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Time-controlled release by the incorporation of superdisintegrants within the coat of zein dry coated tablets

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ABSTRACT

The aim of this work was to develop zein-based press coated tablets for delayed, time-controlled drug release. Press coated tablets containing dextrates and chlorpheniramine maleate (BCS class 1 drug) in the core, and zein and either NaCl, sodium starch glycolate (SSG) or crospovidone (XPVP) in the coat were produced. Results show that tablets containing zein and NaCl in the coating could not release nearly any drug over 8 h. On the contrary, when SSG and XPVP were incorporated at a level of 8 % in the coating, a delayed drug release pattern was obtained, characterised by a lag-time of 3 h, followed by a burst of >80 % drug release over 6–7 h. Drug release was dependent on the concentration of SSG and XPVP in the formulations. Images of the tablets showed that during the lag-time the dosage forms did not change shape, although they started to swell. After this time, tablets gradually deformed and eventually ruptured. The lag-time is due to the time needed for the water to diffuse in, for the drug to dissolve and for the coating to become sufficiently permeable. The addition of the hydrophilic and swellable superdisintegrants SSG and XPVP to zein shifted the hydrophilic/hydrophobic balance of the coatings to higher hydrophilicity, thus enabling rapid hydration and drug release after the lag-time. This study demonstrates that zein-based macroscopic drug delivery systems can be tuned to tailor drug release to specific needs, i.e. delayed release in this case.

1. Introduction

Zein is the primary storage protein of corn. In the last few years zein has been broadly explored as a biomaterial for drug delivery applications. Besides being used for the fabrication of nanoparticles, microparticles and films, zein has been investigated as release modifier in macroscopic drug delivery devices, including tablets, capsules and hot-melted extruded dosage forms [1–9]. When it is incorporated as an excipient in macroscopic drug delivery systems, zein behaves as a matrix-former, thus prolonging the release of the drug. Yet, zein cannot be classified neither as a purely hydrophilic, swellable polymer, like HPMC, nor as an insoluble, non-swellable polymer, like ethyl cellulose and polyvinyl acetate [2]. Owing to the presence of both hydrophilic and hydrophobic domains within its structure, zein hydrates and slowly swells similarly to a hydrophilic polymer, yet it is insoluble and not-erodible as typical of more hydrophobic polymers. Moreover, zein insoluble matrices swell without gelling, forming hydrated plugs that appear rubbery and tough in nature [7,8].

Guo et al. have studied the release of 5-flourouracil from zein press coated tablets. Upon incorporation of microcrystalline cellulose (MCC) or starch in zein press-coatings, a sustained and constant release from the tablets could be obtained over the 12 h of the dissolution tests. To explain the mechanism of release, authors described the formation of an apex, which was generated by the internal force resulting from the dissolution of the core. It is through this apex that the drug could diffuse out [10]. In another study, zein was used as coating polymer in dry coated gastro-retentive floating tablets containing captopril both in the coat and in the core. The tablets could float rapidly (i.e. within 10 s) owing to the presence of gassing agents in the core and could provide sustained release over a period of 12 h. The formation of an apex was described also in this article [11].

Carboxymethyl zein, a chemically modified version of zein, has been previously used as an enteric, i.e. pH-controlled, polymer for delayed drug release from tablets [12]. Yet, to the best of our knowledge, native zein has never been investigated as a polymer for delayed release in tablets. We aimed in this work to prepare zein press coated tablets

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Table 1
Compositions and abbreviations of the tablet formulations.

Formulation	Core compositions (% w/w)			Coat compositions (%w/w)				
	Diluent	Drug	Lubricant	Polymer	Co-excipient			Lubricant
	Dextrates	Chlorpheniramine maleate	Mg St.	Zein	SSG	XPVP	NaCl	Mg St.
Uncoated cores	89	10	1	–	–	–	–	–
Zein	89	10	1	99	–	–	–	1
Zein_5%SSG	89	10	1	94	5	–	–	1
Zein_8%SSG	89	10	1	91	8	–	–	1
Zein_10%SSG	89	10	1	89	10	–	–	1
Zein_5%XPVP	89	10	1	94	–	5	–	1
Zein_8%XPVP	89	10	1	91	–	8	–	1
Zein_10%XPVP	89	10	1	89	–	10	–	1
Zein_8%NaCl	89	10	1	91	–	–	8	1
Zein_10%NaCl	89	10	1	89	–	–	10	1

