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Using spray-dried lactose monohydrate in wet granulation method for a low-dose oral formulation of a paliperidone derivative ☆

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ABSTRACT

Content uniformity (CU) is a crucial evaluation factor, especially for low-dose oral formulations. Spray-dried monohydrate lactose is generally recommended for direct compression/dry granulation, but we observed that it showed advantages in the wet granulation tableting method for low-dose tablet formulation. In this study, several commercial brands of lactose were selected and suitable tableting methods were applied to a low-dose oral formulation of pentyloxyl paliperidone derivative (PD6) with drug loading at 1.5% (w/w) and lower. The effects of spray-dried/sieved/milled monohydrate and anhydrous lactose on CU were investigated. Granules/powder mixtures were studied in terms of their size distribution, repose angle, flowability and bulk/tapped density. In addition, SEM, DSC, CU, tablet weight, hardness, friability and *in vitro* cumulative release profiles were investigated. The relationships between the powder characteristics and CU results were also studied. Wet granules using spray-dried lactose monohydrate presented satisfied flowability, fair compressibility and a low particle size span compared with all the other tested types of lactose. The product tablets also presented optimal evaluation results for 1.5% (w/w) drug loading (CU = 12.22) and displayed good repeatability among 100 g to 2 kg levels. Further study using another two brands of lactose produced similar results, indicating using spray-dried monohydrate lactose in wet granulation may apply universally to low-dose formulations.

1. Introduction

Paliperidone was launched by Johnson and Johnson under the trade name of Invega® at the end of 2006 to treat schizophrenia. The poor absolute oral bioavailability (only 28%) and high daily dose may lead to an increased risk of side effects and thus inhibit its effectiveness. A series of paliperidone derivatives (PDs) were synthesised in our lab. Among these derivatives, pentyloxyl paliperidone hydrochloride (PD6) displayed higher bioavailability and lower toxicity in animal experiments than Invega®. The chemical structure and physico-chemical properties are shown in Fig. 1 and Table 1. Due to the nearly doubled bioavailability of PD6, a low-dose oral formulation was needed [1].

Content uniformity (CU, or the uniformity of dosage unit, defined as the degree of uniformity in the amount of the active substance in each unit) may be the most important evaluation factor of oral solid preparations. CU testing of dosage units is conducted throughout different phases of pharmaceutical research and development to ensure the consistency of dosage units regarding the content of the active pharmaceutical ingredient (API, the substance in a pharmaceutical drug or a pesticide that is biologically active; this can be substituted for drug in certain cases). Numerous methods have been invented and developed to conduct this testing. Methods that generally sample a certain amount of tablets from lots/batches and novel means, such as near-infrared spectroscopy [2], have also been developed, but their limitation is the time-consuming work required for making a standard model for each different API. In addition, predication models have been established to estimate the outcome CU results via excipient characteristics but are limited in their requirement of similar tablet weight and/or excipient size distribution [3]. These limitations make the models unable to properly apply to low-dose formulation because the overwhelming majority of powder mixtures involve different types of excipients.

With respect to low-dose formulation, in the 1970s, the British Pharmacopoeia described low-dose formulation as "containing less than 2 mg or 2% drug loading (w/w) of active pharmaceutical ingredients (API)" [4,5], whereas U.S. standards limit the API to less than 1%[6]. Over the last few decades, the pharmaceutical industry has discovered and developed many low-dose drug products. In most cases, these products were in the form of tablet. However, low-dose tablet manufacturing remains a very challenging task due to the (1) difficulty in achieving CU, which is the most important evaluation factor; (2) low potency due to manufacturing loss and (3) instability due

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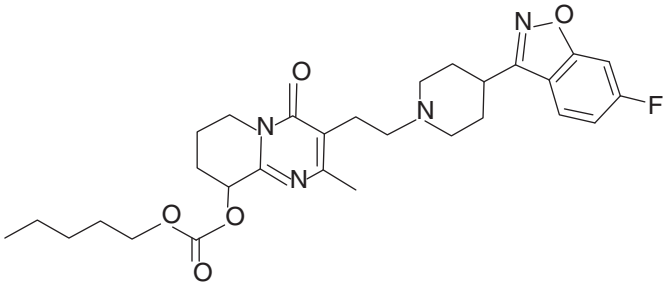

Fig. 1. Chemical structure of PD6.

to the huge ratio of excipients to drug substance and thus a lack of compatibility [7,8]. To obtain better CU results for low-dose tablets, manufacturing methods have been studied, and some advances have been made in various aspects [7–14].

