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RESEARCH PAPER

Development of a Control Strategy for Benzene Impurity in HPMCAS-Stabilized Spray-Dried Dispersion Drug Products Using a Science-Based and Risk-Based Approach

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ABSTRACT

Purpose To develop a strategy to control benzene, an ICH Q3C Class 1 impurity that may be present in spray solvents at ppm concentration, in amorphous polymer-stabilized spray-dried dispersion (SDD) products.

Methods Risk assessments included determining the probability for benzene concentration in primary spray solvents, the physical properties of volatiles, and the potential enrichment of benzene from solution to solid. Mechanistic understanding of benzene removal was gained through a benzene-spiked fate and tolerance (F&T) study simulating worst-case spray-drying conditions and application of diffusion models for secondary drying.

Results The mass ratio of spray solution to solid presented the highest risk of benzene enrichment. With slow spray-drying kinetics, benzene was reduced about 700-fold. Under standard secondary-drying conditions to remove residual solvents, residual benzene was further removed. Using diffusion models, the maximum benzene concentration was approximated for SDDs dried to the in-process control (IPC) limit of primary solvents.

Conclusions Two critical control points were established to eliminate any risk of residual benzene reaching patients: (1) upstream control of benzene in solvents (≤10 ppm) and (2) IPC of residual solvents in polymer-stabilized SDDs.

KEY WORDS benzene · control · impurity · solvent · spray-dried dispersion (SDD)

ABBREVIATIONS

%RSD	Percentage of relative standard deviation
$[\text{imp}]_{\text{solids}}$	Impurity concentration in the SDD
$[\text{imp}]_{\text{solvent}}$	Impurity concentration in the primary spray solvent
API	Active pharmaceutical ingredient
EP	European pharmacopoeia
F&T	Fate and tolerance
FID	Flame ionization detector
GC	Gas chromatography
HPMCAS	Hydroxypropylmethyl cellulose (hypromellose) acetate succinate
ICH	International conference on harmonisation
IPC	In process control
JP	Japan pharmacopoeia
LOQ	Limit of quantification
NF	National formulary
ppm	Parts per million
RER	Relative evaporation rate
RH	Relative humidity
RS_{out}	Relative saturation of solvent at the spray-dryer outlet
SDD	Spray-dried dispersion
$T_{\text{condenser}}$	Condenser temperature
T_g	Glass-transition temperature

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T_{in}	Spray-dryer inlet temperature
T_{out}	Spray-dryer outlet temperature
β	Diffusion parameter
ΔH_{vap}	Heat of vaporization

INTRODUCTION

The use of polymer-stabilized amorphous spray-dried dispersions (SDD) containing active pharmaceutical ingredient (API) is a valuable formulation strategy to increase the bioavailability of poorly soluble drug candidates through enhancing their solubility and dissolution rate (1, 2). Due to the relative ease of scale-down and scale-up of spray drying technology and applicability to compounds with a broad range of physical-chemical properties, SDDs have been widely used in preclinical formulations through clinical supplies to commercial products (3, 4). SDDs may be used with no further formulation (e.g., drug-in-capsule, drug in bottle, on-site compounding) or be further formulated as a solid dosage form (e.g., tablet).

The spray-drying process (1, 2) involves dissolving the API and stabilizing polymer [e.g., hydroxypropylmethyl cellulose (hypromellose) acetate succinate (HPMCAS)] in a volatile organic solvent that is rapidly removed during spray-drying to form SDD particles (referred to as “wet” SDD), followed by a separate secondary-drying step to remove the residual solvent to an acceptable limit (the final SDD is referred to as “dried” SDD). The importance of controlling the residual-solvent concentration in final dried SDD for clinical studies to meet International Conference of Harmonisation (ICH) Q3C (R5) requirements is well-recognized (5, 6). However, the risk from solvent-related impurities, specifically benzene, has not been reported. ICH Q3C defines benzene as a Class 1 carcinogenic solvent, which, if unavoidable in a drug product, should be restricted to a limit of 2 parts per million (ppm) (6).

Acetone and methanol are the primary solvents used to prepare the spray solutions and may contain benzene at ppm concentrations as a by-product of the solvent production process, depending upon the choice of process (7–11). During the SDD spray-drying process, most of the primary spray solvent and benzene is removed via evaporation. However, since benzene has a higher boiling point (80.1°C) than acetone (56.5°C) and methanol (64.7°C), a potential may exist for benzene to be concentrated in the wet SDD. During the subsequent secondary-drying, the residual solvent will be further reduced to a target concentration below the ICH Q3C limit. Depending on the relative removal rate between the primary solvent and benzene impurity during secondary-drying, higher benzene concentrations in wet SDD could translate to higher benzene concentrations in the final dried SDDs. This potential enrichment of benzene in the SDD from acetone and methanol spray solvents represents a potential safety risk and could result in noncompliance with the ICH limit of 2 ppm. Therefore, a strategy is needed to control the benzene concentration in SDDs through risk assessment and development of a mechanistic understanding of benzene removal during spray-drying.

This paper describes our science-based and risk-based approach, as detailed below, to establish a control strategy for limiting the benzene concentration in SDDs.

Risk analysis was performed by a) assessment of the probability that benzene is present as an impurity in acetone and methanol lots through a literature review of production methods and verification by measuring the benzene concentrations in actual solvent lots typical of those used to manufacture clinical SDDs; and b) understanding of the likelihood that benzene is concentrated in the SDD during spray-drying by comparing the physical properties of benzene to those of acetone and methanol and understanding how low solids concentration in the spray solutions impact enrichment even if the primary spray solvents contain benzene only at sub-ppm concentrations.

A mechanistic understanding of the capability of the SDD process for benzene removal was developed by a) quantitative understanding of the fate of benzene through a fate and tolerance (F&T) study using conditions simulating worst-case scenarios (high benzene concentration in incoming solvent, low solids concentration in spray solution, and slow spray-drying kinetics), in conjunction with standard secondary-drying conditions in a tray dryer; and b) application of mathematical diffusion models of secondary drying to estimate the maximum residual benzene in dried SDDs at given concentrations of benzene in the incoming primary spray solvent, solvent in wet SDDs, and residual solvent in final SDDs.

Finally, based on the findings of this study, we derived a strategy embracing a significant safety margin to control the concentration of the benzene impurity in HPMCAS-stabilized SDDs spray-dried from acetone and methanol. This paper is not only the first to discuss the control strategy for residual benzene in SDDs, but it is also the first to report benzene removal efficiency during spray-drying and subsequent secondary-drying. The science-based and risk-based approaches described in this paper can be easily adapted to establish a control strategy for volatile impurities in any spray solvent, especially for impurities with high boiling points.

MATERIALS AND METHODS

Materials

Methanol and acetone (HR-GC grade) were purchased from Omnisolv for use in analytical testing. Methanol and acetone

[National Formulary (NF) grade, > 99.5%] were purchased from Ultra Pure Solutions for use in spray solutions. Benzene (analytical-standard grade, 99.99%) was purchased from Fluka for use in analytical testing and spiking of spray solutions. NF-grade HPMCAS (AQOAT, LG grade) was purchased from Shin-Etsu Chemical Co.

