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A mesoporous silica based platform to enable tablet formulations of low dose drugs by direct compression

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ABSTRACT

Achieving adequate content uniformity (CU) is a significant challenge in the development and manufacturing of low dose oral tablets. Using four model active pharmaceutical ingredients (APIs), we show that loading APIs into a grade of mesoporous silica, Aeroperl®, is effective for achieving excellent CU. All APIs in the Aeroperl® composites were amorphous. After six months under accelerated stability conditions, the drug-Aeoperl composites exhibited good physical stability for all four APIs. The performance of Aeroperl®-based formulations was robust since their good CU and manufacturability were insensitive to model APIs. In addition, the dissolution rate of composite-based formulations was higher than corresponding physical mixtures. Overall, the Aeroperl®-based platform formulation is a promising approach for successfully developing low dose oral tablet products.

1. Introduction

High potency drugs are playing an increasingly important role in healthcare, because of the steadily increasing number of potent compounds arising from current drug discovery (Mehrotra, 2010). While potent drugs more effectively treat diseases by selectively binding with biological targets (Harris, 2015), they pose a significant challenge to tablet development and manufacturing in term of delivering a consistent dose. This is a risk for potent drugs because slightly sub-potent tablets may be ineffective while super-potent tablets can result in serious side effects. Thus, the risk of unsatisfactory tablet content uniformity (CU) and consequently batch rejection is higher.

Mesoporous silicas have received attention in drug delivery due to their unique properties of high specific surface area, stable mesoporous structure with tunable pore size (2–50 nm in diameter), and hydrophilic surface property (Qian and Bogner, 2012; Vallet-Regí et al., 2007; Wang, 2009). It was shown that drugs loaded into the pores of mesoporous silica can enhance drug dissolution rate and, therefore, potentially increase bioavailability of poorly soluble drugs. This dissolution advantage arose, in part, because drugs existed in the amorphous state in the composites (Khanfar and Al-Nimry, 2017; Wei et al., 2017). Interestingly, such amorphous drugs usually exhibited good stability likely because of a) the inhibitory effect of small pores on crystallization, and b) H-bonding interactions between drug molecules and silanol group (Qian and Bogner, 2012). Recently, the CU of low drug dose tablets was found to be significantly improved by using composites of drugs and a mesoporous material, Neusilin® (Sun et al., 2017). However, the long-term physical stability of amorphous drug in the Neusilin® composites was not rigorously tested. Moreover, an alternative platform formulation based on a chemically different porous carrier is desired in certain cases of chemical incompatibility between Neusilin® and drugs.

The aim of this work was to develop an alternative direct compression formulation platform based on Aeroperl® 300 Pharma, which is commercially available mesoporous silica, to enable expedited tablet development of low dose drugs.

2. Materials and methods

2.1. Materials

Carbamazepine (CBZ; BASF, Ludwigshafen, Germany), celecoxib (CEL, Aarti Drugs Ltd., Mumbai, India), griseofulvin (GRS; Glaxo laboratories, London, UK), and ritonavir (RTV; Wuhan Beier Biopharm Ltd., Wuhan, China) were chosen as model drugs. Although not potent drugs themselves, these model drugs have a wide range of chemical structures for testing the robustness of the alternative platform formulation. Mesoporous inorganic materials, Neusilin® S1 (Fuji Chemical Inc., Toyama, Japan) and Aeroperl® 300 Pharma (Evonik Inc., Essen, Germany) were selected as carriers. Microcrystalline cellulose (MCC;

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Avicel PH102, FMC, Philadelphia, PA), lactose monohydrate (Fast-Flo, Foremost Farms, Dallas, TX), colloidal silica (Cab-O-Sil M-5P, Cabot Corporation, Boston, MA), croscarmellose sodium (Ac-Di-Sol, FMC, Philadelphia, PA), and magnesium stearate (MgSt; Covidien, Dublin, Ireland) were used for preparing tablets. Sodium lauryl sulfate (SLS; Ward's Science, Rochester, NY) was used as a surfactant in dissolution tests.

2.2. Methods

2.2.1. Preparation of drug–carrier composites

Drug was dissolved in dimethylformamide (DMF) at a specified concentration. Under stirring, the drug solution was added to an Aeroperl® (1.6:1, v/w) or Neusilin® (1:1, v/w) powder, which imbibed the solution completely. The volume of drug solution was chosen so that the respective porous carrier was saturated with drug solution, but without excess solution that required filtration before drying. The wet powder was dried at 55 °C for 24 h to remove solvent. This condition was sufficient for drying composites to a constant weight. The drug–-carrier composite was then stored in a 43% relative humidity (RH) chamber until further characterization. The yield was essentially 100%, as supported by complete recovery in the dissolution studies, because the mass of drug at the surface is negligible relative to that in the pores. Drug loadings of 0.05%–10% (w/w) in each carrier were attained by controlling the concentration of drug solution.

