Disintegration test journal pdf

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This study provides scientific justification for using disintegration testing rather than dissolution testing as a quality control method for certain immediate release (IR) formulations. A mechanistic approach, which is beyond the current FDA criteria, is presented. Dissolution testing via United States Pharmacopeial Convention Apparatus II at various paddle speeds was performed for immediate and extended release formulations of metronidazole. Dissolution profile fitting via DDSolver and dissolution profile predictions via DDDPlus™ were performed. The results showed that Fickian diffusion and drug particle properties (DPP) were responsible for the dissolution of the IR tablets, and that formulation factors (eg, coning) impacted dissolution only at lower rotation speeds. Dissolution was completely formulation controlled if extended release tablets were tested and DPP were not important. To demonstrate that disintegration is the most important dosage form attribute when dissolution is DPP controlled, disintegration, intrinsic dissolution and dissolution testing were performed in conventional and disintegration impacting media (DIM). Tablet disintegration was affected by DIM and model fitting to the Korsmeyer–Peppas equation showed a growing effect of the formulation in DIM. DDDPlus was able to predict tablet dissolution and the intrinsic dissolution profiles in conventional media and DIM. The study showed that disintegration has to occur before DPP-dependent dissolution can happen. The study suggests that disintegration can be used as performance test of rapidly disintegrating tablets beyond the FDA criteria. The scientific criteria and justification is that dissolution has to be DPP dependent, originated from active pharmaceutical ingredient characteristics and formulations factors have to be negligible. Keywords: API, dissolution, disintegration, DDDPlus, quality-by-design, product specification, model fitting Introduction Quality-by-design (QbD) approaches aim to utilize the most appropriate performance or quality control tests for a drug product.1,2 Still, the critical quality attributes (CQAs) are often more based on empirical values and guidelines, instead of understanding mechanistic processes and excipient-active pharmaceutical ingredient (API) interactions. The ICH Guideline Q6A “Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances” outlines acceptance criteria for different dosage forms and routes of administration. The guidance document contains decision tree #7.1, which allows disintegration instead of dissolution testing to be used as a performance/quality control test for rapidly dissolving dosage forms (Q>80% in 15 minutes) containing highly soluble drugs (BCS class I/III), if a relationship between dissolution and disintegration has been established.3 The new United States Pharmacopeial Convention (USP) Chapter “Oral drug products – Product quality test”4 follows the ICH guidance criteria and states under specific tests for tablets (excerpt of the original text): The disintegration test, if included, is used only as a quality control test and not as a product performance test and should conform with the specifications in the monograph.4 The US Food and Drug Administration (FDA) draft guidance on “Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System (BCS) Class 1 and 3 Drugs” allows the use of disintegration testing as a surrogate for routine release and stability dissolution testing for rapidly dissolving BCS class I/III drug products (Q=80% in 15 minutes). The acceptance criterion is disintegration within 5 minutes in 0.01M HCl.5 The current FDA guidance on “Dissolution Testing of Immediate Release Dosage Forms”, which the new draft will supersede, suggests a single-point dissolution tests specification of “Q=80% in 60 minutes” as a replacement for dissolution testing for rapidly dissolving BCS class I/III drugs.6 In industry, there is little consensus on how to apply these guidelines. Many companies simply default to dissolution testing rather than justify disintegration as the easiest path forward for a global product. However, with a better mechanistic understanding and knowledge of critical parameters in the dissolution process, this aversion can be avoided. A modeling-based approach is needed to justify important product specifications and support CQA beyond guideline assumptions. This will enable globally operating companies to justify their product specifications beyond sometimes contradicting national