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Understanding the *in Vivo* Performance of Immediate Release Tablet Formulations with Atypical Disintegration by Using Non-Conventional Disintegration and Dissolution Methods

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Abstract

Disintegration and dissolution testing is often seen as in-process/release control step, not relevant from the perspective of product bio-performance. The aim of this paper was to develop discriminative and bio-relevant (Fasting conditions) disintegration and dissolution methods for an immediate release generic tablet with poorly soluble BCS 4 drug substance with known wetting issues and tendency to aggregate. Tablet with atypically long disintegration, similar to reference product, had to be developed. Several non-standard disintegration methods were designed and those simulating no mechanical stress and fasting gastric environment were found to correlate best with in vivo result. To assure fast high-throughput screening of samples for developmental purposes, conditions identified in disintegration tests were incorporated into custom made dissolution test that covers both disintegration and drug release while simulating bio-relevant fasting conditions. With all available data we were able to correlate in vitro data to the in vivo result and identify critical parameters responsible for product bio-performance.

Keywords: Disintegration; Dissolution; Bioequivalence; Abso rption; Texture analysis; Magnetic aesonance imaging

Introduction

Oral route of drug administration remains the most convenient, with tablets being most frequently prescribed dosage form [1]. Even though tablet design and production are well established practices, finding appropriate in vitro methods and tools, which enable predicting the in vivo behavior is of crucial importance and attracts the attention of many professionals working in this field.

Disintegration is an integral property that enables tablet decay into smaller pieces and in this manner promotes drug liberation and dissolution. As such, disintegration is crucial for the fast onset of therapeutic action in the case of immediate release dosage forms [2]. Disintegration rate and mechanism depend on both, product and process related properties. Namely, immediate release formulations contain often one or more disintegrants, which enable fast decay by mechanisms such as wicking, swelling, strain recovery etc [3]. Additionally, fillers, binders, wetting agents, lubricants might also affect disintegration by additional swelling, and gelling behavior, altering local viscosity and/or influencing system's wettability. Furthermore, changes in processing conditions may impact formulation microstructure in a different manner (particle size, morphology, porosity) triggering differences in the product performance [2,4]. Overall, each of the above-mentioned factors can affect disintegration process, thus, disintegration must be regarded as critical product property to ensure repeatable drug exposure in vivo. Often the disintegration importance is overseen, and its evaluation is done just in the scope of in-process control. Commercial availability of sophisticated dissolution approaches on one hand, and a gap in knowledge as well as analytical methods to understand and reliably assess complex stages in disintegration on the other are the main reasons for neglecting disintegration during product development. Since 1934 the concept of disintegration test has not changed much, and it still includes shaking of tablets in the selected medium at pre-set temperature until complete unit decay is achieved. There were several modifications accepted by different pharmacopoeias in terms of volume and type of media, meshes, disks etc. [2,4] but at the end, information obtained from such evaluations are valuable mostly as quality control step especially if this in vitro test undersees critical in vivo steps involved in disintegration process. Disintegration starts with penetration/imbibition of medium/water into the compact leading to hydration, swelling and/or strain recovery of polymer chains. This subsequently triggers force development, which breaks down the bonds within the tablet [4]. Another factor that may promote tablet disintegration is dissolution of soluble components within the formulation [5]. All these microstructural changes induce further porosity increase and water uptake, which ends in disintegration. Mechanistically the disintegration process can be divided into 2 phases–breakdown of tablet into coarse fragments or granules and subsequent decay into primary particles [3].

Liquid penetration is the first and therefore a rate-limiting step for the entire process of disruption of structural integrity of tablets [6]. Therefore, it has received in-depth scientific interest regarding which fluid, fluid/matrix, and solid/matrix properties must be considered during product development. Aggregation and gelling of materials are another phenomenon, which could cause impairment of the disintegration process by affecting liquid imbibition. Several publications describe impaired disintegration due to gelling behavior of disintegrants and superdisintegrants, which increased liquid viscosity and subsequently impaired liquid penetration into the formulation. Altogether resulted in prolonged tablet decay and decreased drug release rate [7,8]. Gelling behavior, however, is not native to the excipients alone. This phenomenon has been also reported for some drugs that tend to agglomerate in gastrointestinal fluids or show profound tendency to aggregate [9,10], which may impact bioavailability.