Analytical Methods

An Agilent Model 6890 gas chromatograph (GC) equipped with a split/splitless injector, a flame ionization detector (FID), and an Empower data-acquisition system was used for GC separation and detection. Three GC test procedures with FID were developed and validated to determine (1) benzene concentration in acetone; (2) benzene concentration in methanol; and (3) benzene concentration in placebo spray-dried HPMCAS. A previously validated method was modified for determining the methanol and acetone concentration in placebo spray-dried HPMCAS. All test procedures utilize multiple-concentration external standardization. The first three methods for determining benzene concentration have a limit of quantification (LOQ) at 0.5 ppm (*w/w*) and a linear range 0.5 to 250 ppm (*w/w*) of benzene with respect to solvent or SDD weight. Chromatographic conditions and sample preparation are briefly described below and accuracy and precision data are provided to support analytical-method validation.

Benzene in Acetone and Benzene in Methanol

Both methods were performed on an Agilent HP-5 capillary column with a 5% phenyl-95% dimethylpolysiloxane stationary phase (30 m×0.32 mm×0.25 μm). The injector temperature was set at 250°C and the detector temperature was set at 300°C. The GC oven temperature was held at 40°C for 5 min and then programmed to increase to 200°C at a rate of 40°C/min. Helium was used as the carrier gas at a constant flow rate of 1.5 mL/min. A split flow of 1:10 was used. An Agilent Model 7683 autosampler was used to inject 2 μL of the acetone solution and 1 μL of the methanol solution. The signal-to-noise ratio for benzene at 0.5 ppm (LOQ) was > 15.

For the benzene-in-acetone method, the percentages of relative standard deviation (%RSDs) of benzene peak area response were within 10% for 6 injections of standard solution at three concentrations (1, 10, and 104 ppm). Recoveries at three spiked concentration concentrations (1, 10, and 103 ppm) were within 15%.

For the benzene-in-methanol method, the %RSDs of benzene peak area response were within 10% for six injections of standard solution at three concentrations (1, 10, and 99 ppm). Percent recoveries at three spiked concentration concentrations (1, 11, and 107 ppm) were within 15%.

Benzene in SDD and Residual Methanol and Acetone in SDD

Both methods were performed on a Restek RTX-624 capillary column with a 6% cyanopropylphenyl-94% dimethylpolysiloxane stationary phase (30 m×0.32 mm×1.8 μm). The injector temperature was set at 180°C and the detector temperature was set at 260°C. The GC oven temperature was held at 40°C for 5 min, then programmed to 90°C at a rate of 10°C/min, further increased to 225°C at a rate of 30°C/min, and then held at 225°C for 2 min. Helium was used as the carrier gas at a constant flow rate of 1.6 mL/min. A split flow of 1:5 was used. Standard and SDD sample solutions were prepared in 5 mL of dimethylacetamide and injected by an Agilent Model 7694 or 1888a headspace autosampler. For the headspace autosampler, the sample loop was 2 mL, the oven temperature was set at 105°C, the transfer line temperature was set at 115°C, the carrier pressure was 7 psi, and the vial pressure was 20 psi. The times for injection, loop equilibration, loop fill, pressurization, and vial equilibration were 1.0, 0.05, 0.20, 0.33, and 10 min, respectively.

For the benzene-in-SDD method, sample solutions are prepared with sample weight range of 0.5 to 0.7 g. The %RSDs of benzene peak area response were within 5% for six injections of standard solution at three concentrations (1 ppm, 10 ppm and 100 ppm). Recovery was within 25% at the 0.5-ppm concentration and within 20% at the 7- and 70-ppm concentrations. The signal-to-noise ratio for benzene at 0.5 ppm (LOQ) was > 10.

For the residual-methanol/acetone-in-SDD method, sample solutions are prepared with sample weight range of 0.1 to 1.5 g to facilitate wet-SDD and dried-SDD analysis. The %RSDs of acetone and methanol peak area response were within 5% for six injections of standard solution at mid- and maximum-range concentrations [4000 ppm, 200,000 ppm (*w/w*) solvent in SDD based on a 0.1-g sample] and within 10% for six injections of standard solution at LOQ concentration (75 ppm *w/w* solvent in SDD based on a 0.1-g sample). Accuracy was inferred based on meeting the acceptance criteria for specificity, linearity, and precision. Recovery was determined for each standard's calculated concentration using appropriate calibration curves compared to the prepared concentrations. At mid- and maximum-range concentrations, the recovery was within 5% for both analytes. The signal-to-noise ratio for methanol and acetone at 70 ppm (LOQ) was > 10.

Benzene Fate and Tolerance Study

In this study, a placebo SDD was manufactured at a 400-g scale from a low-solids-concentration spray solution consisting of HPMCAS (4% *w/w*) in a spray solvent (either acetone or methanol) spiked with 200 ppm of benzene. The benzene-spiked spray solution was spray-dried using conditions simulating a worst-case scenario for retention of high amounts of residual primary spray solvent (i.e., acetone or methanol) and benzene in the wet SDD. The concentration of benzene in solvent was determined prior to spray-drying, and the concentrations of residual primary solvent and benzene were determined in wet SDD and in SDD at different time points during secondary drying.

Preparation of Spray Solutions Spiked with 200 ppm of Benzene

Spray solutions were prepared using the compositions shown in Table I.

Spray-Drying Conditions

A pilot-scale spray dryer (GEA Pharma PSD1) was used with proprietary modifications by Bend Research to emulate the closed-loop (recycle) mode typical of large pilot-scale and production-scale spray dryers. The recycle-mode emulator used a 4.3-kW heater (H-02) to vaporize a stream of pure solvent vapor directly into the ingoing drying gas to the spray-drying chamber. Liquid solvent fed to the emulator heater was controlled using a pressurized process tank with an inline needle valve. Solvent flow was monitored using an inline Coriolis flow meter. A Spraying Systems SK 80–16 pressure-swirl nozzle (Spray Systems Co., Wheaton, Illinois) was used to atomize the spray solution.

The spray-drying process conditions shown in Table II were used to push the drying kinetics and thermodynamics in the least favorable direction for benzene removal (i.e., wet and cold conditions) thereby directing SDD production towards the worst case scenario of wet SDD that retained high amounts of residual solvent and benzene.

Secondary-Drying Conditions

Benzene-spiked SDD lots sprayed from acetone or methanol were dried using a convection tray dryer at standard low-humidity secondary-drying conditions [40°C/15% relative humidity (RH)] for 24.5 h to remove residual solvent. Samples were collected before and after tray-drying for 1, 2, 4, 8, 16, and 24 h and analyzed for primary spray solvent (i.e., acetone or methanol) and benzene concentrations.