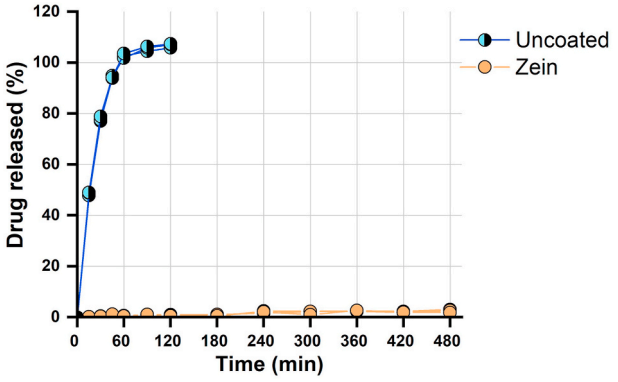


Fig. 1. Drug release from uncoated tablet cores and from tablets containing pure zein in the coating. Three replicates for each formulation are presented.

containing superdisintegrants in the coat, and highly soluble drug-containing cores that could provide delayed time-controlled release.

Zein hydrated matrices have been described as rubbery in nature [2] and both zein dry coatings and matrices can substantially deform upon swelling, yet without easily rupturing (e.g. the apex formation) [10,11,13]. Owing to the robustness of zein matrices, we hypothesised that upon incorporation of highly swellable superdisintegrant excipients within zein press coated tablets, a highly stretchable matrix system could be formed. The swelling of the coat could also be sustained by the dissolution of the core components of the tablet, which would generate hydrostatic pressure against the coat and thus further swelling force. Drug release from such system is hypothesised to be rapid, yet the time needed for the entire hydration of both coating and core might delay the onset of swelling and retard the rapid drug release. Thus, the type of release of such system could be delayed after an initial lag-time. To test this hypothesis in our work, we prepared zein press coated tablets containing zein and 0, 5, 8 and 10 % of either sodium starch glycolate (SSG), crospovidone (XPVP) or sodium chloride (NaCl) in the coat. NaCl being soluble but not swellable was used as control. Cores were made of soluble dextrates (≈95 % glucose [14]) and chlorpheniramine maleate (BCS class 1 model compound [15], solubility in water: 576.7 ± 16.2 mg/mL [16]). Drug release and swelling of the developed tablets were monitored over 8 h.

Guo et al. obtained prolonged drug release from the incorporation of moderately swelling excipients (i.e. MCC and starch) into zein press coatings [10]. In the present study we described instead how the incorporation of low amount of highly swellable superdisintegrants in the coat can be used to obtain delayed, time-controlled drug release from zein press coated tablets.

2. Materials and methods

2.1. Materials

Zein (Z3625) was purchased from Sigma-Aldrich (Germany). The superdisintegrant sodium starch glycolate (SSG - Vivastar®) and the diluent dextrates (EMDEX®) were received as sample gifts from JRS Pharma (Germany). Crospovidone (XPVP-Kollidon® CL) was kindly donated form BASF (Germany). NaCl was bought from Gainland Chemical Company (GCC-UK). The drug chlorpheniramine maleate was kindly donated by JMP (Jordan). Magnesium stearate was purchased from Laboratory Rasayan (India).

2.2. Methods

2.2.1. Tablets preparation

Table 1 describes the compositions and abbreviations of all formulations. Blends of the core and coat components were prepared separately by weighing and manually mixing the respective ingredients in 115 mL glass vials for 10 min, followed by lubricant addition and further mixing for 2 min. Tablet cores of 500 mg were compressed at 187 MPa for 20 s using a hydraulic press (Riken Seiki, Ojiya, Japan), equipped with 10 mm flat faced punches. To apply the coating, 175 mg (50 %) of the coating powder was placed at the bottom of a 13 mm die. The preformed core was then positioned over the powder inside the die, centred in the middle of the mould by using a PLA 3D-printed chute. Then the core was covered with further 175 mg (50 %) of coating powder. Finally, press coated tablets were compressed at 185 MPa for 20 s.

