasts with Mixes 2 (8e), 5 (8h), and 6 (8i), which demonstrate less smoothness, aligning with their respective swelling behaviors. These morphological characteristics offer valuable insights into the formulation's efficacy, particularly in terms of swelling behavior and drug release profiles.

#### Dissolution study

In this study, 5FU was employed as a model drug to assess the efficacy of various PEC formulations. According to Fig. 9, all PEC mix tablets demonstrated a consistent and gradual increase in drug release under sink conditions. Notably, no initial burst release was observed within the first 30 min for any of the PEC mix tablets. The majority of the PEC mixes sustained drug release, with less than 60 % being released

within the initial 8 h of dissolution. Exceptions were Mix 1 and Mix 3, which exhibited around 80 % drug release during this period. However, this release rate was still considered sustained, particularly when compared to the PAA tablets.

Some formulations, including the controls (PAA and CH), reached their maximum drug release at 24 h, with PAA and CH releasing 119 % (SD 0.54) and 107 % (SD 8.31), respectively. Mix 1, Mix 3, and Mix 6 showed drug releases of 89 % (SD 4.35), 112 % (SD 1.02), and 103 % (SD 3.67), respectively. CL, Mix 2, Mix 4, and Mix 5 reached their maximum drug release at 48 h, with percentages of 111 % (SD 12.23), 96 % (SD 0.822), 94 % (SD 5.94), and 93 % (SD 0.46), respectively. Among the PEC mix batches, Mixes 2, 3, and 6 achieved the optimal drug release of 100 % at 24 h. Notably, Mix 3, with a 25:75 ratio of PAA to CL, released drugs slightly earlier than Mixes 2 and 6, reaching 50 % drug release within the first 6 h. Mixes 2 and 6, despite having different compositions, exhibited similar drug release rates, sustaining half of the drug concentration until 8 h and achieving maximum release at 24 h. This



**Fig. 9.** Tablet's drug release rate (%) of each batch, in sink conditions and maintained at  $37 \pm 1$  °C in SVF (pH 4.2) with 100 rpm.

pattern aligns with the FT-IR findings, where the reduction in chemical interactions after 8 h may lead to decreased entanglements and increased drug release.

While the control groups showed higher drug release rates than the PEC mixes, they did not meet the objectives of this research. PAA demonstrated an early onset of drug release, reaching 50 % within the first 3 h and 100 % at 6 h. In contrast, CL and CH did not show such early onset and maintained a sustained release rate comparable to the PEC mixes. However, their lack of tablet structural stability makes them less suitable, as the drug could be prematurely flushed away due to the vaginal self-cleansing action. The PEC mixes, in comparison, are expected to maintain tablet integrity during drug dissolution in the cervix, thus aligning more closely with the desired outcomes of sustained and

efficient drug delivery.

*Mucoadhesive study*

This study also aimed to assess the mucoadhesive strength of various PEC mix tablet formulations. As illustrated in Fig. 10, it was noted that the tablets from the PEC mixes adhered to the vaginal mucosa well beyond the 24 h mark. Specifically, tablets from Mixes 1, 3, and 5 demonstrated extended adhesion, surpassing 48 h. However, due to the lack of consistent patterns across these batches, it is challenging to conclusively determine which PEC mix exhibits superior mucoadhesive properties from this finding.