Table I Composition Summary of Benzene-Spiked Spray Solutions

Component	Acetone spray solution	Methanol spray solution
Solvent (g)	9600	9599
HPMCAS (g)	400	400
Benzene (g)	1.92	1.92
Measured benzene concentration in spray solution (ppm)	180	200

Table II Spray-Drying Process Conditions

Parameter[a]	Acetone spray solution spiked with benzene	Methanol spray solution spiked with benzene
T_{in} (°C)	116	147
T_{out} (°C)	40	47
$T_{condenser}$ (°C)[b]	−5	−5
Emulator flow rate (g/min)	252	61
Nitrogen flow rate (g/min)	1443	1641
Total gas flow rate (g/min)	1695	1702
Spray-solution flow rate (g/min)	204	110
Atomization pressure (psi)	802	162
RS_{out} (%)	22	16
Wet-SDD yield (%)[c]	90	91

[a] T_{in} is the spray-dryer inlet temperature, T_{out} is the spray-dryer outlet temperature, $T_{condenser}$ is the condenser temperature, and RS_{out} is the relative saturation of solvent in the drying gas at the spray-dryer outlet, which was estimated using the Equation $RS_{out}\% = (y_i)(P)/P_{sat}^* \times 100$. In this equation, y_i = molar fraction of solvent vapor i in spray dryer outlet with the assumption that all solvent was evaporated from particle and total mass = solution × solids fraction + emulator flow; P = system pressure at spray dryer outlet which was assumed to be atmospheric pressure ($P = 680$ mmHG in Bend, OR) and spray dryer operated slightly positive gauge pressure, but significantly less than atmospheric pressure; and P_{sat}^* = saturation vapor pressure of solvent i at spray dryer outlet temperature which was calculated by Antoine's equation $\mathrm{P}_{\mathrm{sat}}^{\rightarrow} = e^{\left(C1+\frac{C2}{T}+C3\ln(T)+C4T^{C5}\right)}$ with coefficients C1 to C5 taken from Perry's Chemical Engineers' Handbook (8th Edition)

[b] Simulated under open-loop conditions by introducing solvent vapor to the drying gas stream (emulator flow rate)

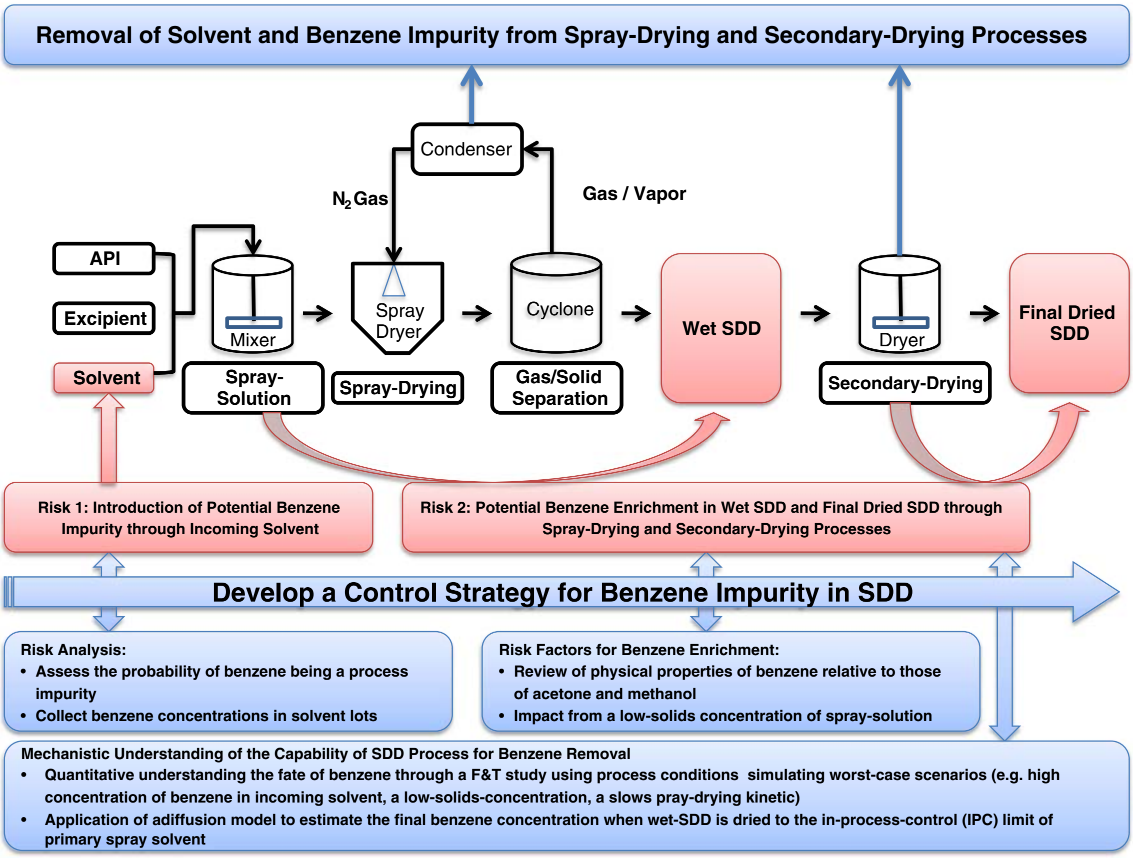
[c] Calculated based on the mass of solids recovered before secondary drying

RESULTS AND DISCUSSION

In this study, to establish a control strategy for limiting the benzene concentration in SDDs, we performed a risk analysis and developed a mechanistic understanding of benzene removal during spray-drying, as illustrated in Fig. 1.

Risk Analysis: Probability of Benzene Being a Process Impurity in Acetone and Methanol and Factors Affecting the Extent of Benzene Enrichment in SDD

As shown in Fig. 1, during the risk analysis, we sought to determine (1) the probability of benzene being present as a process impurity in the primary spray solvent (i.e., acetone and methanol) and (2) the likelihood of benzene being concentrated in the SDD during spray-drying. For the first body of work, we conducted literature review of the solvent production methods, followed by determination of benzene concentrations in typical bulk acetone and methanol lots used to manufacture clinical SDDs. For the second body of work, we considered the physical properties of benzene relative to those of the primary solvents and also evaluated the effect of



Risk 1: Introduction of Potential Benzene Impurity through Incoming Solvent

Risk 2: Potential Benzene Enrichment in Wet SDD and Final Dried SDD through Spray-Drying and Secondary-Drying Processes

Risk Analysis:
- Assess the probability of benzene being a process impurity
- Collect benzene concentrations in solvent lots

Risk Factors for Benzene Enrichment:
- Review of physical properties of benzene relative to those of acetone and methanol
- Impact from a low-solids concentration of spray-solution

Mechanistic Understanding of the Capability of SDD Process for Benzene Removal
- Quantitative understanding the fate of benzene through a F&T study using process conditions simulating worst-case scenarios (e.g. high concentration of benzene in incoming solvent, a low-solids-concentration, a slows pray-drying kinetic)
- Application of adiffusion model to estimate the final benzene concentration when wet-SDD is dried to the in-process-control (IPC) limit of primary spray solvent

Fig. 1 A science-based and risk-based approach to establish a control strategy for limiting the residual benzene concentration in SDDs.

the spray-solution solids concentration on the final benzene concentration in the SDD. On the basis of our analysis, the risk factors described above were ranked as follows.

- Spray-solvent type: acetone > methanol (based on a review of production methods and physical properties)
- Spray-solvent purity grade: nonpharmaceutical grade > NF grade > European Pharmacopoeia (EP) grade
- Solid concentrations of spray solution: Low solid concentration > high solid concentration

Considerations taken into account during the risk analysis and ranking are now detailed below, which are the basis for the subsequent F& T study design.