2.2.2. Tablets tensile strength

Tablets thickness and hardness were measured for three tablets per batch; tensile strength (TS) was also calculated based on conventional and previously established methods described in details in Refs. [17–19].

2.2.3. Drug release studies

The release of chlorpheniramine maleate from the tablets was measured in a paddle apparatus (Pharma Test PTW 2, Hainburg, Germany) operating at 50 rpm and at a temperature of 37 °C. The volume of the medium was fixed at 900 mL; all tests were conducted in phosphate buffer (50 mM) pH 6.8. 10 mL samples were withdrawn at various time intervals and then filtered using 0.45 μm PTFE filters. Drug concentration was determined by UV spectrophotometer (Milton Roy 601, Rochester, USA) at a wavelength of 261 nm using an appropriate standard curve as reference. Three tablets per formulation were tested.

2.2.4. Swelling studies

For the formulations zein_8%SSG and zein_8%XPVP the test performed in the dissolution apparatus (described in 2.2.3) was repeated using a new set of tablets. At the various time points during the

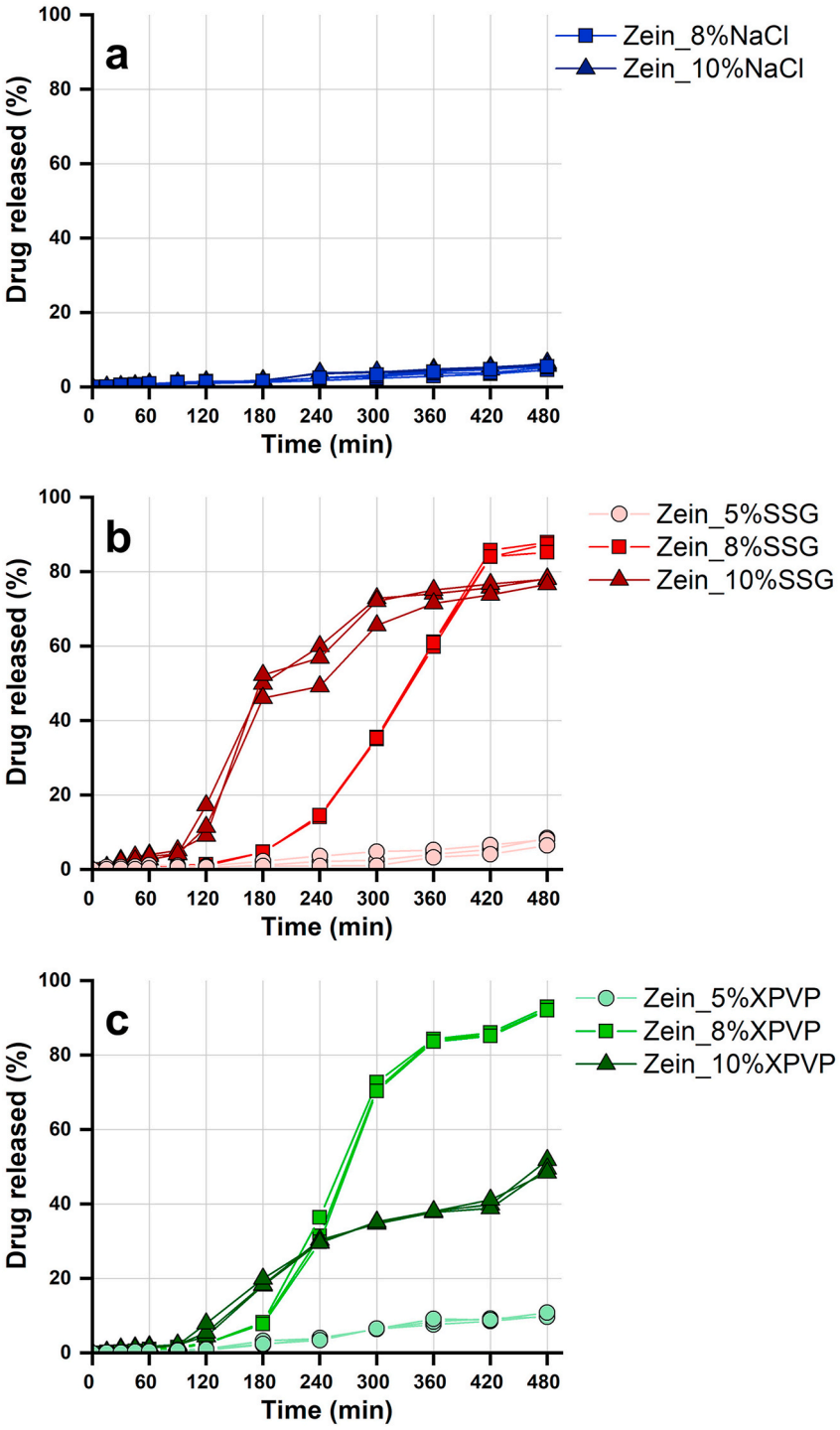


Fig. 2. Drug release from tablets containing zein and either NaCl (a), SSG (b), or XPVP (c) in the coating. Three replicates for each formulation are presented.

operation of the apparatus, tablets were rapidly scooped out of the media. Then, using tweezers, the tablets were carefully placed at the bottom of a 15 cm (diameter) Petri dish that had been previously filled with 300 mL phosphate buffer (50 mM) pH 6.8. Pictures of the morphological appearance of the tablets were taken using a USB microscope (Plugable 250 × Digital USB