Gastro-resistant characteristics of GRAS-grade enteric coatings for pharmaceutical and nutraceutical products

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ABSTRACT

The use of naturally derived excipients to develop enteric coatings offers significant advantages over conventional synthetic polymers. Unlike synthetic polymers, they are biodegradable, relatively abundant, have no daily intake limits or restrictions on use for dietary and nutraceutical products. However, little information is available on their dissolution properties under different gastrointestinal conditions and in comparison to each other. This work investigated the gastric resistance properties of commercially available GRAS-based coating technologies. Three coating systems were evaluated:ethyl cellulose + carboxymethyl cellulose (EC-CMC), ethyl cellulose + sodium alginate (EC-Alg) and shellac + sodium alginate (Sh-Alg) combinations. The minimum coating levels were optimized to meet USP pharmacopeial criteria for delayed release formulations (<10% release after 2 h in pH 1.2 followed by >80% release after 45 min of pH change). Theophylline 150 mg tablets were coated with 6.5%, 7%, and 2.75% coating levels of formulations EC-CMC, EC-Alg and Sh-Alg, respectively. In vitro dissolution test revealed a fast release in pH 6.8 for ethyl cellulose based coatings: 78% value of 65 and 45 min for EC-CMC and EC-Alg respectively, while a prolonged drug release from Sh-Alg coating was observed in both pH 6.8 and 7.4 phosphate buffers. However, when more biologically relevant bicarbonate buffer was used, all coatings showed slower drug release. Disintegration test, carried out in both simulated gastric and intestinal fluid, confirmed good mechanical resistance of EC-CMC and EC-Alg coating, and revealed poor durability of the thinner Sh-Alg. Under elevated gastric pH conditions (pH 2, 3 and 4), EC-CMC and EC-Alg coatings were broken after 70, 30, 55 min and after 30, 15, 15 min, respectively, while Sh-Alg coated tablets demonstrated gastric resistance at all pH values. In conclusion, none of the GRAS-grade coatings fully complied with the different biological demands of delayed release coating systems.

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1. Introduction

Nutraceutics and dietary supplements are on major demand for both patients and healthcare advisers. In 2013 their global retail value was estimated at US $18.4 billion, and is predicted to grow 5% annually (Feldman, 2014). Amongst nutraceutics and dietary supplements, a considerable number of products are delivered in enteric-coated forms. Widely common examples are enzymes e.g. lactase, fish oils, omega fatty acids, probiotics, mineral salts such as sodium, potassium, magnesium, calcium and iron, as well as plant extracts (Thoma and Bechtold, 1992).

The leading technology for protecting nutraceutical products from the hostile gastric environment is via applying enteric coating as a protective layer. Although enteric coating started with natural products, the attention shifted to developing semi-synthetic and synthetic alternatives such as hypromellose derivatives and polymethacrylates (Nollenberger and Albers, 2013; Sakae and Hiroyasu, 2008). These polymers prevailed as coating films due to their good film-forming and protective properties (Liu et al., 2009).

The synthetic coatings allow tailoring drug release profile and site-specific drug delivery in the bowel; however, they are also subjected to certain restrictions. These coating systems are not biodegradable and have strict daily intake limits (Evonic, 2008; Shin-Etsu, 2010). Moreover, they are not approved for nutraceuticals and dietary supplements.

In the light of regulatory law, all additives must be approved as a food additive or GRAS-deemed. This has brought the attention back to GRAS-grade and naturally occurring enteric polymers which may exert gastric resistant properties. Indeed, a reliable GRAS-affirmed system can offer significant advantages. Unlike synthetic polymers, they are biodegradable, relatively abundant, and have no daily intake limits.

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Several formulation strategies have been proposed to fabricate an enteric coating system based on GRAS-rated materials. One strategy employed the use of cellulose derivatives. This comprised of an aqueous dispersion of water insoluble polymer ethyl cellulose (EC), and a pH-dependent pore former, sodium carboxymethyl cellulose (CMC) (Colorcon, 2013a). The combination is exemplified by a commercially available enteric coating system called Nutrateric®. The original formulation has been amended by increasing the CMC:EC ratio (from 15:85 to 25:75) to achieve faster decomposition of the coating upon hydration (Tan et al., 1999).