guidances. In this study, metronidazole, a BCS class I drug, was chosen as the model API.7 Four different formulations were tested, with two being fast disintegrating, immediate release (IR#1 and IR#2) tablets, and the other two formulated for a slow erosion and drug release (slow eroding tablet [SET] and granulated tablet [GT]). API and excipient interactions were investigated using model fitting and computer simulations of the obtained dissolution profiles. The influence of disintegration on API-controlled dissolution was studied using new disintegration impacting media (DIM). This study mechanistically investigated disintegration and dissolution behavior of different formulations. Model fitting was utilized in order to differentiate between API and formulation controlled drug release. This approach enables formulation scientists to identify CQAs for IR tablets. Disintegration testing might be used if drug particle properties (DPP) control dissolution. This was confirmed by simulations using DDDPlus software. Dissolution testing is required if the formulation significantly controls the dissolution process. This approach goes beyond the current FDA criteria for IR tablets and provides scientific justification for using disintegration instead of dissolution testing in a QbD environment. Materials and methods Materials Metronidazole (for tablets and quantification standard) was purchased from Medisca® (Richmond, BC, Canada; LOT 601124/C). Microcrystalline cellulose (Avicel® PH-102 NF; for IR#2 formulation) was obtained from FMC Biopolymer (Philadelphia, PA, USA). Microcrystalline cellulose NF, dicalcium phosphate dihydrate NF (for IR#1 formulation) and croscarmellose sodium were purchased from PCCA Canada (London, ON, Canada). Galen IQ™ 801 was obtained from BENEO-Palatinit GmbH (Mannheim, Germany) and magnesium stearate from H.L. Blachford Ltd (Mississauga, ON, Canada; IR#1) and Street Chemicals & Co (Montreal, QC, Canada; IR#2). Mannitol was purchased from EM Science (Gibbstown, NJ, USA), Starch 1500 from Colorcon (Indianapolis, IN, USA), Povidone K30 “Kollidon® 30” from BASF (Mt Olive, NJ, USA) and sodium carbonate (anhydrous) was obtained from BDH Inc. (Toronto, ON, Canada). Ethanol was obtained from GreenField Specialty Alcohols Inc. (Brampton, ON, Canada). Buffer media for dissolution testing were prepared according to USP specifications for acetate buffer pH 4.5 and SGFsp (simulated gastric fluid sine pepsin).4 Sodium acetate trihydrate was purchased from Caledon Laboratories Ltd (Georgetown, ON, Canada) and glacial acetic acid USP, hydrochloric acid NF and sodium chloride USP were purchased from Fisher Scientific (Fair Lawn, NJ, USA). For the sugar solutions, Rogers Granulated Sugar from Lantic Inc. (Montreal, QC, Canada) was used. High-performance liquid chromatography (HPLC) grade water and water for the dissolution and disintegration test media were generated in an Elgastat Maxima UF and an Elgastat Option 3B water purifier by ELGA Laboratories Ltd. (Mississauga, ON, Canada) and filtered through a 0.45 µm membrane MCE filter by Fisher Scientific (Pittsburgh, PA, USA; for immersion media) and a Durapore® 0.22 µm GV filter by Millipore Canada Ltd. (Etobicoke, ON, Canada; for HPLC mobile phase), respectively. Acetonitrile for the HPLC mobile phase was purchased from VWR International LLC. (Radnor, PA, USA) and filtered through a Durapore 0.45 µm HV filter by Millipore Canada Ltd. (Etobicoke, ON, Canada). Methods Tablets Tablets were pressed with a Carver Laboratory Press by Fred S Carver Inc. Hydraulic Equipment (Manomonee Falls, WI, USA). Direct compression IR tablets (IR#1 and IR#2) were pressed at 1 metric ton pressure for 30 seconds, after blending the formulation ingredients (Tables 1 and 2) in a rotating blender by Erweka GmbH (Heusenstamm, Germany) for 30 minutes. These parameters had previously been established as a starting point that usually provided tablets of adequate quality in this group.8 Direct compression SETs (Table 3) were pressed for 1 minute at 1 metric ton pressure. The granulate for the GTs (Table 4) was prepared by adding ~5 mL of 70% ethanol to about 11 g of intragranular formulation mix, granulating through a No 20 sieve, drying in vacuum at 45°C and sieving the granulate through a No 20 sieve, onto a No 40 sieve. Magnesium stearate was then added as lubricant and the tablets were pressed for at 1 metric ton pressure for 30 seconds. Table 1 Immediate release formulation #1 (IR#1) Table 2 Immediate release formulation #2 (IR#2) Table 3 Slow eroding tablet (SET) formulation Table 4 