Lately some scientific articles point out the usefulness of applying alternative methods and apparatuses to determine disintegration rate and disintegration pattern in a more bio-predictive manner. Studies based on measuring media uptake with (Out) measuring disintegration force are described within literature sources [11]. Some scientific groups were focused on the usage of in vitro imaging techniques such as magnetic resonance imaging and terahertz pulse imaging to visualize liquid penetration, swelling and disintegration [12,13]. In vivo evaluation of tablet disintegration has also been described [14].

In this paper an attempt was made to prepare bioequivalent generic product containing poorly soluble and poorly permeable drug that shows gelling tendency in aqueous medium and understand it's in vivo performance through different techniques. Since the exact quantitative composition of the listed reference product regarding excipients was unknown, development of generic product was guided by tailoring the disintegrant amount and position and by careful selection of several in vitro methods evaluating disintegration and dissolution, which were discriminatory enough to assess formulation behavior to the extent relevant for bio-performance.

Materials and methods

Materials

The Drug Substance (DS) was purchased from Pliva, Prigorje Brdovečko, Croatia; Mannitol was purchased from Roqquete, Lestrem, France; Microcystalline Cellulose was purchased from FMC Biopolymer, Cork, Ireland; Povidone K25 and Crospovidone were purchased from Ashland, Texax City, USA; Colloidal Si dioxide was purchased Evonik, Rheinfelden Germany; Magnesium stearate was purchased Peter Greven, Venlo, Netherlands and Polyvinyl Alcohol (PVA) based coating mixture was purchased from Colorcon, Dartford, UK. All other reagents were of analytical grade. Quantitative amount of crucial/variable components within tested formulations are shown in Table 1. All other excipients are present on the same position and in the same amount within both formulations.

Table 1: Mass percentage composition of formulations under evaluation.

Compound	Fast formulation	Slow formulation	Position
Drug substance	38.96	38.96	Intra-granular
Mannitol	38.14	38.86	
Crospovidone	0.73	0.00	
Crospovidone	0.97	0.97	Extra-granular

Methods

a) Film coated tablet preparation

Intra-granular components were mixed, screened and re-mixed. Obtained mixtures were placed in a fluid bed processor where they have been granulated with a water solution of Povidone K25 and obtained granules further dried. After drying step was completed granules were screened through 1 mm oscillating bar mill and extra-granular components were added and mixed with the granules. Final mixtures were further compressed in tablet-cores on a rotary-tablet press with a compression force of 6 kN. Obtained tablet cores (Hardness of 100 N) were further coated in a perforated pan with a water dispersion of the PVA based pre-mix. Obtained film coated tablets had hardness of 110 N ± 10 N.

b) Film coated tablet characterization

Disintegration of film coated tablets in standard apparatus

Tablet disintegration was determined using standard tablet disintegration tests. 900 mL water preheated at 37 °C ± 1 °C was used as disintegration medium. Each tablet (total number:6) was inserted into one tube of the basket, optionally a disk was afterwards added above the tablet, the basket was subsequently immersed in the medium and automatically and continuously moved in the vertical axe. Disintegration endpoint was determined when tablets decayed into small enough fragment which went through the mesh of the tube.

Disintegration in small volume of medium with mechanical agitation

6 Tablets were placed in a 100 mL beaker filled with 50 mL 0.001 M HCl with salts p^H 3.0 and tap water in ratio 1:5 (preheated at 37°C ± 2°C) and 20 g of glass beads. The glass was put onto a magnetic stirrer and stirring on to level 2 was adjusted. Disintegration endpoint was determined when there were no larger tablet fragments floating inside the beaker.