An alternative strategy was the replacement of CMC with a natural polysaccharide, sodium alginate (Fegely et al., 2010). The formulation comprised of water dispersion of EC and alginate salts in different ratios. The primary film former in this composition is EC, while alginate provides its pH dependent properties. The gastro-resistant barrier in the stomach is achieved due to free carboxylic groups in the alginate molecule that contribute to pH-dependent solubility. Above pH 3, alginate is ionised, solubilised and leaches from the film coating, creating pores through which the drug is released.

Another approach of achieving gastric resistant coating film was through rejuvenating the use of shellac resin which possesses gastric resistance and pH-dependent aqueous solubility. However, shellac applicability is limited due to its poor water solubility and compromised stability (Farag and Leopold, 2008). This can pose the probability of prolonged dissolution time of the ageing coated products. These drawbacks have been partially overcome by specialized processing (Limmatvapirat et al., 2004) and different chemical modifications of the raisin (Limmatvapirat et al., 2007). More recently, a new technology integrated the use of its watersoluble ammonium salt with sodium alginate. The latter is likely to regulate the dissolution pattern of shellac and reduce variability (VanNess, 2013).

Although these natural coating systems specifically designed for nutraceutics and dietary coatings have already been introduced to the market, there is limited literature information about their performance under different gastric conditions or in the comparison with one another. In this work, the gastric resistant properties of three commercially available GRAS-based technologies were assessed in phosphate as well as bicarbonate buffers. Disintegration test were carried out in 0.1 M HCl followed by simulated intestinal fluid. In order to determine acid resistance of coating, acid uptake test and dissolution test under elevated gastric conditions were also performed.

### 2. Materials and methods

#### 2.1. Materials

The model cores were prepared from following excipients: theophylline anhydrous (Acros organics, New Jersey, USA), directly compressible lactose monohydrate – Ludipress (BASF SE, Germany), polyvinylpyrrolidone K90 (Sigma–Aldrich Co., Ltd., Dorset, UK), microcrystalline cellulose (MMC) PH 101 (FMC Biopolymer, Belgium), crosscarmellose sodium SD–711 (FMC Biopolymer, Belgium) and magnesium stearate (Sigma–Aldrich Co., Ltd., Dorset, UK). Methocel grade E5 LV, Surelease® (ethylcellulose, 20 cP dispersion type B NF) and NS Enteric® (sodium carboxymethylcellulose) were donated by Colorcon Ltd., Inc., UK. Protect™ EN-RX (shellac) and Protect™ Clear SA (sodium alginate) were donated by Sensient Pharmaceutical Coatings Systems, US. Sodium alginate (grade 15–20 cps) was supplied by Sigma–Aldrich Co., Ltd. (Dorset, UK).

#### 2.2. Preparation of theophylline tablets

Theophylline tablets (150 mg) were used as a model core to explore the performance of applied coating systems. The final weight of the tablet was chosen to be 600 mg to reflect the typical bulky size of several dietary supplement products. The model drug, theophylline, was selected due to its small molecular weight and high aqueous solubility (Lentz et al., 2002), which allows scrutinising the quality of controlling in vitro drug release.

The model theophylline cores were prepared by wet granulation. Firstly, 250 g theophylline, 240 g lactose monohydrate, 10 g PVP grade K90, and distilled water (110 mL) were mixed and passed through 1 mm sieve granulator. Granules were dried in 60°C until no weight loss. Secondly, granules (500 g) were mixed with 310 g lactose monohydrate, 150 g MCC, 30 g Ac-Di-Sol and 10 g magnesium stearate. Afterwards, resultant mass was compressed using a Riva Minipress single punch tabletting machine (Riva, Argentina).

#### 2.3. Enteric coating of tablets

Formulations of enteric coatings used in this study are listed in Table 1. In order to enhance film adhesion and eliminate the potential interaction between the drug and the enteric polymers, the tablets were subcoated with 10% (w/w) Methocel E5 prior to enteric coating (2.0% weight gain). The coating solutions were