Granulated tablet (GT) formulation Dissolution and disintegration testing The pH of the dissolution and disintegration media was measured using an accumet® XL 20 pH-meter by Fisher Scientific (Fair Lawn, NJ, USA). Dissolution testing was performed using a VK 7020 system from Varian Inc. (Cary, NC, USA) equipped with 70 µm Full Flow™ Filters (Varian Inc.), since smaller pore sizes proved to be problematic with the more viscous DIM, and a VK 8000 auto sampler (Varian Inc.). All tests were performed with USP Apparatus 2 and 900 mL dissolution medium (SGFsp, acetate buffer USP pH 4.5, 10%/20%/30% sucrose solution). SGFsp and acetate buffer were deaerated by filtration, ultrasound and vacuum. Samples (1.0 mL) were withdrawn without replacement at each time point (5, 10, 15, 20, 30, 45 and 60 minutes) and were transferred into 2.5 mL vials for HPLC analysis. The drug concentration in the vessel was adjusted by calculation. Disintegration testing was performed in an ED-2L disintegration tester by Electrolab India Pvt. Ltd. (Navi-Mumbai, India) in the same media as the dissolution tests according to USP standards.4 Intrinsic dissolution testing was performed in the same media as the dissolution tests using a modified version of the rotating disk apparatus described in USP Chapter .4 Approximately 160–170 mg were pressed into the die to be used as a rotating disk apparatus using the Carver Laboratory Press at 2 metric tons pressure for 90 seconds. The apparatus was mounted in a type RZR50 stirrer by Caframo Ltd. (Wiarton, ON, Canada) and immersed in a beaker containing 100 mL dissolution medium, with the temperature being kept constant at 37°C±0.5°C by a hot water bath. The test was performed at 100 rpm and 1.0 mL samples were drawn using a BD 1 mL syringe (Franklin Lakes, NJ, USA) and transferred into HPLC vials for analysis by filtering them through a 13 mm syringe filter with a 0.2 µm PTFE membrane by VWR International LLC (Radnor, PA, USA). SGFsp and acetate buffer were deaerated by filtration, ultrasound and vacuum. HPLC The standard solution for HPLC quantification of metronidazole was prepared by dissolving metronidazole in the respective medium, using a Branson 3800 ultrasonic bath from Emerson Industrial Automation (Ferguson, MO, USA), and the calibration curve was prepared for a range from 3.75% to 120% of the expected maximum drug concentrations. Quantification of metronidazole was performed via a slightly modified version of a previously published HPLC method.7 A VP-class Shimadzu Scientific Instruments (Kyoto, Japan) liquid chromatograph, equipped with a Lichrospher® 60 RP Select B column (5 µm, 12.5×4 mm, by Merck Darmstadt, Germany) with a matching guard column and connected to a CBM-20A system controller, two LC-10AS pumps, an SIL-10ADVP auto sampler and a SPD-M10AVP diode array detector, was used. The system was controlled using the data acquisition software “EZ Start 7.4” (Shimadzu). The mobile phase was deaerated before use, using a combination of vacuum filtration, and ultrasound and the flow rate was set to 1 mL/minute, using a 70:30 mix of water and acetonitrile. A sample volume of 10 µL was directly injected without dilution and the retention time for metronidazole was ~2 minutes with a total run time of 3 minutes. For all dissolution tests, the correlation coefficient (r2) for the calibration curve was ≥0.998. DDDPlus™ simulation software DDDPlus (Dose Disintegration and Dissolution Software) version 5.0.0011 by Simulations Plus, Inc. (Lancaster, CA, USA) was used to simulate dissolution behavior of different formulations by defining excipients and test conditions.9 The software is divided into three main tabs – formulation, dissolution method and simulation. The formulation tab lets the user chose from eight different dosage forms – such as IR tablet, coated tablet, powder or capsule – and provide manufacturing properties, such as compression force or tablet diameter, as well as the formulation composition. The latter can be made up from excipients in the included database or user-defined ingredients. The role of the ingredient (API, disintegrant, polymer, etc.) can be set by the user; the physicochemical properties, such as solubility, pKa, diffusion coefficient or logD and the particle size distribution can be defined and a dissolution model (eg, mass transfer, Nernst-Brunner, intrinsic dissolution) is chosen. An excipient-specific coefficient which represents the influence of the excipient on the formulation, as well as a calibration coefficient, can be defined. The parameters which were used for the