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Direct visualizing of paracetamol immediate release tablet disintegration in vivo and in vitro

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ABSTRACT

The purpose of the present study was to study tablet disintegration by direct visualization, in vivo and in vitro. Based on literature data, a standard conventional paracetamol (CP) tablet, Panodil®, and a rapidly absorbed paracetamol (RP) tablet, Panodil® Zapp, were chosen as model systems to study tablet disintegration in the human stomach. Based on the obtained in vivo results, an in vitro disintegration method was designed to reproduce the visualized disintegration process occurring in the human stomach.

For the clinical study, CP and RP tablets fastened to digital endoscopic camera capsules were administered to fasted human volunteers (n = 4). The disintegration time and process were visualized by the real time video recordings, using the endoscopic capsule camera. The average disintegration time was found to be 26 ± 13 min and 10 ± 7 min, for CP (n = 4) and RP (n = 4) tablets, respectively.

It was possible to reproduce the in vivo disintegration data in vitro using a USP 2 dissolution apparatus with 250 mL of viscous Fasted State Simulated Gastric Fluid (vFaSSGF®), simulating the rheological profile of human fasted state gastric fluid following administration of a glass of water. The viscosity of the simulated fasted state gastric fluid was found to have a large impact on the disintegration time of the tested immediate release tablets. Therefore, it is recommended to mimic gastric fluid viscosity during in vitro tablet disintegration studies.

1. Introduction

Tablet disintegration refers to the mechanical break up of a compressed tablet into small particles upon exposure to aqueous fluids, e.g. following oral ingestion. The process is characterized by the breakdown of the interparticulate bonds, which were created during compaction. The main mechanisms of tablet disintegration are generally accepted to be swelling, wicking and shape recovery, and a number of factors have been shown to affect the process [1,2].

As disintegration is considered a fundamental quality attribute of immediate release tablets and the first step in the bioavailability cascade, it is important for formulators to have a good understanding of the disintegration process when developing a new tablet formulation. During the past decades, a multitude of studies have examined the tablet disintegration, yet, as pointed out in key review articles by Desai et al., Markl and Zeitler, Quodbach and Kleinbudde, and most recently by Baradi et al., “the complex puzzle of tablet disintegration is far from being resolved” [1-4].

To study tablet disintegration, both direct and indirect visualization techniques have been utilized. In vitro, image analysis-based techniques have been shown to be both rapid and accurate, with respect to evaluating tablet swelling and the effects of various tablet disintegrants [5-7]. With these in vitro techniques, microscopes and video cameras can be placed in close contact with the disintegration tablet, which allows direct visualization of the process. In vivo, however, the situation is a bit more complex. γ-scintigraphy and X-rays are techniques which have commonly been used to examine dosage form behavior in the gastrointestinal tract (GIT) [8,9]. However, both techniques have the drawback of using ionized radiation. Furthermore, these techniques do not provide supplementary information about 3D position [9,10]. Several alternative radiation free visualization techniques have been introduced, including the “magnetic pill tracking” [11,12] and the “magnetic marker monitoring” [10,13]. Both of these imaging techniques are based on the measurement of the magnetic dipole moment of a magnetic solid oral dosage form. The primary disadvantage of the techniques is, that it is not possible to identify an anatomical reference simultaneously to
tracking a dosage form. The magnetic marker/pill technique has mostly been used to examine transit of dosage forms through the GIT [10–13]. Furthermore, a number of studies have investigated transit behavior and distribution of drug delivery systems using magnetic resonance imaging (MRI) [10,14–17]. MRI is based on the principle of nuclear magnetic resonance and provides a very high spatial resolution together with good contrast resolution [10,18]. However, the MRI technique has two key drawbacks. The first drawback is the acquisition time, i.e. a visualization takes around 15–20 s and during that time, motions must be avoided and subjects have to hold their breath, which reduces the achievable sampling rate [10,14,19]. The second drawback is the low signal to noise ratio that makes it demanding to clearly distinguish dosage forms from other materials in the GIT using MRI [10] and imaging is difficult in an empty stomach or if a dosage form has passed to the intestine [17].