Disintegration in small volume of medium with minimal agitation applied and texture analysis

Tablets were placed in petri dish filled with 50 mL 0.001 M HCl with salts p^H 3.0 and tap water in ratio 1:5. Tablets were positioned inside the petri-dish while visually observing the disintegration process and taking photos at predetermined time points. At intervals of 5 min, 15 min and 30 min the remaining parts of 3 tablets were withdrawn from the medium and submerged to textural analysis with Instron 3342 single column texture analyzer (Instron, Norwood, Massachusetts USA). Tablets were tested with flat-end, round shaped stainless-steel probe with Ø 2 mm tip and length of 30 mm. All experiments were performed in triplicate. Texture analyzer was equipped with 10 N load cell operated by Bluehill3 software. During analysis, the needle probe moved toward the hydrated tablet at a rate of 0.5 mm/s, until the surface of the tablet was detected at the force of 0.02 N (load 1). At this point, the probe penetrated the hydrated tablet with the rate of 0.2 mm/s until the force of 5 N (load 2) was detected, at which point the probe retracted to its original position. In the case of the slow formulation, tests were not performed at 5 min due to high robustness of the formulation at this time point. The tests for fast formulation were not performed at later time points (30 min) since the amount of the remaining dry core was insignificant.

Disintegration in 3 mL medium followed by magnetic resonance microscopy (imaging)

Magnetic resonance imaging (MRI) experiments were performed on a Magnetic Resonance Imaging system consisting of a TecMag Redstone (Houston TX,USA) MRI spectrometer with a 9.4 T (400 MHz proton frequency) high-resolution superconducting vertical bore magnet and a Bruker Micro 2.5 gradient system. To follow changes of tablets during disintegration 3D MRI was performed using the gradient-echo (GE) technique with parameters: field of view (FOV) of 20 x 20 x 10 mm^3, imaging matrix 128×128×64 (isotropic resolution was 156 µm), echo time (TE) of 1.6 ms, repetition time (TR) of 27 ms, and total imaging time of 4 min and 23 s. 3D imaging with 64 slices was performed inside a 10 mm slab which was excited using a soft excitation pulse.

At the bottom of a glass tube with an outer diameter of 20 mm glass beads were placed and 3 mL of the medium (0.001 M HCl with salts pH 3.0 and tap water in ratio 1:5) was added, so that the tablet was fully covered with the medium throughout the experiment duration. The tube was inserted into a 20 mm radio-frequency coil and inserted in the magnet. After all imaging parameters were set, the tablet was inserted into the medium from the top of the magnet and the measurement was started. The first MR image was taken immediately after the tablet came in contact with the medium and then every 5 min for 100 min (20 images).

Image processing and analysis: Three-dimensional MR images of the tablets were processed by the ImageJ software (National Institutes of Health, Bethesda, MD, USA) for digital image processing. The signal intensity, seen as brightness on MR images, results from the chosen experimental conditions and the differences in the physical state of the water during tablet hydration, expressed by changes in relaxation times. The dry tablet core is black in the MR image, since there is only a small amount of water and spin-spin relaxation time (T2) of the dry tablet is too short to give any MR signal. In the hydrated part of the tablet T2 becomes longer, therefore the MR signal intensity increases and the hydrated part of the tablet becomes brighter in the MR image.

By rotation of the MR images, the longitudinal and transverse slices through the tablet were obtained and were used to study the difference in the disintegration dynamic between both formulations. The images showing disintegration dynamic in the central longitudinal intercepts were analysed through measurement of the surfaces of being wet and disintegrated to different degree. At every time point the surface of the whole tablet and the dry core was measured. By subtraction of the dry core part from the whole tablet, the surface of the wetted part of the tablets was obtained.

Medium absorption

Tablets of each formulation with peeled off coating were placed on an analytical balance (XS203S, Mettler Toledo, Greifensee, Switzerland). 0.02 mL medium (0.001 M HCl with salts pH 3.0 and tap water in ratio 1:5) was dropped on the surface of each tablet in time interval of 5 min. Maximal absorbed weight of medium was detected at the point where the droplet did not soak into the structure but fell aside the surface.

Dissolution in USP2 apparatus

Dissolution was performed in 900 mL of 0.1 M HCl, USP Apparatus 2 (Agilent 708-DS, Santa Clara, USA), 50 rpm with tablet placed in USP sinker.

Dissolution in small vessel dissolution apparatus

To evaluate the worst-case possible *in vivo* hydrodynamic conditions along gastrointestinal tract that could potentiate differences among tested samples, dissolution test was performed as follows: tablets were incubated in media simulating no mixing in the stomach (tablets were immersed in 290 mL of media, composed from 50 mL 0.001 M HCl with salts p^H 3.0 and 240 mL tap water for 15 min without any mixing) and then they were transferred into 200 mL of FeSSIF-v2 for dissolution testing in small vessel dissolution apparatus 2,100 rpm.