### Table 1 Formulations of three commercially available GRAS-based enteric coatings.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>EC-CMC</th>
<th>EC-Alg</th>
<th>Alg-Sh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology</td>
<td>Acrylic and extended release cellulose based polymers combination</td>
<td>Ethyl cellulose-alginate combination</td>
<td>Shellac-alginate combination</td>
</tr>
<tr>
<td>Components</td>
<td>Quantity (%)</td>
<td>Quantity (%)</td>
<td>Quantity (%)</td>
</tr>
<tr>
<td>Surelease</td>
<td>15</td>
<td>45.0</td>
<td>–</td>
</tr>
<tr>
<td>NS enteric</td>
<td>1.25</td>
<td>–</td>
<td>15.0</td>
</tr>
<tr>
<td>Protect Clear SA</td>
<td>–</td>
<td>–</td>
<td>12.5</td>
</tr>
<tr>
<td>Protect EN-TX</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>–</td>
<td>3.75</td>
<td>–</td>
</tr>
<tr>
<td>Distilled water</td>
<td>83.75</td>
<td>51.25</td>
<td>86.0</td>
</tr>
<tr>
<td>Weight gained (%)</td>
<td>6.0</td>
<td>6.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Coating level (mg/cm²)</td>
<td>15.5</td>
<td>16.8</td>
<td>18.1</td>
</tr>
</tbody>
</table>
applied using a Strea-1 bottom spray fluidised bed coater (GEA Pharma Systems AG, Aromatic-Fielder, Bubendorf, Switzerland).

2.3.1. EC-CMC coating
A coating solution was prepared in accordance with the manufacturer guidance (Colorcon, 2013b) with the exception of using more diluted coating suspension (5% w/w). The coating conditions were: inlet air temperature 58.5 °C, product temperature 53.8 °C, outlet air temperature 45.9 °C, atomizing pressure 0.25 bar and spray rate 1.6 mL/min. During coating process the resultant solution was continuously mixed using a magnetic stirrer.

2.3.2. EC-Alg coating
A coating composition was prepared following specifications in the US Patent 7,709,025 B2 (Fegely et al., 2010). Sodium alginate was dispersed in 10 mL of ethanol, then poured to distilled water and stirred for 45 min, until complete hydration. Later, ethyl cellulose dispersion – Surelease® was added to alginate solution, mixed for about 60 min and homogenised for 2 min afterwards. The coating conditions were: inlet air temperature 57.8 °C, product temperature 49 °C, outlet air temperature 45.7 °C, atomizing pressure 0.25 bar and spray rate 1.3 mL/min. The dispersion was gently stirred throughout the coating process.

2.3.3. Sh-Alg coating
Preparation of a coating solution was performed according to the manufacturer guidance (Sensient, 2012) except that a more dilute solution than the original formulation was employed as detailed in Table 1. The coating conditions were: inlet air temperature 57.5 °C, product temperature 53 °C, outlet air temperature 45.5 °C, atomizing pressure 0.25 bar and spray rate 1.5 mL/min. Throughout the coating process, the suspension was continuously mixed using a magnetic stirrer.

2.4. Morphology of the coating films
In order to assess coating appearance, digital images of the tablets were captured using Canon EOS Rebel SL1 model DS126441 18 MP Digital SLR camera. For comparison reasons, uncoated and coated tablets were photographed side by side. A cross-section of the coating was examined using a Quanta-200 scanning electron microscope (SEM) microscope at 20 kV. Samples were placed on metallic stubs and gold scattered under vacuum for 2 min using JFC-1200 Fine Coater (Joel, Tokyo, Japan), prior to imaging.

2.5. In vitro drug release – pH change dissolution tests

2.5.1. pH change method
In vitro drug release studies for all gastro-resistant coating formulations used in this study were conducted in dissolution USP II apparatus (AT 7 Smart, SOTAX, Switzerland). Each experiment was carried out in triplicate in dissolution medium at 37 ± 0.5 °C with paddle speed of 50 rpm. The tablets were tested in 750 mL of a simulated gastric fluid (0.1 M HCl, pH 1.2) for 2 h, followed by 4 h exposure to pH 6.8 phosphate buffer (Sh-Alg coated tablets were also examined in pH 1.2 followed by pH 7.4 phosphate buffer).

Within all the experiment the amount of released theophylline was determined at 5 min intervals by UV/vis spectrophotometer (PG Instruments Ltd, UK) at the wavelength of 272 nm and path length of 1 mm. Data were analysed using IDISis software (Automated Lab, 2012).

2.5.2. Dissolution test at elevated pH
The dissolution test was carried out for all enteric coating formulations under the same conditions as in vitro release studies described above. The experiment was conducted in triplicate for 2 h in following dissolution media: pH 2: 0.01 M HCl solution, pH 3: 0.001 M HCl solution, and pH 4: 0.01 M phosphate buffer.