Nevertheless, when compared to the control formulations, the PEC

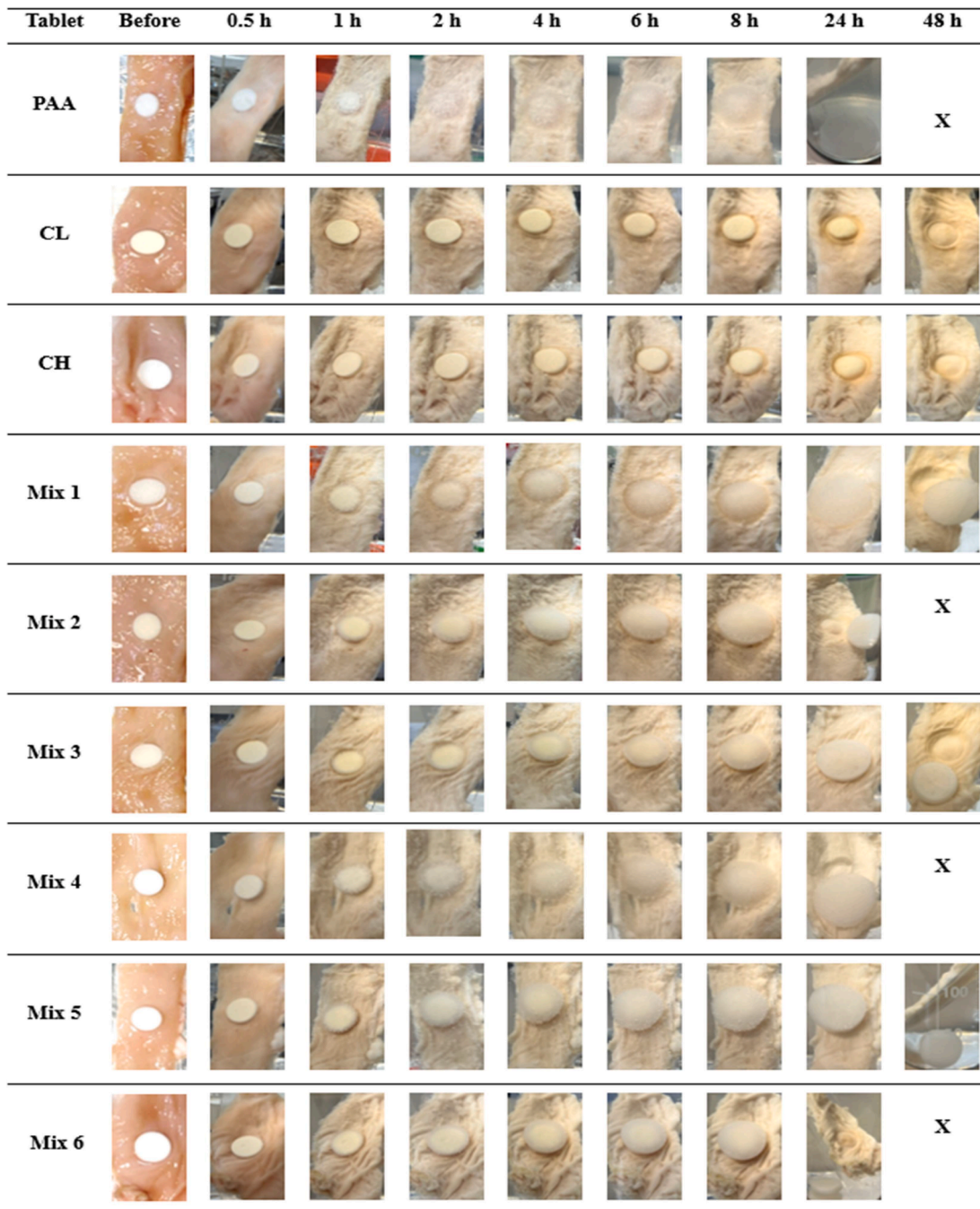


Fig. 10. Mucoadhesive ability of tablet from each batch over time.



mixes displayed noticeable improvements. The PAA tablets, for instance, adhered to the cervical tissue but detached within the first 24 h. In contrast, Mix 1, containing 75 % PAA and 25 % CL, significantly enhanced adhesion, maintaining contact for up to 48 h. This improvement was not mirrored in Mix 4, which combined PAA with CH in the same ratio. Interestingly, the control tablets of CL and CH showed complete adhesion until they fully dissolved at 48 h. While this could be seen as advantageous, it poses a potential drawback due to the self-cleansing mechanism of the cervix, which could remove the dissolved drug, potentially leading to suboptimal dosing.

Considering the ability of tablets from all PEC mix batches to preserve structural integrity during adhesion, it is plausible to infer that PECs can enhance dosage efficiency and potentially increase the bioavailability of the drug at the target site in chitosan-based formulations. This suggests that PEC incorporation into these formulations can effectively balance the need for sustained adhesion with the requirement for maintaining drug dosage efficacy.