Microscope, USA) positioned over the tablets and connected to a computer. Immediately after the images were taken, tablets were returned to the operating paddle apparatus. Images of the dry tablets were also taken before the experiment started. Three tablets per formulation were tested.

3. Results

Preliminary studies were conducted to define the appropriate coating weight of the tablets (shown separately in the "preliminary tests" file). 350 mg coats were more homogeneous than 250 and 300 mg coats. As a result of their greater coating thickness and homogeneity, 350 mg coats were the only ones that did not to rupture during exposure of the tablets to aqueous fluids for 8 h in a disintegration apparatus. Owing to the greater homogeneity, thickness and reproducible performance, the coating weight of 350 mg was selected for the formulation of tablets in all further studies.

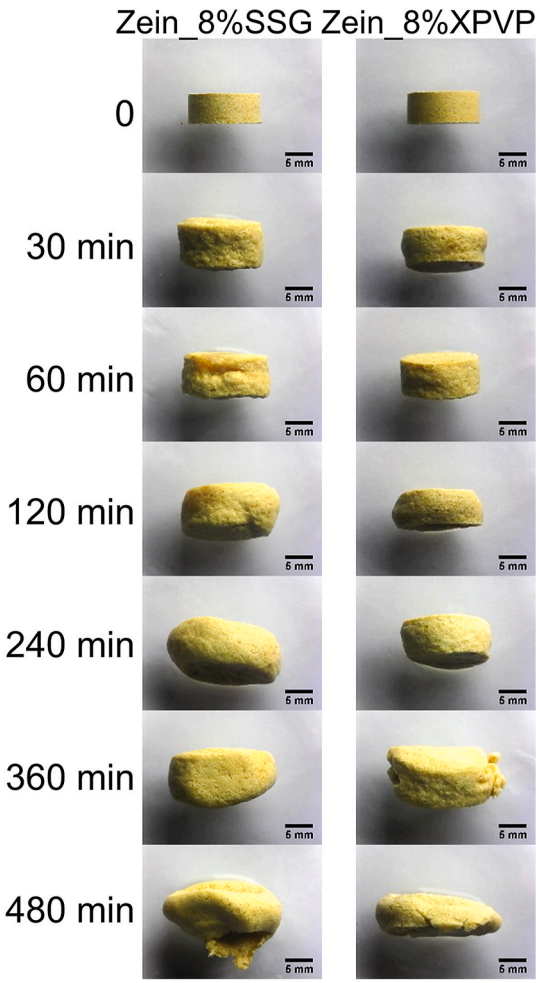


Fig. 3. Images of one of three tablets of zein_8%SSG and zein_8%XPVP at various time intervals, upon exposure to aqueous fluids in the dissolution apparatus.

All press coated tablets had tensile strength (TS) values between ≈3.4 and ≈4.5 MPa, as shown in Table S1, indicating that all formulations would be strong enough to withstand handling [20,21]. Fig. 1 shows that the drug release from uncoated tablets was very rapid, with more than 75 % drug released in 30 min. The fast release can be attributed to the high hydrophilicity and solubility of both tablet components, which are the filler dextrates [14] and the drug chlorpheniramine maleate [15]. On the contrary, encapsulation of these cores within the pure zein coatings completely hampered drug release.