simulations in this study can be found in Tables 5 and 6 and were either measured, collected from literature, or part of the default excipient database in DDDPlus. A solubility vs pH profile was established using the “pKa Table” dialog and literature values, which were also used in the biowaiver monograph for metronidazole, and an “.spd” (solubility-pH data) file was created.10,11 Table 5 DDDPlus™ parameters for intrinsic dissolution simulationAbbreviations: DDDPlus, Dose Disintegration and Dissolution Software; HPLC, high-performance liquid chromatography; SD, standard deviation; SGFsp, simulated gastric fluid sine pepsin. Table 6 DDDPlus™ parameters for IR#2 formulationNotes: Parameters without a source were part of the DDDPlus excipient database, standard values or calculated using the integrated conversion tool (diffusion coefficient). Croscarmellose disintegration constant and metronidazole mean radius were optimized to fit buffer pH 4.5 and SGFsp in vitro data via DDDPlus. Metronidazole solubility at pH 4.5 was measured via HPLC and general properties were gathered during the tablet manufacturing process. Tablet Tensile Strength was calculated using the modified Fell and Newton equation by Pitt et al.37,38 aOptimized calibration constants for each medium: SGFsp: 0.3564, acetate buffer pH 4.5: 0.2330, 10% sucrose: 0.2270, 20% sucrose: 0.1910, 30% sucrose: 0.1471. ‘–’ indicates no value.Abbreviations: DDDPlus, Dose Disintegration and Dissolution Software; HPLC, high-performance liquid chromatography; IR, immediate release; MCC, microcrystalline cellulose; SD, standard deviation; USP, United States Pharmacopeial Convention. Simulation test conditions were chosen to be identical to the actual dissolution and intrinsic dissolution test conditions of the in vitro tests performed, using 900 mL medium and 100 mL medium, respectively, as well as paddle speeds of 25, 50 and 75 rpm (basket speed: 100 rpm) and a 60 minutes (25 minutes) simulation length. New media were defined using DDDPlus integrated medium composition tool, with the pH being the measured pH and dynamic viscosity at 37°C being estimated values based on inter- and extrapolation of literature data.12 The chosen parameters for the simulations can be found in Table 7. Table 7 Medium parameters used for simulations in DDDPlus™Notes: Medium pH was measured. Medium viscosity was either taken from DDDPlus (SGFsp, USP acetate 4.5) or estimated (sucrose solutions; see “Methods” section). USP acetate was used directly from the database. SGFsp was created as a custom medium, using the “USP Hydrochloric Acid 1.2” medium as a template and adjusting the ingredient concentrations. Sucrose media were created from scratch. ‘–’ indicates no value.Abbreviations: DDDPlus, Dose Disintegration and Dissolution Software; NA, not applicable; Sucr, sucrose; SGFsp, simulated gastric fluid sine pepsin; USP, United States Pharmacopeial Convention. The third tab in the software is used to simulate either a single simulation, a parameter sensitivity analysis, a virtual trial, parameter optimization using provided in vitro data, or compare the simulation results to the provided in vitro data using f1/f2-testing. The results can be displayed graphically for each ingredient and can be exported for further use. Data analysis All data analysis was performed via either DDDPlus or using Microsoft Excel™ with DDSolver. Dissolution and intrinsic dissolution tests were graphically plotted in Microsoft Excel and statistically evaluated using DDSolver, a free excel plugin designed for dissolution profile data analysis, like profile comparison or modeling.13,14 Profiles showing a higher dissolution rate than 100%, due to calibration inaccuracy, were normalized to a maximum of 100% for better compatibility with DDDPlus. This was achieved by defining the highest fraction dissolved value as 100% and multiplying all the other profiles in the plot figure by the same factor in order to maintain comparability. Pairwise dissolution data comparison was performed via f2 statistics for both in vitro and in vitro data, as well as for evaluating in silico predictions. The coefficient of determination (R2) for evaluating in silico data correlation to in vitro data was obtained from DDDPlus. Model fitting in DDSolver was used to determine drug release mechanisms of the different tablet formulation, by using zero order, first order, Gompertz, Weibull and Hopfenberg functions, as well as the Korsmeyer–Peppas equation.15–17 Korsmeyer-Peppas modeling requires Q-values of

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