Acetone Production Process

Most acetone is manufactured industrially as a byproduct of the Hock process for synthesis of phenol (7, 10, 11). In this process, benzene is alkylated with propylene to form cumene. The cumene intermediate is further oxidized to form cumene hydroperoxide, which is then cleaved to form acetone and phenol through a series of chemical steps. Acetone is further purified from phenol and other by-products through multiple distillation steps. In addition to benzene being a starting material in the acetone process, benzene may be introduced into acetone by thermal degradation of phenol. Based on this review, commercially available acetone lots could contain trace (<100 ppm) benzene amounts depending on the process conditions and extent of purification.

Methanol Production Process

Methanol is typically synthesized in the gas phase over a heterogeneous catalyst from a synthesis gas containing a combination of hydrogen, carbon monoxide, and carbon dioxide (8). Worldwide, there are two common routes to produce synthesis gas. The most common route uses natural gas (>80% methane) and converts any residual higher hydrocarbon (such as C6 ~ 0.22%) to methane during the production process. Another common route is based on coal gasification, in which benzene is a minor component of the gas stream. Depending upon the geographical sources of the coal (9), the benzene concentration could be as high as 483 ppm in methanol. When coal is used as the production feedstock, the risk that methanol lots may contain residual benzene is high. However, less than 25% of the world's methanol is produced from coal feedstocks (8), so the likelihood of benzene is low and the risk may be negligible.

Analysis of Benzene in Solvent Lots Used for Clinical SDD Manufacturing

The quality of compendial-grade solvents is tightly controlled. Usually, these solvents contain low concentrations of impurities and are used to manufacture SDD for clinical studies. A review of the EP and NF reveals that only the EP specifies a maximum 2 ppm (*v/v*) limit for benzene in the monographs for acetone and methanol. Therefore, NF-grade acetone and methanol may present a higher risk than EP grade. The Japanese Pharmacopoeia (JP) does not have a quality standard for acetone or methanol.

Five lots of NF-grade acetone (from three suppliers) and two lots of NF grade methanol (from a single supplier) were tested for benzene using validated GC-FID methods. The results, presented in Table III and IV, respectively, demonstrated that one lot of acetone contained 1.4 ppm benzene, but all of the other solvent lots had benzene concentrations below the LOQ (0.5 ppm). Therefore, there is a possibility that NF-grade acetone may contain a low ppm concentration of benzene.

Review of Physical Properties of Benzene Relative to those of Acetone and Methanol

Table V summarizes relevant physical properties of benzene, acetone, and methanol: molecular weight, boiling point, density, heat of vaporization (ΔH_{vap}), relative evaporation rate (RER), and kinetic diameter.

Two major physical properties of benzene relative to those of acetone and methanol are pertinent to the potential risk for benzene enrichment in wet SDD as a result of spray-drying: the boiling point and the RER. The boiling point of benzene is higher than that of acetone and methanol, so it is not unreasonable to assume that the removal efficiency for benzene is less than that of acetone or methanol. This suggests that after spray-drying, the ratio of benzene to primary spray solvent in the SDD could be higher than the initial ratio in the spray solution. However, benzene has a higher RER than methanol, due to its lower heat of evaporation, and should be more efficiently removed than methanol. Conversely, benzene has a lower RER than acetone, suggesting that acetone has a higher risk than methanol for benzene enrichment during SDD manufacture.

Table III Benzene Concentrations in NF-Grade Acetone Lots

Acetone lot	Supplier	Benzene concentration (ppm, *w/w*)
1	A	<0.5
2	A	<0.5
3	B	<0.5
4	B	<0.5
5	C	1.4

Table IV Benzene Concentrations in NF-Grade Methanol Lots

Methanol lot	Supplier	Benzene concentration (ppm, *w/w*)
1	D	<0.5
2	D	<0.5

With regards to the diffusion-based secondary-drying, solvent removal is related to the transport property of solvent molecule in SDD, where the molecular size (e.g., kinetic diameter) plays a significant role. Since benzene has a larger kinetic diameter than acetone and methanol, it would diffuse more slowly in a polymer-based SDD, consequently, it would have a slower removal rate than either acetone or methanol. The details of this relative diffusion rate of methanol (acetone) with respect to benzene were described by using a mathematical model and provided by authors (12). In this model, it is assumed that the solvents including spraying solvents (methanol and acetone) and benzene are evenly distributed in the slab before the start of drying, which is the initial condition of the diffusion equation. A very good agreement between the experimental data and the model prediction was demonstrated in the figures 14 and 15 by the author (12).

Impact of a Spray-Solution Solids Concentration on Benzene Enrichment

When spray-drying solutions contain low concentrations of solids (i.e., API and polymer), even a small amount of less-volatile impurity in the solution may concentrate to a significant concentration in the final dried SDD. This effect can be further amplified when the SDD has a low ratio of API to

Table V Physical Properties of Acetone, Methanol, and Benzene

Solvent	Property					
	Molecular weight (g/mol)	Boiling point (°C)	Density (g/ml)	ΔH_{vap} (kJ/mol)	RER	Kinetic Diameter (Å)
Acetone	58.08	56.5	0.79	31.3	560	4.7
Methanol	32.04	64.7	0.79	35.3	300	3.8
Benzene	78.11	80.1	0.88	33.9	393	5.85

polymer if we apply the solvent impurity limit defined by ICH Q3C in a conservative manner as relative to the amount of API. Using the worst-case assumption that benzene is a nonvolatile impurity, Eqs. (1) and (2) use the concept of concentration factor to predict the combined effect of spray-solution solids concentration and incoming benzene concentration in the spray solvent on nonvolatile impurity enrichment. The concentration factor can be expressed either on a basis of total SDD weight (Eq. 1) or on a basis of API amount in SDD (Eq. 2):

$$Concentration\ Factor\ (based\ on\ total\ SDD\ weight)$$
$$= \frac{[imp]\ solids\ (ppm)}{[imp]\ solvent\ (ppm)} = \frac{Mass\ of\ Solvent\ (g)}{Mass\ of\ SDD\ Solids\ (g)}, \quad (1)$$

where $[\mathrm{imp}]_{solids}$ is the impurity concentration in the SDD if the impurity is not volatile and $[\mathrm{imp}]_{solvent}$ is the impurity concentration in the incoming primary spray solvent; and

$$Concentration\ Factor\ (based\ on\ API\ amounts\ in\ SDD)$$
$$= \frac{Mass\ of\ Solvent\ (g)}{Mass\ of\ SDD\ Solids\ (g) x\ Drug\ Load\ of\ SDD\ (\%)} \quad (2)$$

As an example calculation for an SDD containing 25% API and 75% polymer, prepared from 100 g of spray solution with a 4% solids concentration:

- Mass of Solvent (g)=(100 g of spray-sution - 4 g of solid in spray-solution)=96 g
- Mass of SDD Solids (g)=4 g
- Drug Load of SDD (%)=25%
- Concentration Factor (based on total SDD weight as defined in Eq. 1)=Mass of Solvent (g) / Mass of SDD Solids (g)=96 g / 4 g=24
- Concentration Factor (based on API amounts in SDD as defined in Eq. 2)=Mass of Solvent (g) / [Mass of SDD Solids (g)×Drug Load of SDD (%)]=96 g / (4 g×25%)=96

In this example, with the assumption of nonvolatility, 1 ppm of benzene in the spray solvent can be concentrated to 96 ppm benzene with respect to API in the final SDD. While we expect most benzene to be removed during spray-drying and secondary drying, this calculated benzene concentration represents a maximum theoretical value and was used in this work to assess findings from the F&T study.