Gastroscopy is a direct visualization method, which provides real-time visual examination of the upper part of the GIT. The method has been used to increase the understanding of dosage form and drug behavior in the GIT [9,20,21]. The method is, however, invasive and can cause significant discomfort for the subjects, since the gastroscope, which consist of a thin flexible fiber optic tube, has to pass through the esophagus to the stomach [9,22]. Sedation can be used to limit the discomfort of the patient, however, this might influence the behavior of the dosage form [9]. Capsule endoscopy is considered a minimally invasive technique, which is well tolerated by patients [22–26]. Additionally, the method is able to show direct real time visualization [22–27]. Capsule endoscopy is often used for diagnosing and screening diseases in the GIT [23,24,27]. The PillCam™ Colon 2 endoscopic camera capsule is equipped with two image sensors on both ends and provides a near 360° view. The PillCam™ Colon 2 have bidirectional communication between the endoscopic camera capsule and the data recorder. Therefore, the image capture rate can be adjusted in real time from 4 frames per second up to 35 frames per second to maximize tissue coverage and can keep working for approximately 10 h. Capsule endoscopy provides advantages such as increased angle of view, depth of field, and image numbers, which makes the technique a well-suited alternative for visualizing drug delivery systems in the fasted stomach [27].

Using capsule endoscopy, two studies have studied drug release in vivo [22,28]. In 2014, Pedersen et al. used capsule endoscopy for direct imaging of capsule rupture and dispersion of a lipid based drug delivery system in the fasted upper-GIT [22]. Based on the results presented by Pedersen et al. it was proposed that capsule endoscopy could be used to study tablet disintegration in vivo, generating new insights to the fate of solid drug delivery systems following oral administration [22]. In support of this conclusion, Blaabjerg et al. recently used capsule endoscopy to study tablet disintegration in awake beagle dogs and concluded that the capsule endoscopy method was well tolerated by the animals, and the tablet disintegration process could be followed visually [28]. Moreover, in the specific investigated case of Panadol Rapid (a rapidly absorbed paracetamol (RP) tablet), it was shown that the pharmacokinetic parameters maximum serum concentration (Cmax), time to maximum serum concentrations (tmax), and Area under the curve (AUC)/dose did not change significantly when the tablet was dosed with and without capsule endoscopy, indicating that capsule endoscopy has little to no effect on RP tablet performance and, thus, RP tablet disintegration [28].

Paracetamol is a widely used analgesic and antipyretic over-the-counter drug used for both adults and children to relieve mild to moderate pain. It is recommended due to few adverse effects in therapeutic doses, and few drug interactions [29,30]. A conventional paracetamol (CP) tablet contains 500 mg of paracetamol; however, paracetamol is also formulated as a RP tablet containing 500 mg of paracetamol and 630 mg sodium bicarbonate [31]. Previous studies have demonstrated that RP tablets have a significantly shorter time to tmax alongside a significantly higher Cmax in the fasted state, as compared to CP tablets [31–34]. The faster rate of absorption has been explained by a faster disintegration of the RP tablets, followed by a faster gastric emptying of the disintegrated particles and the dissolved drug, as compared to CP tablets [32,33]. In support of this concept, one study have investigated the disintegration of both CP and RP tablets in vivo using the indirect visualization method, γ-scintigraphy, and found a difference in the mean disintegration time of CP and RP tablets in both fed and fasted state [33]. A difference between the mean disintegration time of CP – and RP tablets in fasted state beagle dogs were also observed in the study by Blaabjerg et al. [28].

The purpose of the present study was to study tablet disintegration by direct visualization in the human stomach in vivo and in vitro. Based on the data described above, a standard CP tablet, Panodil®, and a RP tablet, Panodil® Zapp, were chosen as model systems to study tablet disintegration in the human stomach. Based on the obtained in vivo disintegration data, an in vitro disintegration model was design to reproduce the observed in vivo disintegration results, and therefore be used to study tablet disintegration in vitro, in a physiologically relevant manner.