Dissolution in USP3 apparatus

Simulation of more mechanically stressed conditions was performed in USP Apparatus 3 (Agilent Bio Dis, Santa Clara, USA). Tablet was placed into the apparatus cell with glass beads and dissolution was performed under conditions simulating gastric (250 mL of 0.001 M HCl with salts) and intestinal milieu

(250mL of FeSSIF p^H 5.0) conditions. Agitation was set to 20 dpm.

c) Pharmacokinetic study

To investigate the in vivo behavior and compare the bioavailability of the two test formulations to that of the reference product, a comparative bioavailability study was conducted under fasting conditions. The pharmacokinetic study had a single-dose, open-label, randomized three-period, three-treatment, crossover design and enrolled healthy adult volunteers. The protocol for the study was approved by the relevant Independent Ethics Committee and was conducted in accordance with Good Clinical Practice and Declaration of Helsinki. Plasma concentrations of the active substance were measured by a validated, sensitive and specific LC/MS/MS assay. The pharmacokinetic parameters AUC (area under the plasma concentration time curve) and Cmax (peak plasma concentration) were calculated using a non-compartmental approach

Results

Comparative bioavailability study results

The geometric mean ratios of parameters AUCt and Cmax derived from the pharmacokinetic analyses of the relative bioavailability study are presented in Table 2. While fast formulation was found bioequivalent, slow formulation failed to show bioequivalence under fasting conditions. The geometric mean ratios of parameters Cmax and AUCt derived from the analysis comparing bioperformance of fast formulation versus slow formulation are also presented in Table 2.

Table 2: Geometric mean ratios (%) (Test formulation/reference product) and fast/slow formulation ratio observed in the bioequivalence study.

Pharmacokinetic parameter	FAST formulation	SLOW formulation	FAST/SLOW formulation
AUCt	91.9	70.7	1.30
Cmax	96.3	71.5	1.35

A clear disparity between slow and fast formulation was observed following oral administration in fasted state, which is considered to be the most sensitive condition to detect a potential difference between formulations. Since AUC reflects the extent of absorption whereas Cmax is used to characterize the rate of absorption, the results demonstrate significantly higher bioavailability of the fast formulation compared to the slow formulation.

Disintegration results

Disintegration results from the standard apparatus are shown in Figure 1 a. Fast formulation shows faster disintegration compared to the slow formulation regardless of discs presence. This result is expected since fast formulation contains also a portion of crospovidone in the intra-granular phase, while slow one contains only extra-granular crospovidone. Visually the disintegration behavior of both formulations followed erosion pattern with gradual particle detachment up until when only small pieces of the tablet remained floating. Usage of discs decreased disintegration time through the mechanical stress caused by the discs on the tablets being submerged in the media. Discs additionally broke down the small pieces remaining after the tablet has already disintegrated.

Disintegration within small volume of medium with the usage of glass beds simulates mechanically more stressed conditions that formulation experiences during passage through the pylorus. Similar disintegration times (Figure 1b) was observed as with standard disintegration apparatus without discs for both formulations. Disintegration followed erosion pattern with the absence of smaller pieces floating in the medium which may relate to the usage of glass beds in constant motion.

Absorption results (i.e., media uptake by tablet) (Figure 1c) reflect significantly higher tendency of the fast formulation to interact with the medium compared to the slow formulation. Namely, fast formulation absorbed 28 % larger amount of medium compared to the slow formulation. This finding again could relate to the higher portion of crospovidone within the fast formulation and thus its increased ability to attract the used medium.

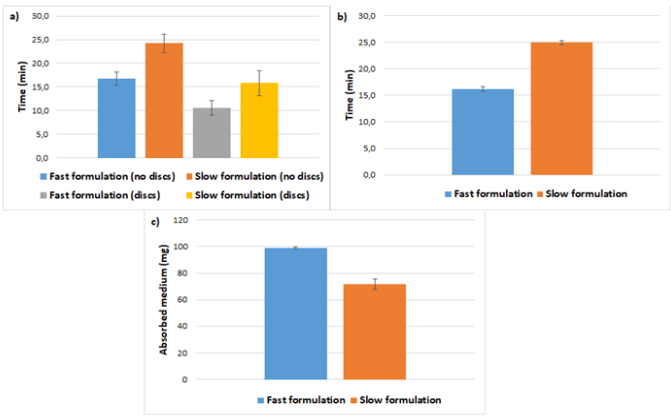

Figure 1: a) Disintegration in standard apparatus with (out) usage of discs;

b) Disintegration in small medium volumes using glass beads in constant motion;

c) Medium absorption of fast and slow formulation.