F&T Study: A Worst-Case Scenario Approach

The purpose of this F&T study was to quantitatively understand the fate of benzene (1) after the primary spray-drying process driving towards the worst-case scenario for solvent retention, and (2) during secondary drying at standard conditions (40°C/15% RH) with a tray dryer. The rationale for the study conditions is discussed below.

Selection of Benzene Spiking Concentration

A 200 ppm concentration of benzene was selected to be spiked into each spray solvent (i.e., acetone or methanol). This concentration was approximately 100-fold higher than the concentrations observed in NF-grade solvent lots. Additionally, a 200 ppm concentration was expected to give detectable concentrations of benzene in the wet SDD based on historic experience for SDDs with residual-solvent concentrations as high as 8%, thereby allowing benzene purging to be monitored during secondary drying.

Selection of Polymer

HPMCAS is one of the most common stabilizing polymers used in SDD formulation and has been applied to many drug candidates to enhance bioavailability (1, 13). It is also the polymer used in two recently launched commercial products employing SDD technology: Incivek® (teleprevir) and Zelboraf® (vemurafenib).

Selection of Solids Concentration of Spray Solutions

The lower limit for solids concentration of SDD spray solutions is generally 1% (*w/w*) on an API basis. For a typical SDD with a 25% API load, this equates to 4% total solids concentrations. This is largely due to throughput for Phase 1 and 2 studies, but it is also a realistic lower limit for commercial-scale production due to manufacturing economics. Therefore, a "worst-case" solids concentration of 4% (for a placebo HPMCAS spray solution) was selected for this F&T study. As reported (3), placebo HPMCAS SDD using the polymer can be successfully used to represent the bulk spray-drying behavior mainly because (a) the film-forming nature of the polymer is largely responsible for drying phenomena; (b) the high molecular weight of the polymer dominates the rheological properties of the spray solution; and (c) the polymer concentration of SDDs typically is ≥ 50%. Thus, the API plays only a minor role relative to the polymer regarding the rate of drying. It is recognized that the placebo HPMCAS used in the F&T study may not apply to exceptional SDDs containing API with very low or very high T_g compared to that of pure HPMCAS (120°C), particularly if the API load is high, since this will result in SDD with markedly lower or high T_g than pure polymer. Solvent removal from SDD occurs by diffusion through the glassy polymer matrix (12) and at a given drying temperature, the solvent diffusion coefficient, and hence solvent removal rate, is impacted by the T_g of the dispersion (14). For exceptional API-HPMCAS SDDs having high T_g and hence slow solvent removal, the pure polymer model may not represent "worst case" conditions. The placebo model also does not take account of potential specific API-benzene interactions, however these are considered less likely and less impactful than the effect of API on SDD T_g.

Selection of Spray-Drying Processing Conditions

Spray-drying process conditions for this placebo-based F&T study, which are presented in Table II, were biased toward colder and wetter drying conditions to reduce the thermodynamic driving force for heat and mass transfer, thereby slowing the solvent drying rate and increasing the amount of solvent retention in the SDD. Cold conditions were maintained throughout the process by keeping T_{out} values low. Wet conditions were created by introducing solvent vapor to the drying gas using an emulator as described under Materials and Methods to simulate closed-loop operation and, therefore, increasing the RS_{out} of the drying gas in the spray-drying chamber. These spray-drying conditions push towards a worst-case situation for drying and lie near the edge of the available processing space. When hotter and drier processing conditions are used, the thermodynamic driving force for heat and mass transfer are increased. Based on the above considerations, the benzene reduction rate in this F&T study should be applicable to a variety of HPMCAS-stabilized SDDs whose spray-drying conditions are typically optimized at a more robust operating condition.

Secondary-Drying Conditions

Secondary drying was performed at standard conditions (i.e., 40°C/15% RH and atmospheric pressure) with a tray dryer since these conditions are widely used in SDD preparation from laboratory to pilot scales to remove residual solvent without impact on the physical and chemical stability of the SDD. During secondary drying, the kinetics of solvent removal from polymer-based SDDs follows a Fickian diffusion behavior (12). This means that the diffusion of solvent in polymer is dependent upon the diffusion temperature and the diffusion length. Once the process temperature is controlled and kept constant, the removal of solvent from polymer is independent of the scale or type of dryer.

Results of Benzene F&T Study

Effect of Spray-Drying

Table VI summarizes the concentrations of benzene, acetone, and methanol in the spray solutions and wet SDD. The benzene-spiked acetone and methanol spray solutions contained 180 and 200 ppm of benzene, respectively. After spray-drying, the measured benzene concentrations in the wet SDDs were 6.3 ppm for the acetone-based SDDs and 5.6 ppm for the methanol-based SDDs. Table VI also shows the maximum theoretical concentration of benzene in wet SDDs (calculated using a concentration factor of 24 as defined in Eq. 1) and the benzene reduction rate achieved in this study compared to that of the theoretical maximum. The results demonstrate that the benzene concentration was successfully reduced 686-fold (for acetone-based SDDs) and 857-fold (for methanol-based SDDs) from the maximum theoretical concentration, if all the benzene in the primary spray solvent had been concentrated in the wet SDD.

The reduction rate of each spray solvent is also provided in Table VI (calculated as shown) and indicates benzene reduction was 60 to 80% less than that of the primary spray solvent. As considered in the risk analysis, the boiling point of a volatile may affect its final residual concentration in a SDD. The trend of reduction rates (in Table VI) from high to low supports the risk assessment: methanol and acetone > benzene in methanol and benzene in acetone. Although the reduction rate of benzene is lower relative to the reduction rates of acetone and methanol, the results of this F&T study unambiguously demonstrate that the spray-drying process itself has high capability to remove benzene (~700-fold) even using worst-case processing conditions.

Effect of Secondary Drying

The benzene concentration of the SDDs sprayed from acetone and methanol was reduced from ~ 6 ppm to ≤ 0.5 ppm (*w/w*) with respect to total weight of SDD after 8 h of secondary drying and was undetectable after 16 h of secondary drying. Table VII summarizes the concentrations of benzene and acetone in the SDD sprayed from acetone before and at different time points during secondary drying. Table VIII summarizes data for the SDD sprayed from methanol. The drying profiles are illustrated in Fig. 2.

Application of a Mathematic Diffusion Model To Estimate the Final Benzene Concentration when SDD is Dried to an IPC Limit of the Primary Spray Solvent

A Fickian diffusion model developed by the same team successfully simulated acetone, methanol, and benzene removal from placebo HPMCAS SDDs during secondary drying using a single controlled β value (diffusion parameter) as described in a separate paper by Hsieh *et al.*(12). The details of this model including the assumptions, geometric shape, mathematical derivation and diffusion equations have been discussed in detail by the authors (12). Only the application of this model to estimate the concentration of benzene in dried SDD when the concentration of spray solvent reaches a particular concentration in the final dried SDD is illustrated here.

