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Optimization of the Büchi B-90 spray drying process using central composite design for preparation of solid dispersions

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ABSTRACT

A central composite design approach was applied to study the effect of polymer concentration, inlet temperature and air flow rate on the spray drying process of the Büchi B-90 nano spray dryer (B-90). Hypromellose acetate succinate-LF was used for the Design of Experiment (DoE) study. Statistically significant models to predict the yield, spray rate, and drying efficiency were generated from the study. The spray drying conditions were optimized according to the models to maximize the yield and efficiency of the process. The models were further validated using a poorly water-soluble investigational compound (BI064) from Boehringer Ingelheim Pharmaceuticals. The polymer/drug ratio ranged from 1/1 to 3/1 w/w. The spray dried formulations were amorphous determined by differential scanning calorimetry and X-ray powder diffraction. The particle size of the spray dried formulations was 2–10 μm under polarized light microscopy. All the formulations were physically stable for at least 3 h when suspended in an aqueous vehicle composed of 1% methyl cellulose. This study demonstrates that DoE is a useful tool to optimize the spray drying process, and the B-90 can be used to efficiently produce amorphous solid dispersions with a limited quantity of drug substance available during drug discovery stages.

1. Introduction

The pharmaceutical industry is facing a big challenge with low productivity in small molecule product development. (Bunnage, 2011) Thousands of new chemical entities need to be evaluated before the approval of a new drug product. However, most of the newly discovered compounds have poor physicochemical properties such as high molecular weight, high hydrophobicity and low solubility. (Leeson, 2012) This may lead to decreased bioavailability and increased variability in the PK profiles for orally administered compounds. There are a number of approaches to formulate water insoluble compounds in order to achieve desired systemic exposure in vivo. These approaches include salt formation, use of solubilizing excipients, complexation agents, particle size reduction and amorphization, etc. (Fakes et al., 2009; Newman et al., 2011; Semalty, 2014; Serajuddin, 1999) Amorphous compounds usually present high levels of super-saturation and apparent solubility compared to crystalline compounds due to higher internal energy and specific volume. (Hancock and Zografi, 1997) In order to prevent recrystallization of amorphous compounds, amorphous solid dispersions (ASDs) are usually prepared by dispersing the amorphous compound in a polymer matrix to enhance dissolution and oral bioavailability. Several methods were reported to formulate ASDs, which include confined impinging jet method (Kumar et al., 2014a), hot melt extrusion (Wilson et al., 2012) and spray drying (Chen et al., 2014; Friesen et al., 2008), etc.

Spray drying is capable of generating ASDs directly from solutions by fast drug/polymer solidification from rapid removal of organic solvents in a single step, which is an efficient process. Traditional spray drying processes and applications were reviewed by Krzysztof Cal and Krzysztof Sollohub. (Cal and Sollohub, 2010; Sollohub and Cal, 2010) However, the yield for traditional spray drying is low, especially when the sample volume is small. This makes it impractical for formulating poorly water-soluble compounds with limited amounts available during drug discovery stages. The Büchi B-90 nano spray dryer (B-90) utilizes a nozzle with vibrating mesh (4, 5.5 or 7 μm aperture) to spray droplets, and an electrostatic particle collector to capture spray-dried particles. The former is able to generate consistent

Abbreviations: DoE, design of experiment; B-90, Büchi B-90 nano spray dryer; ASDs, amorphous solid dispersions; LF, AS-LF, hypromellose acetate succinate; IT, inlet temperature; FR, air flow rate; AS, polymer concentration; PXRD, powder X-ray diffraction; PLM, polarized light microscopy; mDSC, modulateddifferential scanning calorimetry; SEM, scanning electron microscopy; ANOVA, analysis of variance; Sqrt, square root; API, active pharmaceutical ingredient.

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Table 1
Physicochemical properties of BI064.