Disintegration in small volumes without mechanical agitation discriminates better among fast and slow formulation. Namely soaking in 50 mL 0.001 M HCl with salts and tap water in ratio 1:5 visually showed drastically different disintegration behavior between the fast and slow formulation (Figure 2). Slow formulation up to 30 minutes remained intact with slightly soaked surface, while fast formulation after 10 min already started decaying with edges slowly eroding and detaching from the tablet body. After 30 minutes tablets were mechanically destructed without possibility determine the consistency. Edges of slow formulation detached, and partially wet core remained. Fast formulation on the other hand was smashed into a powder form.

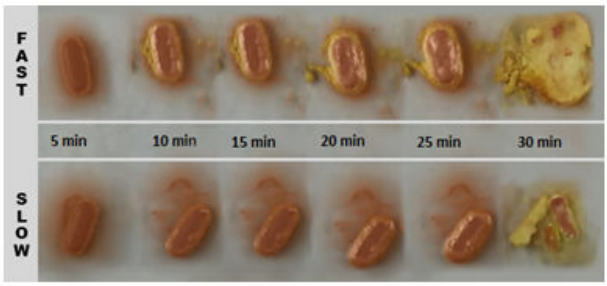

Figure 2: Disintegration in small medium volumes without mechanical agitation.

Textural analysis reflected similar findings. Namely, soaking both formulations in 50 mL 0.001 M HCl with salts and demineralized water in ratio 1:5 showed different tablet consistency. In the case of the fast formulation, the needle probe did not penetrate the tablet after 5 minutes of soaking. The observed force-distance profiles (Figure 3b) were therefore smooth, meaning the needle probe reached the dry tablet core at maximal pressure load of 5 N and retracted to original position. However, after 15 minutes of tablet soaking, the needle did penetrate the tablets, which can be observed as additional peak in the force-distance profile of the fast formulation; the needle probe penetrated the tablets and stopped when 5 N load was reached with touching the surface of the texture analyzer table underneath the tablet tested. On the other hand, under the same conditions in the case of slow formulation, the penetration of the needle probe was observed in one of the three parallel experiments only after 30 minutes of tablet soakin g, suggesting this formulation was prone to slower process of disintegration (Figure 3a).

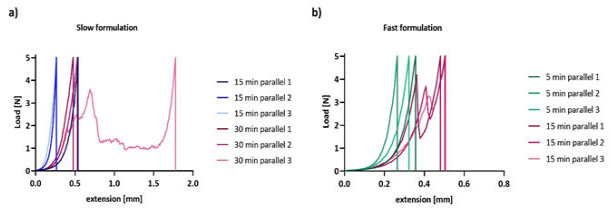

Figure 3: Typical force – distance profiles of slow and fast formulation at specific time points of experiments conducted. a) At 15 and 30 min for the slow formulation and b) at 5 and 15 min for the fast formulation.

In order to visualize the dynamic of tablet decay when exposed to liquid even further, MRI was used. Brightness of the MR images depends on the MR signal and reflects the degree of dryness/wetness of the tablet. The brighter the tablet/tablet part is, the more wet the system is. Measurements were done in triplicate and obtained results were comparable.

The surfaces of the tablets were determined by manual outlining of the regions in the images and image processing in through ImageJ program (see Figure 4a). Changes in the wet and dry segments (surfaces) of the formulations through different time points are shown graphically in Figure 4 b. From Figure 4 c it could be noted that medium penetrated faster in the fast formulation compared to the slow formulation. After 20 minutes the dry part of the fast and slow formulation decreased to 21 ± 3% and 50 ± 8%, respectively. A difference was observed also in the size enlargement rate of whole system, where cross-sectional area of the wetted part after 20 minutes was 185 ± 15% and 96 ± 7% of the primary cross-section for the fast formulation and slow formulation, respectively.