Table VI Reduction Rate of Benzene, Acetone, and Methanol after Spray-Drying for a Worst-Case Scenario

Spray Solvent	[Benzene] in primary spray solvent, ppm *w/w*	Maximum theoretical [benzene] in SDD, ppm *w/w*[a]	Measured [benzene] in wet SDD, ppm *w/w*	Benzene reduction rate[b]
Acetone	180	4320	6.3	686
Methanol	200	4800	5.6	857
	Input [solvent] mass, g	Measured [solvent] in wet SDD, % *w/w*	Measured solvent mass in wet SDD [c], g	Spray solvent reduction rate[d]
Acetone	9600	2.7	10.8	889
Methanol	9600	1.8	7.2	1333

[a] Calculated based on a concentration factor of 24 as defined in Eq. 1, for example, 180 ppm × 24 = 4320 ppm (acetone case)

[b] Calculated against the maximum theoretical benzene concentration, for example, 4320 ppm / 6.3 ppm = 686 (acetone case)

[c] Calculated based on 400-g solid mass of SDD (i.e., 100% yield), for example, 2.7% *w/w* × 400 g = 10.8 g (acetone case)

[d] Calculated against the amounts of primary spray solvent used to prepare a spray solution, for example, 9600 g/10.8 g = 889 (acetone case)

Since the concentration profiles of acetone, methanol and benzene as a function of drying time were determined and shown in Table VII and Table VIII, corresponding profiles of the fraction of solvent remaining (M_t/M_0) in the wet SDD product *vs*. the square root of diffusion time can be generated, as described in reference (12). M_0 is the concentration of volatile in total wet SDD before secondary drying and M_t is concentration of volatile in total wet SDD at each time point of secondary drying t.

It was demonstrated and verified that the M_t/M_0 *vs* square root of diffusion time secondary drying profile for SDD product can be simulated with one diffusion parameter (β) which is composed of both diffusivity and the diffusion length (12). The value for the parameter β was determined when the diffusion data in Table VII and Table VIII were used to fit the diffusion model, resulting in a very good agreement between the experimental data and the prediction from the diffusion model, as shown in Fig. 14 and Fig. 15 of reference (12).

Tables IX and X, respectively, shows the estimated benzene concentrations in final dried SDD when the initial wet SDD contains either the lowest (1% *w/w*) or highest (8% *w/w*) concentration of acetone typically obtained after spray-drying and the wet SDD is secondary dried to meet a residual acetone limit of 0.2% (*w/w*). The 0.2% (*w/w*) limit is typically used as an IPC for secondary drying of SDDs sprayed from acetone or methanol to ensure the solvent concentration is well within the relevant ICH Q3C limit. β values of 0.016 (acetone) and 0.006 (benzene) were used as described in reference (12) to calculate the concentration of benzene at the drying time required to reach the 0.2% (*w/w*) residual acetone limit solvent for scenarios shown in Tables IX and X where benzene is present at 30, 10, or 2 ppm in the acetone spray solvent. The same information is shown in Tables XI and XII for methanol-based SDD, using β values of 0.02 (methanol) and 0.004 (benzene) as detailed in reference (12). With our F&T study results, these predictions will be used to justify an integrated control strategy for benzene impurity and residual-solvent concentrations.

The drying time to reach IPC limit is proportional to the amount of primary spray solvent in the wet SDD (i.e., higher

Table VII Benzene and Acetone Concentrations In SDDs Sprayed From Acetone Before and During Secondary Drying using a Tray Dryer at 40°C/15% RH

Drying time (hour)	M_t^b - Benzene concentration in total SDD (ppm *w/w*)	M_t^b - Acetone concentration in total SDD (% *w/w*)
0	6.3 (M_0^a)	2.7384 (M_0^a)
1	4.6	1.1533
2	2.7	0.3459
4	1.2	0.0445
8	<0.5	0.0023
16	undetectable	0.0001
24	undetectable	0.0001

[a] *M_0* concentration of volatile in total SDD before secondary drying (i.e., wet SDD)

[b] *M_t* concentration of volatile in total SDD at each time point of secondary drying

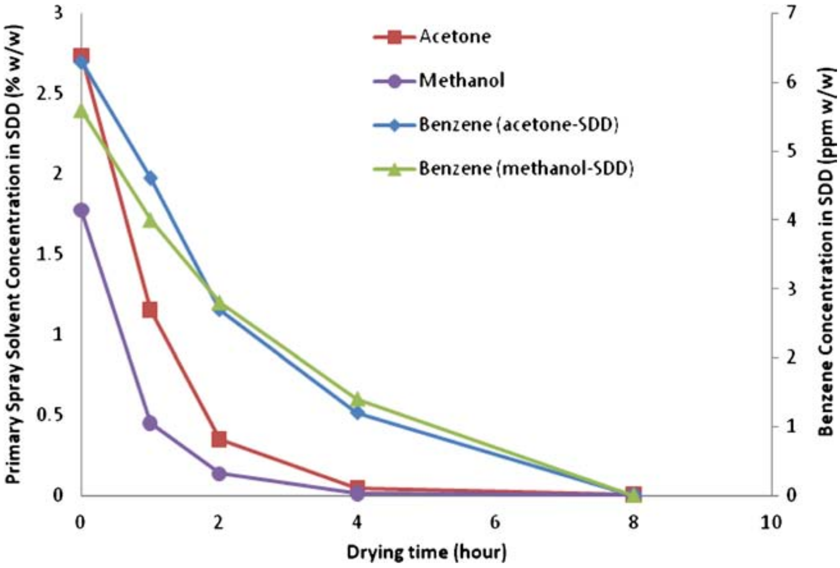
Table VIII Benzene and Methanol Concentrations in SDDs Sprayed from Methanol Before and During Secondary Drying using a Tray Dryer at 40°C/15% RH

Drying time (hour)	M_t^b - Benzene concentration in total SDD (ppm *w/w*)	M_t^b - Methanol concentration in total SDD (% *w/w*)
0	5.6(M_0^a)	1.7748 (M_0^a)
1	4.0	0.4511
2	2.8	0.1340
4	1.4	0.0105
8	0.5	0.0006
16	undetectable	0.0004
24	undetectable	0.0004

[a] *M_0* concentration of volatile in total SDD before secondary drying (i.e., wet SDD)

[b] *M_t* concentration of volatile in total SDD at each time point of secondary drying

Fig. 2 Concentrations of benzene and primary spray solvent in HPMCAS-stabilized SDDs as a function of time during secondary drying using a tray dryer at 40°C/15% RH.



solvent content requires longer drying time). Since drying endpoints are dependent on the primary spray solvent concentrations, wet SDD containing low concentrations of solvent but high concentrations of benzene pose the greatest risk. Thus, a wet SDD that contained 1% acetone or methanol would require a shorter time to reach the IPC 0.2% (*w*/*w*) limit than an SDD containing 8% residual solvent. Therefore, the estimated benzene concentrations in Tables IX and XI represent the worst-case scenario for acetone-based and methanol-based SDD, respectively.

