A Quality-by-Design Study for an Immediate-Release Tablet Platform: Examining the Relative Impact of Active Pharmaceutical Ingredient Properties, Processing Methods, and Excipient Variability on Drug Product Quality Attributes

JOSEPH KUSHNER , IV,[1] BETH A. LANGDON,[1] IAN HICKS,[2] DANIEL SONG,[1] FASHENG LI,[1] LALJI KATHIRIA,[2] ANIL KANE,[2] GAUTAM RANADE,[1] KAM AGARWAL[2]

[1]Pfizer Worldwide Research and Development, Groton, Connecticut 06340
[2]Patheon Inc., Mississauga, Ontario L5N 7K9

Received 31 May 2013; revised 22 October 2013; accepted 29 October 2013

Published online 20 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23810

ABSTRACT: The impact of filler–lubricant particle size ratio variation (3.4–41.6) on the attributes of an immediate-release tablet was compared with the impacts of the manufacturing method used (direct compression or dry granulation) and drug loading (1%, 5%, and 25%), particle size (D[4,3]: 8–114 μm), and drug type (theophylline or ibuprofen). All batches were successfully manufactured, except for direct compression of 25% drug loading of 8 μm (D[4,3]) drug, which exhibited very poor flow properties. All manufactured tablets possessed adequate quality attributes: tablet weight uniformity <4% RSD, tablet potency: 94%–105%, content uniformity <6% RSD, acceptance value ≤ 15, solid fraction: 0.82–0.86, tensile strength >1 MPa, friability ≤0.2% weight loss, and disintegration time < 4 min. The filler–lubricant particle size ratio exhibited the greatest impact on blend and granulation particle size and granulation flow, whereas drug property variation dominated blend flow, ribbon solid fraction, and tablet quality attributes. Although statistically significant effects were observed, the results of this study suggest that the manufacturability and performance of this immediate-release tablet formulation is robust to a broad range of variation in drug properties, both within-grade and extra-grade excipient particle size variations, and the choice of manufacturing method. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:527–538, 2014
Keywords: excipients; quality by design (QBD); solid dosage form; content uniformity; factorial design; formulation; hardness; oral drug delivery; tableting

INTRODUCTION

The science- and risk-based approach to regulating pharmaceutical manufacturing, developed in 2004 by the Office of New Drug Chemistry in the US Food and Drug Administration (FDA), focuses on the impact of chemistry, pharmaceutical formulation, and manufacturing processes on drug product critical quality attributes (CQAs) and their impact on safety and efficacy.[1] In 2012, the FDA released a guidance for Abbreviated New Drug Applications that further affirmed the role of excipient material property understanding (along with drug substance and manufacturing process understanding) as a significant aspect of Quality-by-Design (QbD) drug product development.[2] As a direct result of these regulatory expectations, the impact of excipients on the manufacturability and performance of new drug products has recently received increased scrutiny in the pharmaceutical industry.[3,4] Specifically, USP Excipient Performance chapter <1059> has been designed to provide an overview of typical material attributes associated with functional excipient performance categories along with additional tests for evaluating excipient physicochemical properties.[5] In addition, several QbD-related studies have examined the impact of excipients on drug product performance, either through changes in excipient levels in the formulation[6–12] or the use of alternate sources of an excipient.[4,13–15]

Although the selection of the excipients with the proper functionality and their corresponding levels in the drug product formulation are critical to drug product performance, a deeper understanding of how variability in the excipients can affect drug product performance and the proposed control strategy was also identified as an important component of improved drug product development.[16] A number of drug product recalls identified excipient variability, and, therefore, a lack of an adequate control strategy, as a contributor to failure of the drug product, further underscoring the need for improved excipient variability understanding.[17] However, evaluating the impact of excipient variability on drug product performance has presented a greater challenge to date than evaluating API (active pharmaceutical ingredient) and process impacts on drug product performance. This is partially because of the pharmaceutical manufacturer having more internal capability to manipulate the API and the manufacturing process for experimental study. For excipients, the observed lot-to-lot variability for an individual grade is a function of the control strategy put in place by the excipient supplier. Because of the scales of excipient manufacture and the broader industrial application of many pharmaceutical excipients, it can be difficult for pharmaceutical manufacturers to easily obtain an ideal set of samples to adequately investigate the impact of excipient material properties on drug product performance. Further, the number of excipient material properties combined with the number of

Correspondence to: Joseph Kushner, IV (Telephone: +860-686-1098; Fax +860-715-9169; E-mail: joseph.kushner@pfizer.com)
This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com/.