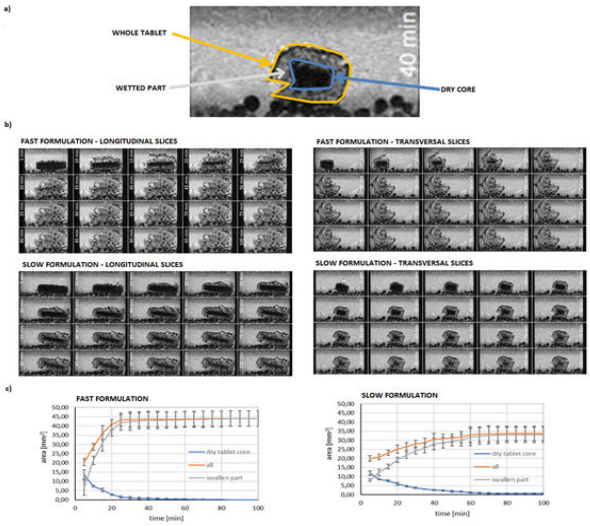

Figure 4: a) Example of determination of differently wetted surfaces in transverse tablet intercept; b) Disintegration dynamics of fast and slow formulation (longitudinal and transversals slices); c) Analysis of disintegration dynamics from transverse intercepts of fast and slow formulation.

Dissolution results

Dissolution results are presented in Figure 5 for all methods that were used to guide the development. Upon arrival of bioequivalence outcome, dissolution in 0.1 M HCl (Apparatus 2,50 rpm, USP sinker, Figure 5a), which is used as quality control method, did not reflect the in-vivo outcome of the formulations. Therefore, one could conclude that under fast conditions, differences in the amount of disintegrant used in test formulations profoundly affects in vivo drug release. Fast bioequivalence results are best described with dissolution performed in small vessel dissolution apparatus, where tablets were initially incubated for 15 min in a mixture of water and acid, which simulates the worst-case conditions in the stomach for this formulation (Figure 5b). Namely, without agitation and

with this short incubation period, it was simulated a scenario, where there is no mechanical stress on the tablet, thus exaggerating impact of disintegrant amount. Also, with short incubation time, we were mimicking that the tablet leaves the stomach immediately after swallowing. In this way, it is not exposed to acidic conditions (i.e., p^H 1.2–2) too long to allow for drug release under solubility-favored conditions, where agglomeration/aggregation is least evident. Differences among samples were observed also in both media and USP3 experimental set-ups (Fig. 5c and 5d) but were less pronounced than in small vessel method.

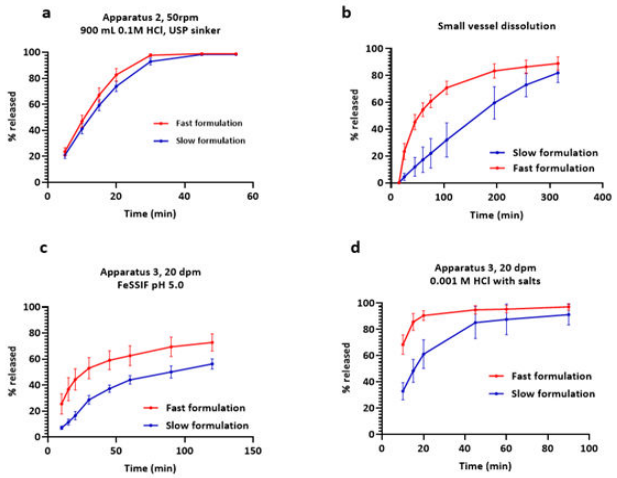

Figure 5: a) Drug release in; b) Disintegration dynamics of fast and slow formulation (longitudinal and transversals slices); c) Analysis of disintegration dynamics from transverse intercepts of fast and slow formulation.

Discussion

Development of orally administrated immediate release products which have long and atypical disintegration behavior poses huge challenge nowadays. Aggregation and gelling of one or more of the formulation constituents coupled with the low solubility and/or permeability of the active compound bring high degree of uncer tainty over the pharmacokinetic performance of the product within the human GIT (gastrointestinal tract).