Upon incorporation of 8 or 10 % NaCl in the zein coating, drug release remained slow with only ≈5 and ≈ 6 % drug release, respectively, over the 8 h of the test (Fig. 2a). On the contrary, the incorporation of both SSG (Fig. 2b) and XPVP (Fig. 2c) in the coat led to substantial changes of the drug release patterns.

Fig. 2b indicates that drug release from the formulation zein_5%SSG was still rather slow. The formulation zein_8%SSG provided <5 % drug release in the first 180 min and rapid drug release thereafter (≈85 % drug released within 420 min). At 10 % SSG the lag-time was shorter than at 8 % SSG. Moreover, at 10 % SSG drug release nearly plateaued at ≈75 % after 360 min. Fig. 2c reveals that also in the case of 8 % XPVP a delayed time-controlled release with a lag-time of 180 min hours was obtained. The formulation containing 5 % XPVP could yield only very slow release. The formulation zein_10%XPVP showed a peculiar behaviour, characterised by 60–90 min lag-time, followed by a moderate and declining drug release pattern thereafter, and only ≈50 % drug release over the 8 h of the test duration. Overall, both zein_8%SSG and zein_8%XPVP could provide delayed release after a lag-time of 180 min. The drug burst after the lag-time appeared slightly more rapid for 8 % XPVP than SSG. To evaluate the reproducibility of release of both these formulations, new batches were tested again on a different day. Figs. S1 and S2 reveals good reproducibility for both formulations.

Next, we took images of the tablets during the dissolution tests in order to capture morphological changes of the hydrating dosage forms that could explain the obtained drug release profiles. Side view images of one replicate per formulation are presented in Fig. 3, while the other two replicates are presented in Figs. S3 and S4. Top views of the same tablets at 480 min are shown in Fig. S5. Both zein_8%SSG and zein_8%XPVP could swell within the first 30 min of exposure to fluids. Zein_8%SSG maintained their rectangular contour for 120 min and then became more rounded and deformed in shape and eventually ruptured within

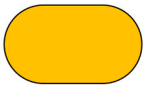
Time	0	0-120/180 min	120/180-360 min	360-480 min
Tablet morphology				
Drug release	0	Negligible (lag-time)	Fast	Fast
Description	-Water wets the tablet surface	-Gradual wicking of water into the system -Core components start to dissolve but do not diffuse out -Tablet integrity maintained, despite some swelling	-Drug diffuses out -Matrix deforms owing to the simultaneous swelling of the coat and emptying of the core	-Coat breaks promoting further drug release

Fig. 4. Descriptive summary of the series of events controlling drug release from zein_8%SSG and zein_8%XPVP.

480 min. Similarly, zein_8%XPVP gradually changed shape over time and ruptured at times >360 min. Both dosage forms seemed to deflate overtime, possibly due to the dissolution and release of the soluble glucose and drug that made up the cores.

4. Discussion

Fig. 1 showed that the incorporation of a coat of zein over a soluble drug core created a potent barrier to drug diffusion. This is in agreement with previous studies on matrix tablets and capsules where it was shown that, particularly at high zein loading within the formulations, the rate of drug release of highly soluble drugs was extremely low, due to both the slow diffusion of water in and of drug out of the devices [6,8,9]. Similarly, Bisharat et al. showed that the release of paracetamol from zein film-coated tablets was very slow (<20 % in 8 h) in absence of other co-excipients in the coat [22].

Fig. 2 revealed that the incorporation of ≤10 % of the soluble pore-former NaCl into the zein coat was not sufficient to speed up drug release. This result can be explained by the ability of zein to form strong matrices upon hydration. It was previously shown that, when lactose was added to zein matrix tablets at concentration ≤20 %, swelling and drug release were only very minimally affected compared to the pure zein matrices [6]. The reason for which pore-formers have little influence on the performance of zein-based tablets is that the pores formed on dissolution are rapidly filled-up by the continuous swelling and coalescence of hydrated zein, thus re-establishing a strong diffusion barrier. In other words, porosity effects brough about by soluble diluents are masked by the tendency of zein to close-up the matrix pores upon hydration [8,23].