2. Materials and methods

2.1. Materials

Panodil® and Panodil® Zapp tablets, each containing 500 mg of paracetamol, were obtained from GlaxoSmithKline (GSK) Consumer Healthcare A/S (Brøndby, Denmark). The excipients of Panodil® and Panodil® Zapp are shown in Table 1. PillCam™ Colon 2 endoscopic camera capsules used for in vivo studies were purchased from Medtronic Denmark A/S (Copenhagen, Denmark). Out of date PillCam™ Colon 2 endoscopic camera capsules, used for in vitro studies, were graciously donated by Medtronic Denmark A/S (Copenhagen, Denmark). Powder to prepare Fasted State Simulated Gastric Fluid (FaSSGF) was purchased from Biorelevant.com (London, UK). Sodium chloride was from VWR BDH Prolab chemicals (Sabsborg, Denmark). Hydrochloric acid 37% (HCl) was purchased from Sigma Aldrich (St. Louis, MO, USA). The polymer methylcellulose, Methocel A40M, was purchased from Don Wolff Cel-lulotics GmbH (Bomlitz, Germany). Plastic free, biobased Maistic Dental floss, and Histoacryl® glue were purchased at a local convenient store. Purified water was obtained from a Milli-Q water purification system purchased by Holm & Halby Service (Brøndby, Denmark).

2.2. Methods

Tablet disintegration was studied in vivo and in vitro. Based on the obtained in vivo results, an in vitro disintegration method was designed to reproduce the visualized disintegration process occurring in the human stomach.

2.2.1. In vivo disintegration studies

The clinical study, conducted to study tablet disintegration in the human stomach, was performed as a single study with two test groups and no crossover. Each test group consisted of four volunteers (n = 4). The present study was approved by the Ethical Committee of Denmark (Copenhagen, Denmark) and followed the convictions of the Declaration

<table>
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<td>Excipients in Panodil® (CP tablet) and Panodil® Zapp (RP tablet)</td>
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of Helsinki (H-1-2011-115). All volunteers gave their written, informed consent to the experimental procedure. The endoscopic visualization study was performed at the Gastro Unit, Division of Endoscopy at the University Hospital of Copenhagen (Herlev, Denmark).

Eight healthy volunteers (4 males and 4 females), aged between 18 and 35 years, participated voluntarily in the study. The volunteers were not allowed to have any prior history of GI diseases or have experienced stomach pain within the last week before the experiment. Furthermore, the volunteers were not allowed to take any medication on the day of the experiment, or to eat or drink, 6 and 2 h prior to the study, respectively. The endoscopic camera capsules (Pillcam® Colon 2; 31 mm × 11 mm) were prepared by tightening a soft string of biodegradable dental floss with a minimum length of 1.0 m to the endoscopic camera capsules, to retain and control the camera in the stomach and avoid passage to the duodenum due to the natural peristalsis of the stomach. A tablet (CP (7.3 mm × 17.5 mm)/RP (9 mm × 19 mm)) was fastened with a dental floss loop just in front of one of the cameras on the endoscopic camera capsule. One drop of Histoacryl® glue was used to ensure that the tablets were fixed to the knot of the dental floss. Fig. 1 shows a schematic illustration and a picture of the combined tablet and camera capsule.

Eight electrodes, connected to a data recorder, were fastened to the volunteers’ torso. The endoscopic camera capsule and the tablet were swallowed with 250 mL of tap water. The volunteers were sitting in an upright position during the observation. The transit and disintegration process of the tablet was video-recorded by the endoscopic camera capsule and viewed on a data recorder in real-time with a frame rate of 4–35 frames per second (fps). The frame rate change from 4 fps to 35 fps when the capsule was in motion or when the system detected a change in the image. When it was confirmed, via the real-time recordings, that the tablet and camera had entered the stomach, the volunteers were asked to fix the dental floss, e.g. by biting down on it, to avoid the tablet leaving the stomach. Each recording was stopped when the tablet was completely disintegrated, i.e. when no tablet was visible in the loop in front of the camera, or at the latest after 50 min from the tablet and camera had entered the stomach. At the end of each recording, the dental floss was cut and the endoscopic camera capsule was allowed to travel with the peristalsis through the GIT and was discarded with the stool. After completing the study, each volunteer was asked to evaluate his/her discomfort during the study giving a score of 1 to 10, with 1 being that the study was easily tolerated and 10 that it was extremely uncomfortable. Furthermore, the volunteers were asked if they would be willing to participate in a similar study again.