2.5.3. Bicarbonate buffer in vitro dissolution tests
The physiological intestine fluids are mostly buffered by bicarbonate ions (Horter and Dressman, 1997). Remarkably, a bicarbonate buffer has lower buffer capacity than the phosphate one used widely in pharmacopeia dissolution test. Therefore, the additional evaluation of drug release was performed in pH 7.4 Krebs bicarbonate buffer, which resembles the human small intestine fluids more appropriately in the terms of buffer capacity, pH and ionic composition (Liu et al., 2011).

Bicarbonate buffer release test was performed under the same conditions as pH change method. First, tablets were exposed to simulated gastric fluid for 2 h. Afterwards dissolution media was replaced with Krebs buffer (1.18 mM KH₂PO₄, 24 mM NaHCO₃, 118.07 mM NaCl, 4.69 mM KCl, 2.52 mM CaCl₂, and 1.18 mM MgSO₄·7H₂O) and the experiment was carried on for further 4 h.

2.6. Disintegration tests
The disintegration test was performed to determine whether tablets disintegrate in a prescribed period of time. The examination was conducted in accordance with United States Pharmacopeia 30 standards (2007). The apparatus ZT122 (Erweka, Germany) was operated for an hour in 0.1 M HCl, then the medium was replaced with simulated intestinal fluid, as specified in USP 30 (USP Convention, 2007). The experiment was continued until complete disintegration of all tablets.

2.7. Acid uptake tests
The acid uptake test was performed to assess acid resistance and uptake of all gastro-resistant coating formulation used in this study. Three coated tablets were weighed individually prior to 2-h exposure to 0.1 M HCl at 37 °C. The tablets were then drained off the acidic medium, dried with filter paper and weighted again. The acid uptake was calculated as follows:

\[
\text{Weight gain (\%)} = \frac{\text{wet mass} - \text{dry mass}}{\text{dry mass}} \times 100
\]

3. Results and discussion
Three different GRAS-based coating formulations were prepared and applied on theophylline tablet cores. The ease of processability for each formulation depended on viscosity of coating dispersions. The EC-CMC formulation was initially too viscous and caused nozzle blockage and tablet-twinning. It was necessary to dilute the recommended concentration of the coating suspension twice. Coating with EC-Alg formulation was facilitated by slowing down the feeding speed to minimize initial tablet sticking while Sh-Alg coating was the most amenable.

An overview of the coated tablets appearance is presented in Fig. 1. All coatings presented in different shades of yellow colouring. Surface of both EC-CMC and EC-Alg was rough and patchy, in contrast to Sh-Alg which was smooth and silky. SEM images show that the thickness of subcoat was approximately 25 μm (Fig. 2). While EC-CMC, EC-Alg, Sh-Alg coating layers showed a thickness of 90, 100, 30 μm for coating level of 6.5%, 7% and 2.75%, respectively. These micrographs confirm that the coating material was distributed homogeneously throughout the tablet surface.
3.1. Optimisation of coating level via pH change method

In order to determine sufficient enteric performance of coated tablets, various coating thicknesses, in the range of 1–11% weight gain, were applied on tablets and tested with in vitro dissolution test (data not shown). A coating level was considered sufficient when USP 30 criteria for delayed release tablets were met (less than 10% of drug after 2 h in pH 1.2 followed by the release of at least 80% of tablets payload within 45 min) (USP Convention, 2007). Fig. 3 illustrates the coating thicknesses, which were the closest to satisfy pharmacopoeial requirements for delayed-release tablets. Optimal coating level of 6.5% and 7% was chosen for EC-CMC and EC-Alg formulations respectively. It is noticeable that the sufficiently protective weigh gain of both was thicker than the suggested values by the innovator (Colorcon, 2013a). The key parameters of pH change in vitro dissolution were scrutinized: a lag time, time during which a drug release do not exceed 10%, and an 80% drug release time after pH change (Table 2). EC-CMC coated tablets with 6.5% wg barely passed USP criteria and release 80% of a drug in 65 min in phosphate phase. Instead, from EC-Alg coated tablets required release was achieved within 45 min.