The aim of our study was to develop bioequivalent generic immediate-release tablet containing BCS 4 drug with poor wetting properties, pH dependent solubility, that readily aggregates and forms gel, and with formulation that shows atypical disintegration pattern, similar as reference tablets. Product development was guided by innovative methods for assessing disintegration and dissolution behavior from bio-relevant perspective of fasting conditions. To tailor drug release, two compositions were proposed, which differ in the amount and position of disintegrant and were tested in bioequivalence study. While one – fast formulation was found bioequivalent, slow formulation showed significantly slower rate and extent of absorption.

For quality control testing of the product classic USP2 dissolution in 900 mL of 0.1 M HCl was proposed. This media was chosen because drug readily dissolves within it, and no addition of surfactants is necessary. However, dissolution in this media shows almost no difference between fast and slow formulation and was thus found non-discriminatory from biorelevant perspective. Disintegration results that were obtaine d with standard disintegration test in water (with and without usage of discs) indicated that there is difference among both formulations in disintegration time, which is in line with the amount of disintegrant contained within the tablet. However, both formulations showed atypically long disintegration times which were shortened when mechanical stress was introduced through the usage of discs. These findings arose a question how important the disintegration time and pattern for the in vivo performance of the product is.

In depth evaluation of disintegration of both formulations followed. Several modifications regarding composition of incubating media for disintegration test and the extent of mechanical stress inflicted upon the formulations were done to obtain more discriminatory in vitro disintegration test that would explain profound in vivo difference under fast conditions. Changing the media from water to mixture of water and 0.001 M HCl with salts (which simulates gastric content after swallowing the tablet with water under fast conditions) and increasing mechanical stress with glass beads on magnetic stirrer did not yield better discriminatory results compared to standard disintegration test.

Only when tablets were immersed in the mixture of water and 0.001M HCl with salts and no mechanical stress was present (disintegration observation in a petri dish), we could visualize different disintegration pattern and profoundly different rate of tablet disintegration. Faster disintegration of sample with higher amount of disintegrant was explained by faster and higher liquid uptake (texture analysis and medium absorption respectively), while in-depth explanation was provided by MRI technique, which showed temporal and spatial differences among tested samples in liquid uptake and wetting pattern.

Since MRI technique is not a high-through put method to be used on regular basis in the industry for product development, with numerous samples needed to cover entire design space, dissolution method was tailored to include the step of liquid penetration and wetting of core material into the experimental procedure. Therefore, tablets were incubated in water for 15 min without any mechanical stress. After removal of incubating fluid, tablets were transferred into the small dissolution vessels containing only 200 mL of dissolution media with pH not favorable for drug dissolution, and dissolution was monitored under non-sink conditions. With this set-up differences among samples were the highest, because when incubation in USP3 apparatus were done, regardless of which dissolution media was used (acidic where the drug readily dissolves or FeSSIF p^H 5.0 where solubility conditions do not favor drug release), mechanical stress of 20 dpm was already sufficient to decrease discriminatory power of dissolution test.

Conclusion

Immediate release tablets which contain BCS 4 compound prone to aggregating and gelling and subsequently show atypically long disintegration time and pattern present huge challenge for evaluation from in vivo perspective. Classic disintegration and dissolution testing often do not reflect the in vivo conditions in the GIT and thus could lead to overseeing of some important product features, which could further affect pharmacokinetics. Therefore, it is desirable that during development of atypical immediate release product their behavior is screened through both bio-relevant /discriminatory disintegration and dissolution tests. Within this study several non-standard tests were employed in order to evaluate and explain in-vivo tablet disintegration and drug release. While QC (Quality Control) dissolution method did not provide significant discriminatory power between formulations containing different amount of disintegrant, classic disintegration test set a focus on the atypically long times for tablet decay and thus the significant effect of disintegrant amount on tablet performance. Disintegration tests based on application of minimal mechanical agitation such as disintegration in 50 mL medium in a petri dish just by tablet standing; medium absorption; texture analysis of soaked tablets after predefined time period and MRI gave insights into a significantly different disintegration rate, medium imbibition and wetting tendency of the two formulations containing different amount of crospovidone. These findings were also confirmed through conducting dissolution testing in small vessel apparatus, which enabled simulation of least aggressive in vivo hydrodynamic conditions along gastrointestinal tract and in such way significantly distinguished both formulations between themselves. All the results obtained through these innovative and non-standard tests reflected the actual in vivo results obtained in a bioequivalence study conducted under fasting conditions.

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