2.2.2. In vitro disintegration studies

Different in vitro disintegration tests were performed to investigate the correlation with the results obtained from the in vivo study. Each disintegration test was performed using different media simulating the gastric fluids following ingestion of 250 mL of tap water. Fasted State Simulated Gastric Fluid (FaSSGF), pH 1.6 was prepared following instructions from the manufacturer, Biorelevant.com [35]. A viscous FaSSGF medium (vFaSSGF) was prepared to simulate the resting fasted state human gastric fluid (HGF), taking its rheological profile into account [36,37] (the rheological profile of the prepared vFaSSGF is available in Figure S1, in the supplementary material (SM)). Based on a polymer screening, it was found that addition of 0.1 % methylcellulose (Methocel A40M), to FaSSGF produced a simulated fasted HGF displaying a rheological profile comparable to human aspires [37,38]. As Methocel A40M gels quickly at room temperature, vFaSSGF was prepared in two steps; (i) Methocel A40M was added very slowly to ice cold purified water stirred vigorously, and (ii) a two-times concentrated FaSSGF medium was prepared and mixed with the cold polymer solution. The mixed solution was stirred overnight to achieve homogeneity, and the pH was adjusted to 1.6 with HCl. To mimic the fasted state gastric fluid following ingestion of the glass of water administrated with the endoscopic camera capsule and CP or RP tablet, a diluted vFaSSGF medium, vFaSSGF®, was prepared as follows: 35 mL of the vFaSSGF was heated to 37 ± 0.5 °C, representing the resting gastric volume, to which 215 mL of purified water (room temperature, 20–21 °C, representing the glass of tap water) was added with the tablet and camera capsule. The 215 mL of water was selected to make the total volume 250 mL to allow comparison to the other test conditions with a similar volume. Furthermore, a study by Mudie et al. has previously shown that the volume of the fasted stomach increases from 35 ± 7 mL in the resting state to 242 ± 9 mL upon drinking a glass of water (240 mL) [39].

The initial in vitro disintegrations studies were performed following the method described in the European Pharmacopoeia (Ph.Eur.) section 2.9.1 Disintegration of tablets and capsules, Test A [40]. The test was performed using the disintegration apparatus Pharma Test (Pharmatest, Hainburg, Germany) equipped with 300 mL dissolution vessels (ProSense, Oosterhout, The Netherlands) were performed. The disintegration of the CP and RP was studied in 250 mL of disintegration medium consisting of purified water, FaSSGF or vFaSSGF® at 37 ± 0.5 °C, and a speed of 30 cycles per minute. Each tablet (CP and RP) was tested with six replicates (n = 6).

To better mimic the in vivo conditions for the disintegration process in vitro, disintegration tests using a dissolution ERWEKA USP 2 system (Langen, Germany) equipped with 300 mL dissolution vessels (ProSense, Oosterhout, The Netherlands) were performed. The disintegration of the CP and RP was studied in 250 mL of disintegration medium consisting of purified water, FaSSGF or vFaSSGF® at 37 ± 0.5 °C. To mimic the in vivo situation, each tablet was fastened to an endoscopic camera capsule (out of date, and therefore not fit for in vivo studies) with dental floss as described in section 2.2.1. The tablet and the endoscopic camera capsule were placed in the dissolution vessels, and the floss was fixed on a dissolution vessel cover, so the camera capsule with the tablet attached hung freely in the dissolution vessel, completely covered by disintegration medium. This experimental setup is illustrated in Fig. 2. For the first set of experiments, using the USP 2 apparatus, no stirring was applied (Fig. 2A), however, to simulate the mild movements of the stomach, a mini paddle with a stirring of 50 rpm was used in a second set of experiments. The paddle height was adjusted to ensure the paddle was below the surface of the disintegration medium while allowing the