On the other hand, the minimal coating thickness of shellac and alginate combination (Sh-Alg) that provided gastric resistance was 2.75% wg (Fig. 3c1 and c2). However, the drug release from these tablets was slow after pH change to 6.8 (phosphate buffer). In fact,
shellac has weak acidic groups and has an average pKₐ of 6.1 (Buch et al., 2009). Thus, the dissolution of coating is likely to be accelerated above this pH value (Farag and Leopold, 2011). It was expected, nevertheless, that the addition of alginate would help to accelerate shellac dissolution at pH 6.8. When the dissolution test was repeated with pH change to 7.4 (Fig. 3c2), the release was slightly accelerated but 80% remained long (105 min). Therefore, it was not possible to apply this coating system with sufficient enteric protection in the acidic phase without prolonging drug release upon pH change.

In comparison, standard pharmaceutical grade enteric coatings prevented drug release at low pH while 80% occurred within less than 40 min in phosphate medium (Liu et al., 2011). The superior ability of these coating systems to provide a pH-dependent release pattern in comparison to GRAS-grade ones might be related to the pKₐ values of pharmaceutical grade polymers. These polymers were engineered to have a pKₐ range of 4.5–5.5 close to the desired pH dissolution threshold of an enteric coating (Dittgen et al., 1997; Grainger and El-Sayed, 2014). In contrast, the pKₐ value of GRAS grade polymers fall outside this range (3.2, 4 and 6.1 for alginate, CMC and shellac respectively (Abughoush et al., 2008; Buch et al., 2009; Shi et al., 2006).

3.2. Disintegration tests

The evaluation of disintegration time of enteric coated tablets was performed as per the pharmacopoeia standards (USP 30) and

![Fig. 3. In vitro release of theophylline from tablet coated at different coating level with (a) EC-CMC; (b) EC-Alg; (c1) and (c2) Sh-Alg and using USP II pH change dissolution test.](image)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Summary of gastric resistant properties of three GRAS-based coating systems.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC-CMC</td>
</tr>
<tr>
<td>In vitro drug release in phosphate buffer*</td>
<td>Borderline</td>
</tr>
<tr>
<td>Lag time in buffer stage (min)</td>
<td>30</td>
</tr>
<tr>
<td>80% release time in buffer stage (min)</td>
<td>65</td>
</tr>
<tr>
<td>Disintegration test*</td>
<td></td>
</tr>
<tr>
<td>Acid medium resistance</td>
<td></td>
</tr>
<tr>
<td>Disintegration time of all tablets in SIF (min)</td>
<td>39</td>
</tr>
<tr>
<td>Acid uptake tests*</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>Weight gained (%)</td>
<td>X</td>
</tr>
<tr>
<td>Dissolution test at elevated pH*</td>
<td>70</td>
</tr>
<tr>
<td>Drug release time in pH 2 (min)</td>
<td>30</td>
</tr>
<tr>
<td>Drug release time in pH 3 (min)</td>
<td>55</td>
</tr>
<tr>
<td>Drug release time in pH 4 (min)</td>
<td></td>
</tr>
<tr>
<td>In vitro drug release in bicarbonate buffer*</td>
<td>30</td>
</tr>
<tr>
<td>Lag time in buffer stage (min)</td>
<td>80</td>
</tr>
</tbody>
</table>

* Criteria for enteric coating system: ☑ pass, X fail.
is summarized in Table 2. Both EC-CMC and EC-Alg successfully resisted 1 h exposure to gastric medium and disintegrated completely in simulated intestinal fluid (SIF) within designated test period, typically 60 min. However, five of six Sh-Alg coated tablets broke and began to release drug while exposed to acid medium. This might be related to the thinner coating thickness of Sh-Alg which appears to be sufficient for gastric resistance of drug release while less robust against the mechanical challenge of the disintegration test. This problem could probably be overcome by applying a thicker film. However, the dissolution profile after pH change is likely to be further prolonged.

3.3. Acid uptake tests

During the acid uptake studies all tested tablets manifested an effective barrier from gastric environment (Table 2). All tested tablets showed acceptable acid protection. Interestingly, data clearly shows that formulations that consisting of sodium alginate demonstrated highest acid uptake. This finding is in accordance with alginate over swelling in different pH media (Soni et al., 2010).