Contrarily to NaCl, small concentrations of superdisintegrants (i.e. SSG and XPVP) had a substantial impact on drug release from the press coated tablets (Fig. 2b and c). Two are the reasons for which superdisintegrants, even at low concentration (i.e. 8 %), can substantially affect kinetics of hydration, swelling and drug release of macroscopic drug delivery devices: i) superdisintegrants are easily wetted, hydrophilic polymers that do not gel; thus these excipients are extremely efficient at wicking water into tablet matrices. ii) superdisintegrants expand massively upon hydration, which might result in breaking up of the tablets [24,25]. In the case of zein-based press coated tablets, the rubbery and elastic swollen matrices, impeded complete disintegration. Yet, the superdisintegrants were able to expand, loosen the coat and create voids to an extent that was sufficient to enhance drug release rates (Fig. 3). In summary, we hypothesise that the superdisintegrants shifted the hydrophilic/hydrophobic balance of the coats to greater hydrophilicity, which means that hydration, swelling and porosity developments were more rapid and thus, the diffusion barrier offered by the coating was substantially reduced compared to tablets made of pure zein coatings.

A descriptive summary of the morphological events leading to the time-controlled release obtained with the zein_8%SSG and zein_8% XPVP tablets is proposed in Fig. 4. Overall, it is believed that the 180 min of lag-time in drug release is due to time that it takes for the water to penetrate the coating barrier and to dissolve the core components. The rapid drug release thereafter is due to the simultaneous drug diffusion through the coat and the gradual deformation of the coat, which permeability becomes increasingly higher till the point of rupturing (at 360–480 min).

A consideration on the effect of the superdisintegrant concentration on drug release should be made (Fig. 2). Zein_5%SSG and zein_5%XPVP provided slower drug release compared to the 8 % superdisintegrants. It can be hypothesised that the lower is the concentration of the wicking and swelling agent (i.e. SSG and XPVP) in the coat, the lower are also the hydration and swelling and the higher is the robustness of the diffusion barrier offered by the zein coat. Zein_10%SSG and zein_10%XPVP showed shorter lag-time than the formulations with 8 % supedisintegrants, owing to the greater rates of wicking and swelling at higher superdisintegrant concentration. Yet, the drug release rate from zein_10%SSG and zein_10%XPVP was rapidly declining (particularly for XPVP). This suggests that after an initial release of the drug the diffusion barrier re-established itself (i.e. closing-up of the pores, leading to a plateau in drug release). It can be hypothesised that the relatively high concentration of superdisintegrants (10 %) was able to expand the zein matrix rapidly and to an extent that the superdisentegrant particles within the coat might have leached out of the coat, before all the drug was released. As the superdisintegrants was released from tablet, the zein coat would coalesce and shrink back, eventually reducing its own porosity [8,23].

In this study, differences in drug release are unlikely to be related to differences in TS across formulations. This is because i) values of TS are relatively high and similar for all formulations (i.e. between ≈3.4 and ≈4.5 MPa – Table S1); and ii) release from swellable matrices is usually minimally affected by small differences in hardness and porosity [7,8,26].

5. Conclusion

We showed in this paper that the incorporation of superdisintegrants within the coat of zein dry coated tablet can substantially alter the release properties of these systems. At a level of 8 % both SSG and XPVP could provide rapid drug release, after a lag-time of 180 min. Thus, zein/superdisintegrant press coated tablets are promising drug delivery devices for time-controlled delayed release. The findings of this work are also significant in broader terms: although zein-based systems hydrate, forming tough, rubbery and self-closing barriers which obstacle and often totally impede drug release, this should not detract from using zein as a biopolymer in drug delivery. Indeed, if the appropriate co-excipients are added to zein-based formulations, release properties can be easily improved and customised.

Future studies should provide insights towards the precise mechanisms by which co-excipients (e.g. superdisintegrants) alter the permeability of zein diffusion barriers. Changes of viscosity, porosity and mechanical properties of simple systems (e.g. thin compacts made of binary mixtures of zein and co-excipients) during exposure to fluids could be monitored over time. Such studies are the prelude for a deeper understanding of the behaviour of zein in pharmaceutical dosage forms, towards a more widespread use of this biopolymer as a pharmaceutical excipient.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2021.102716.

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