Proposed Strategy to Control Benzene Impurity in SDD Product

The results of this well-designed F&T study coupled with the estimates from diffusion modeling of secondary drying enable a quantitative understanding of the effects of both spray-drying and secondary drying on benzene removal from HPMCAS-stabilized SDDs spray-dried from acetone or methanol. To ensure the benzene concentration in the final dried SDDs is well below the ICH Q3 limit of 2 ppm, two

Table IX Estimated Benzene Concentrations in Final Dried SDD when the Initial Wet SDD Contains 1% *w/w* of Acetone and Final Dried SDD Contains 0.2% of Acetone (IPC Limit)

	M_0, concentration of acetone in initial wet SDD, % *w/w*	Drying time, min[b]	M_t/M_0	M_t, concentration of acetone in total dried SDD, % *w/w*
	1%	85	0.2	0.2%
Benzene concentration in incoming acetone, ppm	M_0[a], estimated concentration of benzene in initial wet SDD, ppm *w/w*	Drying time, min	M_t/M_0[b]	M_t[c], estimated concentration of benzene in final dried SDD, ppm *w/w*, with respect to 2% of API
30	1.05	85	0.48	2.02
10	0.35[d]	85	0.48	0.67[d]
2	0.07	85	0.48	0.13

[a] Calculated based on a concentration factor of 24 as defined in Eq. 1 and benzene reduction rate of 686 listed in Table VI. The reduction rate represents the worst-case scenario for benzene in the final SDD, being generated using slow spray-drying kinetics and low solids concentration in the spray solution (i.e., a high concentration factor from solvent to SDD solid), and high incoming benzene concentration

[b] Calculated as described in reference (12) using the model depicted in Fig. 15 of reference (12). A value of 9.2 for $(\text{time})^{0.5}$ was obtained from Fig 15 of reference (12) when M_t/M_0 of acetone reaches 0.2

[c] These values are considered worst-case scenarios, being generated using the shortest drying time

[d] As an example calculation for an SDD containing 25% API and incoming acetone containing 10 ppm of benzene

- Maximum theoretical benzene concentration in SDD = benzene concentration in incoming acetone × concentration factor = 10 ppm × 24 = 240 ppm
- M_0 (estimated concentration of benzene in initial wet SDD) = maximum theoretical benzene concentration in SDD / benzene reduction rate after spray-drying = 240 ppm / 686 = 0.35 ppm
- M_t (estimated concentration of benzene in final dried SDD) = $(M_0) \times (M_t/M_0)$/ drug load of SDD = 0.35 ppm × 0.48 / 25% = 0.67 ppm

Table X Estimated Benzene Concentrations in Final Dried SDD when the Initial Wet SDD Contains 8% *w/w* of Acetone and Final Dried SDD Contains 0.2% of Acetone (IPC limit)

	M_0, concentration of acetone in initial wet SDD, % *w/w*	Drying time, min[b]	M_t/M_0	M_t, concentration of acetone in total dried SDD, % *w/w*
	8%	169	0. 025	0.2%
Benzene concentration in incoming acetone, ppm	M_0[a], estimated concentration of benzene in initial wet SDD, ppm *w/w*	Drying time, min	M_t/M_0[b]	M_t, estimated concentration of benzene in final dried SDD, ppm *w/w*, with respect to 25% of API
30	1.05	169	0.28	1.18
10	0.35	169	0.28	0.39
2	0.07	169	0.28	0.08

[a] Calculated based on a concentration factor of 24 as defined in Eq. 1 and benzene reduction rate of 686 listed in Table VI

[b] Calculated as described in reference (12) using the model depicted in Fig. 15 of reference (12). A value of 13 for $(\text{time})^{0.5}$ was obtained from Fig 15 of reference (12) when M_t/M_0 of acetone reaches 0.025

critical control points were established: (1) limiting the benzene concentration in the primary spray solvent (acetone or methanol) to ≤ 10 ppm and (2) applying an IPC residual-solvent limit of 0.2% (*w/w*) to the final dried SDD. The detailed control strategy is described in Fig. 3 and is justified based on the following results.

- The benzene reduction rate (which ranged from 686- to 857-fold) after spray-drying was obtained under worst-case scenarios with respect to using (1) a slow drying kinetic (cold, wet conditions); (2) a high benzene concentration (200 ppm) in spray solvent; and (3) a low solids concentration (4%) in spray solution (producing a high concentration factor of 24 as defined in Eq. 1). Since solids concentrations of at least 10% (producing a concentration factor of 9.6 as defined in Eq. 1) are typically used to ensure adequate SDD throughput, this consideration alone represents a 2.5-fold safety margin.
- With this experimental reduction rate and a modeling approach, when the benzene concentration of the acetone or methanol spray solvent is 10 ppm, the estimated benzene concentration in final dried SDD (based on a typical drug load of 25%), is 0.67 ppm (*w/w*) for acetone and 0.70 ppm (*w/w*) for methanol in the final dried SDD when a typical IPC solvent limit of 0.2% (*w/w*) is applied. These estimated benzene concentrations in final dried SDDs, based on a worst-case scenario for secondary-drying time, are 3-fold less than the ICH limit of 2 ppm.

Unambiguously, any optimization from the worst-case scenario (e.g., hotter spray-drying conditions, longer or hotter secondary drying, a higher SDD drug load, and especially a higher solids-concentration spray-drying solution (i.e., a smaller concentration factor) would further reduce the benzene concentration, making the safety margin for meeting the ICH Q3C limit of 2 ppm even larger. Furthermore, incoming NF-grade lots of acetone and methanol provided by current suppliers contained less than 2 ppm of benzene. Therefore, with this upstream control of benzene in solvent to less than

Table XI Estimated Benzene Concentrations in Final Dried SDD when the Initial Wet SDD Contains 1% *w/w* of Methanol and Final Dried SDD Contains 0.2% of Methanol (IPC limit)

	M_0, concentration of methanol in initial wet SDD, % *w/w*	Drying time, min[b]	M_t/M_0	M_t, concentration of methanol in total dried SDD, % *w/w*
	1%	72	0. 20	0.2%
Benzene concentration in incoming methanol, ppm	M_0[a], estimated concentration of benzene in initial wet SDD, ppm *w/w*	Drying time, min	M_t/M_0[b]	M_t[c], estimated concentration of benzene in final dried SDD, ppm *w/w*, with respect to 25% of API
30	0.84	72	0.62	2.08
10	0.28	72	0.62	0.70
2	0.06	72	0.62	0.15

[a] Calculated based on a concentration factor of 24 as defined in Eq. 1 and benzene reduction rate of 857 listed in Table VI

[b] Calculated using the model depicted in Fig. 14 of reference (12). A value of 8.5 for $(\text{time})^{0.5}$ was obtained from Fig 14 of reference (12) when M_t/M_0 of methanol reaches 0.20

[c] These values are considered worst-case scenarios, being generated using the shortest drying time

Table XII Estimated Benzene Concentrations in Final Dried SDD when the Initial Wet SDD contains 8% *w/w* of Methanol and Final Dried SDD contains 0.2% of Methanol (IPC Limit)