3.4. Gastric resistance properties at elevated pH – dissolution tests

In accordance with pharmacopoeial requirements, gastric resistance properties have been assessed by exposing tablet to pH 1.2 medium. However, the physiological pH of the stomach can vary between 1.0 and 2.5 at fasted state (Evans et al., 1988) and was reported to rise to 3.9 or 5 upon the ingestion of food (Russell et al., 1993). This was reflected in the design of simulated gastric fluid preparations to mimic the fed state with a pH value of 5 (Jantarid et al., 2008). Nutraceutical products are affected by the change in the pH of the stomach. For instance, probiotic preparations showed different survival percentages in simulated gastric fluids under fed state (pH 3.5) in comparison to fasted state (pH 1.6) (Fredua-Agyeman and Gaisford, 2015). Consequently, it is of significant importance for an enteric coating to show a level of gastric resistant properties at acidic pH values of 2, 3 and 4.

Fig. 4a demonstrates the pH resistance efficiency of EC-CMC coated tablets in varies pH media. The experiments showed that cores coated with EC-CMC formulation started to release drug after 70, 30 and 55 min at pH values 2, 3 and 4, respectively. On the other hand, drug release from EC-Alg was observed after 30, 15 and 15 at pH values 2, 3 and 4, respectively (Fig. 4b). Although the amount of swellable pore-former is the similar (25% of dry mass) in both EC-CMC and EC-Alg, EC-Alg coating exhibited higher permeability at elevated pH. This indicates that alginate swells and dissolves in lower pH than CMC, which results in worse pH-dependent control of release. It is possible that both EC-CMC and EC-Alg coated tablets break prematurely and release a drug, particularly in fed state resulting in a degradation of the acid-labile payload or irritation of
the stomach (Washington et al., 2002). On the contrary, no significant release in Sh-Alg formulation was found during pH 2, 3 and 4 tests (Fig. 4c). This is similar to the level of drug release suppression in elevated pH gastric medium that can be achieved by synthetic coating systems (Eudragit L100-55) (Liu, 2007). These results suggest that only shellac-based coating provided a reliable protection in elevated pH gastric environment.

3.5. Bicarbonate buffer in vitro dissolution tests

In vitro dissolution test conducted in more biologically relevant bicarbonate buffer showed that drug release from all investigated coating formulations is significantly slower than in the phosphate buffer pH 6.8 (Fig. 5). However, EC-CMC formulation demonstrates a better pH change response, in comparison to the other coatings. The deceleration of dissolution rate in Krebs buffer is more significant for shellac based coating systems. The possible repercussion is a diminishing of absorption window for a drug, which poses a risk of insufficient bioavailability, or reducing health benefits that are offered by nutraceutical product. The slower dissolution rate has been attributed to the lower buffer capacity of the bicarbonate buffer in comparison to commonly used phosphate buffers (Fadda and Basit, 2005). Interestingly, a drug release from the pharmaceutical grade coatings was reported to have longer lag times compared to GRAS grade coatings (Liu et al., 2011). Such a trend might be attributed to the relatively lower pHs values of alginate and CMC compared to that of pharmaceutical grade ones.

In summary, an ideal coating system should pass the relevant regulatory criteria to reach the market in addition to more physiologically relevant tests to ensure a sufficient gastric protection and/or prevention of premature release in the stomach. Although these GRAS-based systems are available commercially, their ability to provide protection against the hostile gastric environment is limited by the properties of the naturally occurring or GRAS-grade ingredients.

4. Conclusion

Three commercially available GRAS-based enteric coating technologies were evaluated. In vitro drug release profile in simulated intestine conditions varied significantly depending on the formulation medium. The fastest release in phosphate buffer pH 6.8 was observed for EC-Alg then for EC-CMC. The Sh-Alg coating appeared to be significantly retarding release at both pH 6.8 and 7.4 phosphate buffers. However, when more biologically relevant buffer (Krebs buffer) was used for dissolution study, all coatings showed a slower drug release. Under conditions of elevated gastric pH, ethyl cellulose based coating systems failed to resist exposure to acidic media and released a drug. On the contrary, no significant release in Sh-Alg formulation was found. The disintegration test proved good acid protection of EC-CMC and EC-Alg coating systems and revealed susceptibility of Sh-Alg coating for mechanical stress in acidic medium. All evaluated coatings presented low acid uptake values, demonstrating ability for drug protection inside core at pH 1.2.

All in all, none of the GRAS-grade coatings are fully compatible with the different pharmaceutical demands of delayed release coating systems. More research is needed to fabricate an enteric coating system from GRAS-based materials that can meet the physiological and regulatory challenges of widely used nutraceutical products and dietary supplements.

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