Parameters	BI064
Crystallinity	Highly crystallline
Partition coefficient	2.8
Aqueous solubility	7.5 μg/ml
Acetone solubility	40.5 mg/ml

small particles and the latter to obtain high yields with small spray volumes. (Heng et al., 2011) This process was reported to spray polymer solutions and achieve nanoparticles with high yield (70–90%) when a small nozzle cap (4-μm) was used. (Li et al., 2010a) Amoxicillin nanoparticles were also prepared with Carbopol® or gelatin using the B-90 equipped with a 5.5 μm or 4 μm nozzle, respectively. The yields for both formulations were higher than 90%. (Harsha, 2012,2013) However, much lower yields (approximately 50%) were observed for dexamethasone (a poorly soluble drug) loaded PLGA nano/microparticles when prepared using the B-90. It is difficult to draw a conclusion on the estimation of yields for spray-dried particles prepared from polymer solutions using the B-90 based on the reports. The experiments in these reports were designed with too many variables (Li et al., 2010b), which are unable to provide detailed interpretation of the process factors that affect yields. Another overlooked factor for the process is the efficiency, which can be presented as spray rate and drying efficiency. Since the B-90 is a relatively small scale spray dryer, the spray drying efficiency is important, especially when a limited quantity of drug substance is available. Thus, the purpose of this study was to optimize the process to achieve satisfactory yield and efficiency to meet the needs in drug discovery stages. Efficient factor screening can be performed using DoE through statistically designed experiments to yield valid and objective conclusions. DoE has been widely used in the development of analytical methods and various pharmaceutical formulations. (Kumar et al., 2014a,b; Patil-Gadhe and Pokharkar, 2014; Xu et al., 2012) Meanwhile, appropriate models of corresponding parameters can be generated from DoE for further prediction purposes. (Xu et al., 2012)

In this study the B-90 was also evaluated for the feasibility and efficiency of producing small-size ASDs. To the best of our knowledge, the B-90 has not been utilized to produce ASDs. Hypromellose acetate succinate-LF (AS-LF) was used as a model polymer due to its property of inhibiting recrystallization of amorphous compounds. (Friesen et al., 2008; Tanno et al., 2004) AS-LF solutions were spray-dried and central composite design (a response surface design) was applied to optimize parameters involved in the process. Models were generated to predict spray rate, drying efficiency and yield. The process with the optimized conditions for production of ASDs was also evaluated using an investigational compound (BI064) from Boehringer Ingelheim Pharmaceuticals.

2. Material and methods

2.1. Materials

BI064 was used as a model water insoluble compound. The crystalline drug was white in color with poor aqueous solubility. Physicochemical properties of BI064 are listed in Table 1. AS-LF (soluble in aqueous solution with pH > 5.5) was purchased from Shin-Etsu (Shin-Etsu Chemical Co., Ltd., Japan). All other chemical reagents used in the study were of ACS and high-grade purity.

2.2. Methods

2.2.1. Spray drying

All powders in the study were prepared via spray drying using the B-90 (BÜCHI Labortechnik AG, Flawil, Switzerland). A solution of AS-LF in acetone was prepared by dissolving 800 mg AS-LF in acetone at a specified concentration according to the experiment design shown in Table 2. Because the quantity of material used for spray drying is known to affect yields, the amount of polymer sprayed was kept constant throughout the experiment. Exclusion of this variable allowed for determination of other important factors that affect yield. Those factors are polymer concentrations and drying conditions. All solutions were centrifuged at 3000 rpm for 15 min, and the supernatant was used for spray drying to minimize the nozzle blockage. For the spray-drying process, the flow rate was set as 2, a 7-μm mesh nozzle cap was used, and 100% of the feeding solution was sprayed. Air flow rate and inlet temperature were set as described in Table 2. The dried powder was collected from the particle

Table 2
Central composite design.

Run #	Factor		
	Inlet temperature (IT) (°C)	Air flow rate (FR) (L/min)	Polymer concentration (AS) (%)
1	44	102	1.99
2	56	120	1.40
3	56	120	1.40
4	56	120	2.40
5	56	120	0.40
6	44	138	0.81
7	44	138	1.99
8	68	102	0.81
9	68	138	1.99
10	56	150	1.40
11	68	102	1.99
12	44	102	0.81
13	56	120	1.40
14	76	120	1.40
15	36	120	1.40
16	68	138	0.81
17	56	90	1.40
18	56	120	1.40
19	56	120	1.40
20	56	120	1.40

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