Journal of Pharmaceutical Sciences, Vol. 103, 527–538 (2014)

excipients in a drug product formulation presents an economic and logistic challenge for executing manageable experimental designs. Risk-based approaches to identify the most impactful excipient material properties (e.g., functional properties as described in <1059>) have been previously examined as a way to streamline experimental evaluation of excipient variability impacts on drug product performance.[18] In addition, a data-based, multivariate method was developed, which utilizes quantitative physicochemical property data included in vendor certificates of analysis, to better enable the evaluation of the lot-to-lot variability for a larger number of excipient properties reported by the excipient vendor.[19]

Once evaluated, excipient variability understanding can then be combined with the knowledge of the API properties and the process parameters used to manufacture the drug product to develop an appropriate control strategy that ensures the consistent supply of a safe, and efficacious, drug product. The overall variability in a particular CQA has been suggested to be a combination of the variability of the API, the excipients, the manufacturing process, and the interactions of any of these individual factors.[10] Although the prior studies highlight the development of risk-based, experiment-based, and data-based approaches for evaluating excipient variability and understanding its impact on drug product performance, there has been very little investigation into understanding how much variability in excipients impacts drug product performance relative to variability in API properties and processing parameters or method.

Therefore, the present study provides an example assessment of the relative impact of variability in API, excipients, and the manufacturing process on final performance of two model drug products to aid those that pursue QbD drug product development. Specifically, we examined the relative impact of the following variables—(1) API type, (2) API particle size, (3) API loading, (4) manufacturing method (direct compression and dry granulation), and (5) a range of diluent to lubricant particle size ratios—on the quality attributes and manufacturability of a solid, oral, immediate-release tablet platform consisting of ibuprofen or theophylline (as model APIs), microcrystalline cellulose (MCC) and spray-dried lactose (as model diluents), croscarmellose sodium (as a model disintegrant), and magnesium stearate (as a model lubricant). A statistical design of experiments for investigating the impact of these factors on drug product manufacturability and performance is presented. Our analysis of the results of the investigation is also presented.

MATERIAL AND METHODS

Materials

Table 1 below provides a list of API**s** and excipients used in this study. Ibuprofen and theophylline served as the model APIs, MCC served as the ductile diluent, lactose (spray dried) served as a brittle diluent, croscarmellose sodium served as the disintegrant, and magnesium stearate served as the lubricant.

Table 1. Active Pharmaceutical Ingredient and Excipient Information, Particle Size Results, and Design of Experiments Designation

Material Name (Vendor, Location)	Vendor Grade	Vendor Lot #	D[4,3] (μm)	D10 (μm)	D50 (μm)	D90 (μm)	Factor Level
Ibuprofen API (BASF, Ludwigshafen, Germany)	25	IB1V0817	29.1	8.8	25.4	55.3	LOW
	38	IB1V0311	42.6	11.4	35.4	83.8	MID
	50	IB1V1089	55.3	13.1	44.6	112.6	HIGH
Theophylline API (BASF)	Anhydrous powder	179921AX20	8.0	1.9	6.8	15.8	LOW
	200M	169321AX20	37.6	7.6	29.1	79.7	MID
	PLV Micronized	198721AX20	113.5	13.9	65.9	216.8	HIGH
Croscarmellose sodium (FMC Biopolymer, Philadelphia, Pennsylvania)	AC-Di-Sol SD-711 NF	TN12824180	57.8	19.2	44.8	115.0	–
Microcrystalline cellulose (FMC Biopolymer)	Avicel 200	PN12824026	244.9	42.5	228.1	466.9	1
	Avicel 102-C5b	71138C5BC	136.2	34.2	124.4	254.5	2
	Avicel 102-N3b	P211823545	126.2	33.7	113.8	237.3	3
	Avicel 102-N4a	P212824256	101.9	30.1	90.9	190.3	4
	Avicel 101	P112824137	62.9	20.6	54.4	118.8	5
Lactose (spray dried) (DMV Fontera, Goch, Germany)	Lactopress 250 (screened coarse)	N/A	159.4	92.8	152.0	240.4	1
	Lactose SD11 (NZ)	HV120027	148.3	52.0	139.2	258.2	2
	Lactopress 260	600656	137.6	54.8	126.8	237.8	3
	Lactose SD11 (EU)	10648454	125.9	50.5	116.4	217.1	4
	Lactopress 250 (screened fine)	N/A	77.6	34.8	73.0	128.5	5
	Lactopress 250	600722	124.1	54.6	115.6	208.4	N/A
	Lactopress 250	600848	122.9	54.3	114.6	206.3	N/A
Magnesium stearate (Mallinckrodt, Hazelwood, Missouri)	Magnesium stearate 434	1207000026	19.9	6.1	18.7	35.0	1
	Magnesium stearate VG 1726	1110000870	12.1	2.7	10.7	23.3	2
	Magnesium stearate KP 5712	1005000629	11.7	2.6	10.3	22.5	3
	Magnesium g stearate KP 5712	1203000003	10.6	2.4	9.4	20.2	4
	Magnesium stearate KP 5712	1203000005	5.2	1.4	4.7	9.7	5

 DOI 10.1002/jps.23810