2.2.2. Preparation of tablet formulation

The composition of the drug-Aeroperl® formulation is shown in Table 1. MCC was first coated with colloidal silica using a conical mill (Comil, Model U3; Quadro Engineering Corporation, Waterloo, Ontario, CA) for 10 cycles to improve its flowability (Chattoraj et al., 2011; Zhou et al., 2013). The silica coated MCC exhibited flowability more comparable to that of Aeroperl® and lactose monohydrate, which facilitated uniform mixing of these major components in the formulation. The nanocoated MCC was then mixed with drug-Aeroperl® composite, lactose monohydrate, and croscarmellose sodium in a V-shaped laboratory blender (BlendMaster; Patterson–Kelley, East Stroudsburg, PA) at 25 rpm for 10 min. Magnesium stearate was then added and mixed for an additional 5 min at 25 rpm. A placebo powder, without drug, containing 20% of Aeroperl® 300 Pharma was also prepared as a control formulation.

2.2.3. Powder X-ray diffraction (PXRD)

An X-ray diffractometer (PANalytical X'pert pro, Westborough, MA) was used to analyze the solid state structures of powders. X-ray was generated using a Cu-Kα radiation source at 45 kV and 40 mA. PXRD patterns were obtained by scanning samples from 5° and 35° with a step size of 0.017° and 1 s dwell time at room temperature. Powders were loaded into the sample cells with surfaces flattened using a glass slide to ensure coplanarity between powder surface and the sample holder surface.

Table 1
Composition of drug-Aeroperl® formulation.

	Percentage (%)
Drug – Aeroperl® composite	20.0
Microcrystalline cellulose	56.0
Lactose monohydrate	18.0
Croscarmellose sodium	5.0
Colloidal silica	0.5
Magnesium stearate	0.5
Total	100%

2.2.4. Differential scanning calorimetry (DSC)

Thermal properties of samples were analyzed by a differential scanning calorimeter (Q1000, TA Instruments, New Castle, DE). Approximately 2–4 mg of sample was weighed into an aluminum pan and sealed. Each sample was heated from 25 °C to 10 °C above melting point of respective drug crystals at a heating rate of 10 °C/min under 25 mL/min nitrogen purge.

2.2.5. Scanning electron microscopy (SEM)

Scanning electron microscopy (JEOL 6500F; JEOL Ltd., Tokyo, Japan) was used to observe the shape and surface features of particles. The accelerating voltage was 5 kV. Samples were mounted onto carbon tapes adhered to steel stubs and sputter-coated with a thin layer of platinum (thickness ~50 Å) using an ion-beams sputter (IBS/TM200S; VCR Group Inc., San Clemente, CA) before analysis.

2.2.6. Accelerated stability test of amorphous drug composites

The physical stability of amorphous drug composites with Aeroperl® and Neusilin® was tested using 10% (w/w) drug loading to ensure adequate detection sensitivity and as a worst case for physical stability in term of dissolution. Samples were characterized by PXRD, SEM, and dissolution after 6 months of storage at 40 °C and 75% RH. Drug loading in carrier for potent drugs is expected to be much lower than 10% for low dose drugs. Thus, stability studied here using 10% drug in carrier is the worst case scenario for the targeted application of the platform DC formulation.

2.2.7. Powder flowability

Powder flow properties were characterized using a ring shear tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany) using a shear cell with 30 mL volume at a 1 kPa preshear normal stress. Shear strength of each powder was tested under five progressively increasing normal stresses of 230, 400, 550, 700, 850 Pa, which were used to construct a yield locus. Unconfined yield strength (f_c) and major principal stress (σ_n) were obtained from Mohr's stress analysis of each yield locus. The flowability index, ff_c, was calculated using Eq. (1) (Sun, 2016):

$$ff_c = \frac{\sigma_n}{f_c} \quad (1)$$

2.2.8. Powder tabletability

Powders were compressed into 200 mg tablets on a universal materials testing machine (Zwick-Roell MaterialPrufung 1485, Ulm, Germany) with 8.0 mm round flat-faced tooling. Prepared tablets were allowed to relax in a 43% RH chamber for 24 h before further characterization. Tablet breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY) at a speed of 0.01 mm/s. Tablet tensile strength was calculated from the breaking force and tablet dimensions (Fell and Newton, 1970).

2.2.9. Tablet friability

Tablet friability profile of each formulation was determined using an expedited method (Osei-Yeboah and Sun, 2015). For each powder, 15–20 tablets prepared at different compaction pressures were coded and weighed before being loaded into a friabilator (Model F2, Pharma Alliance Group Inc., Santa Clarita, CA). After the friabilator was run at 25 rpm for 4 min, loose particles were carefully removed from the tablets, which were weighed again. The percentage weight loss was calculated for each tablet and plotted against compaction pressure. The threshold tensile strength corresponding to 0.8% weight loss was determined from the friability plots.

2.2.10. Content uniformity

Tablets (200 mg) were prepared at 150 MPa pressure using a compaction simulator (Presster, Model 252, Metropolitan Computing Corporation, East Hanover, NJ) to simulate a Korsch XL100 (10