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Fig. 1. A) Illustration of the tablet fixed in front of one of the cameras on the endoscopic camera capsule (PillCam® Colon 2) with dental floss (displayed as grey strings). B) Picture of the endoscopic camera capsule (PillCam® Colon 2) attached to a Panodil® tablet with dental floss. The dimensions of the PillCam® Colon 2 were 31 mm × 11 mm.
camera and tablet to hang freely the dissolution vessel (Fig. 2B). All disintegration experiments were video recorded using an iPhone 5S (Apple Inc., Cupertino, CA, USA), and the disintegration time for each tablet was determined with six replicates ($n = 6$).

### 2.3. Data analysis

#### 2.3.1. Determining the tablet disintegration time

The in vivo disintegration time was determined from the video recordings using the PillCam™ Reader software v9.0 (Minneapolis, USA). The disintegration times were measured from the time when the endoscopic camera capsule and tablet entered the stomach to: i) the tablet was completely disintegrated and no tablet remnants was observed in the dental floss loop in front of the endoscopic camera capsule, or ii) the majority of the tablet was disintegrated with a small tablet remnant stuck in/to the dental floss loop and/or the endoscopic camera capsule, presumably due to the glue. The in vitro disintegration time was determined in a similar manner for all studies conducted in the USP 2 apparatus, using the iPhone video recordings.

#### 2.3.2. Statistical analysis

Statistical analysis was conducted using GraphPad Prism software v. 8.3.1 (GraphPad Software, La Jolla, USA). Based on a normal QQ plot, it was found that each data set was normally distributed or acceptably close-to normally distributed. Based on multiple F-tests, it was found that it could not be assumed that each data set had the same variance. Therefore, an unpaired t-test was used to compare the disintegration time of sample sets displaying similar variance, whereas an unpaired t-test with Welch’s correction was utilized to compared sample sets with different variance. Based on the experimental design, the results were deemed independent.

### 3. Results and discussion

The purpose of the present study was to directly visualize tablet disintegration in the human stomach using capsule endoscopy, and based on this, to design an in vitro model reproducing the in vivo disintegration results.

#### 3.1. In vivo tablet disintegration

Figs. 3 and 4 display the swelling and disintegration process of the two tablet formulations in one volunteer each (Figure S2-S8 in the SM display the similar results for the remaining six volunteers, as well as snapshots of the tablets before ingestion). Fig. 3A and 4A show the tablets in the esophagus. The average transit time for the tablets and endoscopic camera capsules through the esophagus was 1 min 39 s ± 42
s (n = 4) for the CP tablets and 1 min 1 s ± 26 s (n = 4) for RP tablets. One of the RP tablets showed signs of swelling and disintegration while passing the esophagus (data not shown). Fig. 3B and 4B show the tablets entering the stomach. The swelling of the tablets that reached the gastric fluids can be seen in Fig. 3C and 4C. Besides the one tablet for which swelling was observed in the esophagus, the remaining seven tablets showed signs of swelling a few seconds after entering the stomach. The RP tablets swelled less, relative to their size, as compared to the CP tablets. Fig. 3D/E, and 4D/E show the disintegration of the two tablet formulations. The CP tablets started to disintegrate between 1 min 4 s and 7 min 17 s with an average of 4 min 21 s ± 2 min (n = 4), while the RP tablets started to disintegrate after 18 s to 1 min 23 s (n = 4). For all four CP tablets and three of the RP tablets, it was observed that the ends of the tablets disintegrated first whereas the middle part of the tablet took longer to disintegrate, possibly due to interference with the dental floss loop. This observation is illustrated in Fig. 3E and 4E, where the middle part of the tablets inside the dental floss loop still appears intact. In one volunteer swallowing a CP tablet and one volunteer swallowing a RP tablet, the tablet was pushed to the side of the endoscopic camera capsule during passage through the esophagus, which caused the tablets to be out of view in parts of the recording, and in front of the camera in other parts of the recording. This made it more difficult to determine the disintegration pattern, but it was still possible to clearly determinate the exact disintegration time as the tablets were in front of the camera for the last part of the disintegration process. In Fig. 3F and 4F the tablets are completely disintegrated.