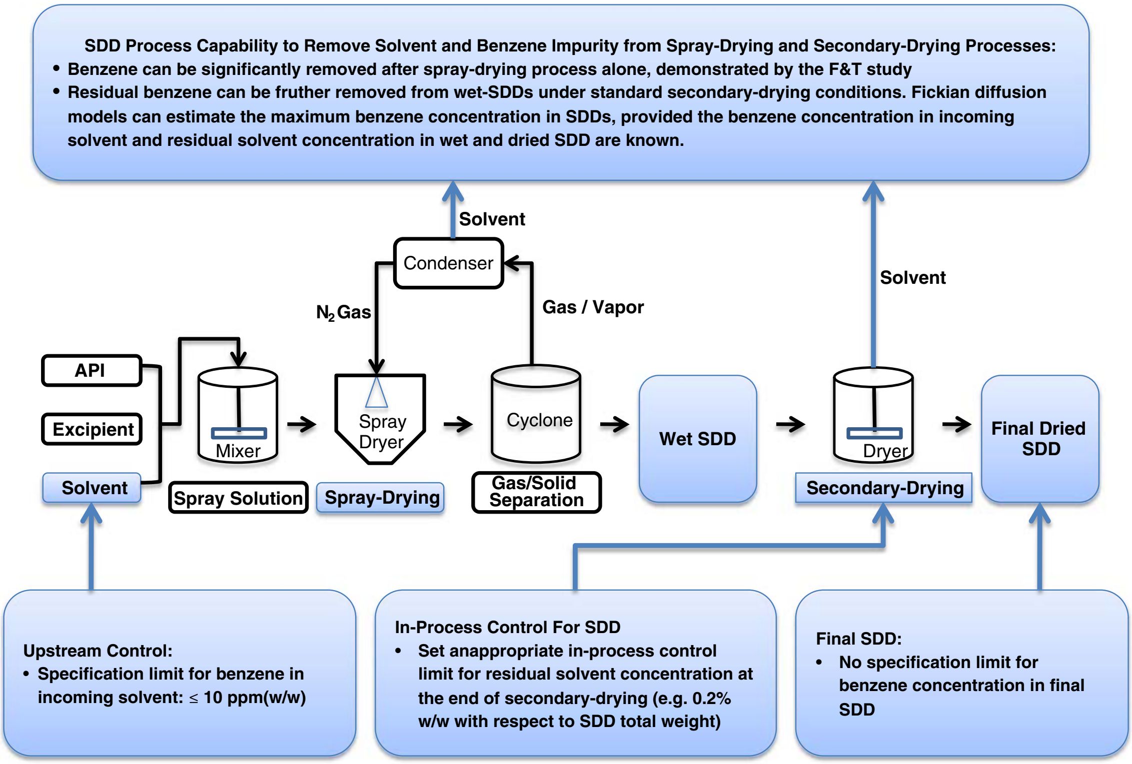
	M_0, concentration of methanol in initial wet SDD, % *w/w*	Drying time, min[b]	M_t/M_0	M_t, concentration of methanol in total dried SDD, % *w/w*
	8%	169	0.025	0.2%
Benzene concentration in incoming methanol, ppm	M_0[a], estimated concentration of benzene in initial wet SDD, ppm *w/w*	Drying time, min	M_t/M_0[b]	M_t, estimated concentration of benzene in final dried SDD, ppm *w/w*, with respect to 25% of API
30	0.84	169	0.42	1.14
10	0.28	169	0.42	0.47
2	0.06	169	0.42	0.10

[a] Calculated based on a concentration factor of 24 as defined in Eq. 1 and benzene reduction rate of 857 listed in Table VI

[b] Estimated using the model depicted in Fig. 14 of reference (12). A value of 13 for $(\text{time})^{0.5}$ was obtained from Fig 14 of reference (12) when M_t/M_0 of methanol reaches 0.025

10 ppm and IPC limit of 0.2% (*w/w*) for residual-solvent concentration at the end of secondary drying, the risk to have benzene exceed the ICH Q3 limit in the final dried SDD is negligible.

As discussed within this publication and also in reference (12), the conclusions of this study are not expected to be significantly impacted even for SDDs prepared using larger spray dryers, or different scales or types of secondary dryers. It is recognized that the placebo HPMCAS used in the F&T study may not apply to exceptional SDDs containing API with very low or very high T_g compared to that of pure HPMCAS (120°C), particularly if the API load is high, since this will result in SDD with markedly lower or high T_g than pure polymer. Solvent removal from SDD occurs by diffusion through the glassy polymer matrix (12) and at a given drying temperature, the solvent diffusion coefficient, and hence solvent removal rate, is impacted by the T_g of the dispersion (14). For exceptional API-HPMCAS SDDs having high T_g and hence slow solvent removal, the pure polymer model may not represent "worst case" conditions. The placebo model also does not take account of potential specific API-benzene interactions, however these are considered less likely and less



SDD Process Capability to Remove Solvent and Benzene Impurity from Spray-Drying and Secondary-Drying Processes:
- **Benzene can be significantly removed after spray-drying process alone, demonstrated by the F&T study**
- **Residual benzene can be fruther removed from wet-SDDs under standard secondary-drying conditions. Fickian diffusion models can estimate the maximum benzene concentration in SDDs, provided the benzene concentration in incoming solvent and residual solvent concentration in wet and dried SDD are known.**

Upstream Control:
- **Specification limit for benzene in incoming solvent: ≤ 10 ppm(w/w)**

In-Process Control For SDD
- **Set anappropriate in-process control limit for residual solvent concentration at the end of secondary-drying (e.g. 0.2% w/w with respect to SDD total weight)**

Final SDD:
- **No specification limit for benzene concentration in final SDD**

Fig. 3 Proposed upstream control and in-process control strategy for benzene in SDDs.

impactful than the effect of API on SDD T_g. However, despite such limitations, the safety margins built into the control-strategy limits and solvent sourcing policy suggest the same strategy may be applied, without introducing unacceptable risk, to control benzene in most HPMCAS-stabilized SDD spray-dried from acetone or methanol spray solutions, regardless of drug choice and concentration.

CONCLUSION

Using a science-based and risked-based approach, a benzene-control strategy incorporating upstream control and IPC has been established for SDDs to essentially eliminate any residual risk to patients. This study demonstrates that the solids concentration of the spray-drying solution (i.e., the concentration factor from solvent to solid) presents the highest risk for benzene enrichment compared with other factors (e.g., solvent production method or grade). It also shows the process (including spray-drying and subsequent secondary-drying unit operations) is unequivocally capable of removing benzene to concentrations of less than 0.5 ppm (LOQ) in SDDs even under worst-case scenario conditions (e.g., high incoming benzene concentration, cold/wet drying conditions, low solids concentration of spray solution). Furthermore, it has been demonstrated that mathematical Fickian diffusion models are excellent tools to approximate secondary-drying kinetics, thereby enabling prediction of benzene concentrations in final dried SDDs for a variety of benzene concentrations in the primary spray solvent and residual-solvent concentrations in SDDs before and after secondary drying.

This work has enabled selection and justification of an appropriate upstream control limit for benzene in the primary spray solvent (10 ppm) and an IPC residual-solvent limit in the final dried SDD (0.2% *w/w*), with significant safety margins to ensure that the benzene concentration complies with the ICH Q3C limit of 2 ppm, applied conservatively as a limit with respect to API, for HPMCAS-stabilized SDDs spray-dried from acetone or methanol.

The methodologies we used to develop this benzene control strategy for HPMCAS-stabilized SDDs are aligned with the principles of ICH Q8 and Q9 on pharmaceutical development and risk management (15, 16). A similar approach can be applied broadly to address the risk of any volatile or semivolatile impurities that could be present in common spray-drying solvents in any SDDs.

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