#### Forced detachment test

Additionally, a forced detachment test was conducted by recording the force (in Newtons, N) required to separate the vaginal tablet that has adhered to a vaginal mucosa, Fig. 11. This finding to some extent can help demonstrate the strength of the adhesion of the PEC in different tablet batches. However, about comparing the tablets of the PEC mix batches, the result is inconclusive. Therefore, from this finding, it is safe to say that the mucoadhesive strength of the tablets does not depend on the PEC mix. For example, Mix 1 was reported to require the least force for detachment as compared to the other tablets. However, in the adhesion time test and *ex vivo* drug dissolution, Mix 1 tablet adhered to the vaginal mucosa for 48 h and had the highest percentage of drug released compared to the others. This observation of the Mix 1 tablet can be due to the carboxylic groups (–COOH) in the acrylic acid backbone since Mix 1 has a high content of PAA (75 %). The –COOH in PAA is said to be responsible for the strong mucoadhesion observed as stated by Nafee et al. (2004) (Nafee et al., 2004). Additionally, due to its strong association with water molecules, it increases the ability of PAA to swell (Elliott et al., 2004) and cross-linked inner structure making them suitable for a controlled drug delivery system (Smart, 2005).

Comparing CL and CH mixes, the force required increases as the amount of CL decreases in the formulation. This was conversely observed in the CH mixes, which decreased as the amount of CH increased in the formulation. This finding contradicts the findings by Sun et al. (2009) that stated that low molecular weight CS are less useful for preparing mucoadhesive formulations compared to high molecular weight CS which has excellent mucoadhesive properties (Sun et al., 2009). However, this cannot be equally compared as the findings by Sun et al. (2009) are based on chitosan-only formulations and not mixed with PAA.

#### Conclusion

In this research, we successfully compared various vaginal tablet formulations derived from the spontaneous polyelectrolyte complex (PEC) formation between chitosan (CHN) and poly(acrylic acid) (PAA). By varying polymer ratios (w/w) and employing different molecular weights of CHN (low molecular weight chitosan, CL, and high molecular weight chitosan, CH), distinct batches were formulated. The formation of PECs within these tablets, resulting from spontaneous chemical interactions between CHN and PAA, was initially indicated by gel fraction (GF) evaluations and subsequently corroborated by FT-IR analysis.

Our findings reveal that PEC strength diminishes over time in formulations with a higher proportion of CHN, a necessary aspect for facilitating drug release. Importantly, despite this reduction in PEC strength, all PEC mix tablets demonstrated remarkable structural integrity during dissolution, thus preventing any formulation loss during drug release. Additionally, PEC incorporation was shown to enhance

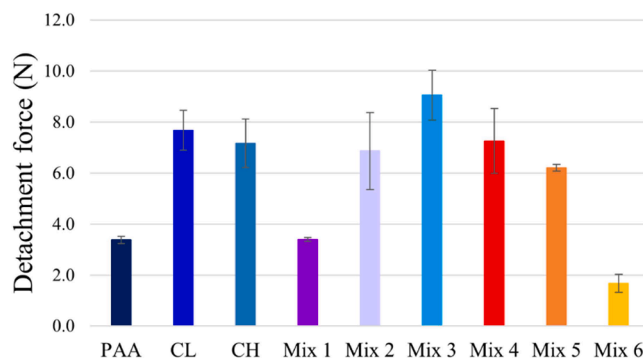


Fig. 11. The force (N) required to detach tablets from each batch from the vaginal mucosa.

several mechanical properties of the tablets, including flowability, uniformity, hardness, friability, and swelling efficiency. The capacity of PECs to absorb minimal moisture and exhibit a high swelling index was instrumental in maintaining structural stability and enabling sustained drug release. The potential of these PEC mix tablets for vaginal drug delivery was further supported by *ex vivo* mucoadhesion tests. These findings validate the suitability of the formulated PEC mix tablets as effective candidates for vaginal drug delivery systems, highlighting the crucial role of PECs in optimizing tablet properties for enhanced therapeutic efficacy.

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#### CRediT authorship contribution statement

**Ismin Zainol Abidin:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Emma J. Murphy:** Writing – review & editing, Supervision, Resources. **Gustavo W. Fehrenbach:** Investigation. **Noel Gately:** Writing – review & editing, Supervision. **Ian Major:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Data availability

Data will be made available on request.

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