Fig. 5 shows the measured disintegration time for each CP and RP tablet in the eight volunteers. The average disintegration time was found to be 26 ± 13 min and 10 ± 7 min, for CP (n = 4) and RP (n = 4) tablets, respectively. These disintegration times suggest a faster disintegration for the RP tablets compared to the CP tablets in vivo. However, due to the small sample size, the study did not have enough statistical power to show a statistical difference in the disintegration time of the CP and RP tablets.

As seen in Fig. 5, there was a much higher variability in the disintegration times of the CP tablets compared to the RP tablets. This observed difference can be interpreted in different ways. Firstly, it might indicate, that the gastric conditions and variations herein, such as e.g. differences in stomach movements, rates of water absorption, and resting gastric fluid volume, pH, and viscosity differences, had a larger influence on CP tablet disintegration compared to RP tablet disintegration [39,41,42]. Secondly, the difference might indicate that the disintegration of the CP tablets was more affected by the experimental setup.
with the attachment to the endoscopic camera capsule, as compared to the
RP tablets. The CP tablets swelled during disintegration due to their
content of starch and povidone, a process that most was likely (at least
slightly) delayed due to the dental floss holding the tablet together.
However, the RP tablets additionally contain sodium bicarbonate, which
generates carbon dioxide bubbles upon dissolution and thereby works as
a disintegration aid and helps to break up the tablets, likely independent
of the dental floss. Thirdly, the result might include outliers, which is
impossible to statistically determine due to the small sample size.

When comparing the presently found mean disintegration times of
CP and RP tablets with literature results presented by Kilian et al. and
Blaabjerg et al., a strong correlation can be observed [28,33]. Using
\( \gamma \)-scintigraphy, Kilian et al. measured the disintegration time of com-
parable CP tablets and RP tablets in 12 healthy volunteers in the fasted
state and reported it to be 22.5 ± 12.8 min and 10.2 ± 9.3 min, for CP
and RP tablets, respectively [33]. Similar disintegration times was re-
ported by Blaabjerg et al., after having studied the disintegration of
comparable CP and RP tablets in dogs using capsule endoscopy without
fixating the tablets in the stomach [28]. In that study, the average
disintegration time was 24.7 ± 4.8 min and 16.5 ± 4.3 min, for the CP
and the RP tablets, respectively. As the reported disintegration time of
CP and RP tablets, were comparable across the three studies (mean and
standard deviation), it appears that the visualization techniques had
little impact on the obtained results. However, due to the large \( \text{in vivo} \)
variations, it is difficult to ascertain if the slightly shorter disintegration
time observed, when using \( \gamma \)-scintigraphy as compared to capsule
endoscopy, is caused by e.g., the dental floss delaying tablet disintegra-
tion when using capsule endoscopy.

3.1.1. Discomfort score system

All eight volunteers evaluated the discomfort of the study. Seven
volunteers graded the participation in the study as easy to moderately
tolerable with scores between 1 and 4, and one volunteer rated the
participation as uncomfortable with a score of 7. All the volunteers said
they would participate in a similar study, if asked again.

3.1.2. Using capsule endoscopy for direct visualization of tablet
disintegration

The present study demonstrated that capsule endoscopy can be used
for direct visualization of tablet disintegration in the human stomach
(Figs. 3-4, and Figures S2-S7 (SM)) which correlates with findings from
previous studies [22,28]. The procedure is considered minimally inva-
sive and was found to be well tolerated by the volunteers participating in
the study. These findings also correlate well with previous studies
reporting that the volunteers found the use of endoscopic camera cap-
sules to be well tolerated [22,25]. With that said, certain practical
limitations of the utilized direct visualization technique were observed;
mainly, the presence of the endoscopic camera capsule and the dental
floss.