For those drugs that have already been approved, complicated formulation design and miscellaneous excipients were used. Some excipients have been particularly noted for usage in low-dose oral formulation, such as spray-dried lactose [15] and CAB-O-SIL [16]. The excipient's (solid powder/particles in most cases) engineering, characterisation, and modelling of particles are three obviously important issues with respect to achieving a deeper understanding of structure–function–performance relationships of pharmaceutical products [17]. It should be noted that these recommended low-dose oral formulation excipients are nearly all emphasised in terms of the function of improving the flowability of the whole mixed materials. However, the interactions between the API and excipients are extremely complex. Some mechanisms have been used to describe the potential effect of excipients on API, but such interactions must still be evaluated on a case-by-case basis [18]. Numerous commercially available excipients have been developed and improved to meet different needs. For instance, for lactose, which is commonly used as a filler and diluent in oral solid formulations, the products vary in secondary processing methods (sieved, milled, spray-dried, etc.) and therefore present different characteristics, such as degrees of fines, particle size and surface morphology. These manufacturing variances are intended to meet the demands of different products and facilitate the task of formulation design. As for the lactose usage guidelines for tablets, sieved α-lactose monohydrate is recommend in direct compression, whereas milled α-lactose monohydrate is strongly suggested in wet granulation. Alternatively, spray-dried monohydrate lactose, which consists of spherical agglomerates of crystalline lactose monohydrate in a matrix of amorphous lactose, is considered to be "free-flowing" and is typically used in direct compression. Due to its brittle nature and lack of crystal water, anhydrous lactose could meet the needs of moisture-sensitive API formulations in dry granulation and direct compression. For different tableting methods, the interactions among the excipients differ both in the physical and chemical respects. External power in processing, i.e., wetting agent in wet granulation and slugging in dry granulation, can greatly alter the properties of the outcome mixed materials eventually affect the tablet evaluation results.

The mentioned research, development of excipients, manufacturing methods and instruments are all intended to achieve materials with a good flow property. The flowability of materials has an impact on nearly all pharmaceutical handling processes, such as blending, transfer, storage, feed and compaction. During all of the processing steps, an ideal even distribution of the API among all excipients is expected. Several evaluation parameters (repose angle, Carr index and Hausner ratio, etc.) of the particles/powder mixture can be used as references for predicting the outcome results as being acceptable or unacceptable [19]. In total, the mixtures of API and excipients need to present not only a small particle distribution span (minimising the segregation and agglomeration) but also good flowability (easy re-dispersion after storing) and good compactability for achieving tablets with small weight variations. In addition, when considering the later processing steps, such as film coating, a smooth surface and certain hardness are required for the product tablets.

Table 1
Physical and chemical properties of PD6 and paliperidone.

Drug	Mw	Melting point (°C)	Solubility in water (mg/ml)
PD6	577.09	225.40–226.60	2.09
Paliperidone	426.48	166.00–172.00	0.22

In our former study, we observed that for a drug loading as low as a 1.5% (w/w, 3 mg dosage strength) tablet formulation with lactose monohydrate, tablets manufactured using dry granulation presented much better tablet CU results than tablets manufactured using wet granulation [1]. However, serious powder pollution (especially for this low-dose oral formulation) and drug loss in the dry granulation (and direct compression) process are not acceptable for actual production. Therefore, the wet granulation method became the only choice, and the amelioration of the CU issue is required. However, due to the long $T_{1/2}$ of PD6 [20], a steady but rapid *in vitro* drug release profile must be achieved. The intent of this study was to find a suitable low-dose formulation using the wet granulation method to produce a tablet with satisfactory evaluation results. After initial exploration and pre-experimentation, a simple formulation was designed: drug 1.5%, HPMC 15% and lactose 83.5% (w/w). Five commercially available lactose products of the same brand (DMV-Frontier) were selected: D 11SD, D 110M, D 125M, D 200M, and D 21AN. Their characteristics are presented in Table 2. Wet granulation, dry granulation, as well as direct compression were adopted.

The repose angle, flowability, bulk and tapped density of the granules/powder were studied. DSC and SEM were conducted to determine the thermal and morphology properties. The cumulative release profiles were documented and fitted with a zero-order equation, a first-order equation, a Higuchi equation, and a Korsmeyer Peppas equation. The most important value, CU, was tested, and tablet weight, hardness and friability properties were also studied. The most suitable form of lactose was selected for lower dosage strength formulations of 1.5 mg (drug loading 0.75% (w/w) and 0.75 mg (drug loading 0.375% w/w), with batch sizes of 500 g and 1 kg.

2. Materials and methods

2.1. Materials

The drug PD6 was synthesised in our lab; 70% ethanol was used as the wetting agent, and the drug was prepared just before use. All other chemicals used were of analytical grade. Deionised water was prepared by purifying using a Milli-Q system (Millipore, Milford, USA).

The excipients used were as follows: magnesium stearate (Sinopharm Chemical Reagent Co., Ltd.) as a lubricant in the tableting process, HPMC K 100LV CR (Lot.PD 355155, Methocel® K100 PremiumLV CR) (The Dow Chemical Company) as a gel-forming matrix material and lactose (detailed information shown in Table 2) as a filler/diluent for achieving the desired tablet weight. The types/brands/batch lot information of lactose were as follows: SuperTab 11SD (Lot. 10587945), SuperTab 21AN (Lot. 10323925), Pharmatose 110 M(Lot.10693215), Pharmatose 125M(Lot.10420314) and Pharmatose 200 M (Lot. 10430981) (DEVELING INTERNATIONAL); FlowLac® 100 (LOT-NO:L 1125 A 4952) and Granulac® 200 (LOT-NO: L1015 A 4172) (MEGGLE Group Wasserburg Representative Office, Shanghai); and Foremost NF Lactose Hydrate Monohydrate Spray Dry Fast Flo 316 (BATCH NO. 8510943147) and Foremost NF Lactose Monohydrate 314WG (BATCH NO.8511042814) (Beijing Fengli Jingqiu commerce and Trade Co., Carbon double-sided Tape, Ltd.). All of the excipients were kept in desiccators at ambient temperature and used directly out of the desiccators.