To ensure the tablet stayed in view of the endoscopic camera cap-
sules, it was necessary to fasten the tablet directly to the endoscopic
camera capsule. In the present study, this fastening was done with dental
floss as described in the method section. Fastening the tablet to the
endoscopic camera capsule increased the overall size of the ingested
dosage form (tablet plus camera) and is expected to have affected the
tablets movement through the GIT. Firstly, the increased size and the use
of dental floss to retain the tablets in the stomach, have very likely
prolonged the transit time in the esophagus. In the present study, the
transit time of the tablet and endoscopic camera capsule through the
esophagus was 1 min 39 s ± 42 s for the CP tablets, and 1 min 1 s ± 26 s
for the RP tablets. These transit times are significantly longer than those
recorded for smaller tablets (5.7 mm x 11 mm) taken with 240 mL water,
as reported by Perkins et al., i.e. 3.1 s ± 3 s (n = 15) [38]. The present
transit times are also longer than those reports in a study by Pedersen
et al., in which a similar experimental setup was utilized with slightly
smaller endoscopic camera capsules (26 mm x 11 mm) and dental floss
to fixate the dosage form in the stomach. That study showed the average
transit times through the esophagus were 35 s ± 14 s, 27 s ± 15 s and 24
s ± 4 s for three different oil containing capsules [19]. Therefore, it
suggests that the size of the endoscopic camera capsules in combination
with other factors such as e.g., the formulations adhesive behavior have
prolonged the transit time in the esophagus.

Aside from ensuring (or attempting to ensure) the tablets stayed in
view of the endoscopic camera, the dental floss was used to retain the
tablets and the endoscopic camera capsules in the stomach and avoid
passage to the small intestine. The fixation of the tablet and endoscopic
camera capsule ensured a more controlled setup as it eliminated the risk
that one or more tablets passed to the small intestine, and thereby would
have disintegrated in a different environment compared to tablets dis-
integrating in the stomach. As it is unknown where un-fixated tablets
would have located during the disintegration process, it is unknown,
how big an impact this fixation had on the present tablet disintegration
process. However, it is recognized, that the fixation will have influenced
the natural intragastric mobility of the tablets, and thereby might have
affected the tablet disintegration process. With the fixation, the tablets
stayed in the proximal stomach and did not reach the antrum where the
motility is more pronounced [43], which might have decreased the
tablet disintegration time.

Furthermore, as discussed in section 3.1, the presence of the dental
floss around the tablets might have affected the disintegration process.
Though the observed impact on the disintegration time of CP and RP
tablets appeared to be small, based on comparison to literature results
obtained using \( \gamma \)-scintigraphy [33] as well as on the reported lack of
difference in the PK profiles obtained for RP tablets administered with
and with endoscopic camera capsules [28], it might still be there, and
also might be more evident for other drugs, disintegrants and dosage
forms in general.

3.2. In vitro tablet disintegration

In vitro disintegration studies were conducted according to Ph.Eur.
Test A, as well as using the USP 2 dissolution apparatus with different
disintegration media, with and without stirring. Like the \( \text{in vivo} \)
studies, the tablet disintegration process was observed and recorded during the
\( \text{in vitro} \) experiments. Fig. 6 shows the disintegration times of CP and RP
tablets determined \( \text{in vitro} \), using the different experimental setups. As a
reference, the \( \text{in vivo} \) disintegration times for both tablet formulations
are also depicted in Fig. 6 (black bars).

The disintegration times obtained from the initial disintegration study
performed with the method in Ph.Eur. section 2.9.1, both with
purified water and FaSSGF, showed significant differences when
compared to the disintegration times observed \( \text{in vivo} \). Disintegration
studies using USP 2 apparatus with and without stirring was therefore
performed in different media. The disintegration times of CP and RP
tablets were found to be comparable to the \( \text{in vivo} \) disintegration times
for both formulations using the vFaSSGF* designed to simulate the
fasted state HGF following administration of a glass of water, and the
USP 2 dissolution setup up with 50 rpm stirring and without stirring
(Fig. 6, red and blue striped bars compared to black bars). The disinte-
gration time for CP and RP tablets was increased in the viscous media,
vFaSSGF*, compared to the non-viscous media, FaSSGF and purified
water (Fig. 6). The disintegration time for both tablet formulations in
purified water and FaSSGF was below 10 min regardless of method, and
whether the medium was stirred or not (Fig. 6, clear and dotted bars).
These results are comparable with results from other studies which have
reported an increased tablet disintegration time in media with increased
viscosity [44-47]. E.g. in a study by Parojć et al., it was shown that the
disintegration of CP tablets in visous media was prolonged compared to
in-non-viscous media [45]. Other studies have reported that an
increased disintegration time in viscous media is mainly mediated
though the water penetration process, i.e. if liquid cannot penetrate the
tablet, the disintegration process is slowed [44,46,47], which may
explain the increased disintegrations times observed in present study in the viscous media.

For the CP tablets, only the disintegration time measured in vFaSSGF® using the USP 2 dissolution setup was comparable to the observed in vivo CP tablet disintegration time (Fig. 6, bars without *). However, for the RP tablets, all USP 2 based in vitro disintegration setups produced comparable disintegration times to the RP in vivo disintegration time. These results illustrate that medium viscosity have a greater influence on tablet disintegration for conventional immediate release tablet formulations, CP exemplified by Panodil®, compared to rapid release tablet formulations containing sodium bicarbonate, RP exemplified by Panodil® Zapp. It, furthermore, illustrates the importance of the used in vitro model for disintegration testing. Previous studies have reported prolonged tablet disintegration times in vitro compared to in vivo [48]. In a study by Steinberg et al. the poor correlation was concluded to be due to the difference in intensity of agitation in vitro and in vivo [48]. The disintegration apparatus has a higher hydrodynamic flow compared to the UPS 2 apparatus [49], which could explain the prolonged disintegrations times and better comparison to the in vivo data for the USP 2 apparatus in present study.

4. Conclusions

Camera capsule endoscopy can be used as a direct visualization technique to study the disintegration of CP and RP (Panodil® and Panodil® Zapp) tablets fastened to endoscopic camera capsules in the human stomach under normal fasting conditions. The method was proved to be well-tolerated and minimally invasive. From the obtained recordings it was possible to evaluate both the process of tablet disintegration and the total disintegration time.

It was possible to reproduce the in vivo disintegration data in vitro using a USP 2 dissolution apparatus with 250 mL of vFaSSGF® medium. The viscosity of the fasted state simulated gastric medium had a large impact on the disintegration time of the tested immediate release tablets, especially conventional immediate release tablets, for which reason it is recommended to simulate the viscosity of the gastric fluids in the medium used for in vitro tablet disintegration studies.

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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Fig. 6. Disintegration times for Panodil® (CP) and Panodil® Zapp (RP) determined under varying conditions; in vitro using the Ph.Eur. disintegration test A with 600 mL of water (grey bars) or FaSSGF (dotted grey bars), in vitro using the USP 2 dissolution apparatus with 250 mL of unstirred water (blue bars), unstirred FaSSGF (dotted blue bars), unstirred vFaSSGF (striped blue bars), water stirred with 50 rpm (red bars), FaSSGF stirred with 50 rpm (dotted red bars), and FaSSGF stirred with 50 rpm (striped red bars), and in vivo (black bars). Mean ± SD. (n = 6 for in vitro and n = 4 for in vivo). For each formulation, i.e., CP and RP, significant differences between the in vivo disintegration time and in vitro disintegration times in different media are expressed with * for p value < 0.05.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpb.2022.09.007.

References


