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An approach to engineer paracetamol crystals by antisolvent crystallization technique in presence of various additives for direct compression

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ABSTRACT

Paracetamol is a popular over-the-counter analgesic and a challenging model drug due to its poor technological and biopharmaceutical properties such as flowability, compressibility, compactibility and wettability. This work was aimed to alter the crystal habit of paracetamol from elongated to polyhedral-angular via particle engineering whilst maintaining the stable polymorphic form (form I: monoclinic form). The engineered paracetamol crystals obtained in the present investigation showed better technological and biopharmaceutical properties in comparison to the commercial paracetamol. Engineered paracetamol crystals were obtained using antisolvent crystallization technique in the presence of various concentrations (0.1, 0.5 and 1%, w/w) of additives, namely, polyvinyl alcohol (PVA), Avicel PH 102 (microcrystalline cellulose), Brij 58, methylcellulose (MC) and polyethylene glycol having different molecular weights (PEGs 1500, 6000 and 8000). Paracetamols crystallized in the presence of Avicel (or physically mixed with Avicel), Brij 58 and PEG 6000 demonstrated the best compactibility over a range of compaction pressures. Brij-crystallized paracetamol provided the fastest dissolution rate among all the paracetamol batches. Paracetamols crystallized in the presence of PVA or Avicel, or physically mixed with Avicel demonstrated a reduced degree of crystallinity in comparison to the other paracetamols. This study showed that the type, the grade and the concentration of additives could influence the physical stability such as flow, crystallinity and polymorphic transformation of paracetamol, the technological and biopharmaceutical properties of paracetamol. Stable polymorphic form of paracetamol with optimal tableting characteristics can be achieved through particle engineering.

1. Introduction

Crystals in the lower micrometre range are conventionally produced by milling (Willis, 2003). However, milling has many drawbacks such as polydispersity of the resultant particles in terms of size and shape. In addition, particles obtained through milling are highly charged leading to cohesion between particles (leading to poor flowability) and adherence to the punches, dies and feeding hopper. These undesirable behaviours could jeopardize the uniformity of tablet weight and hence drug content uniformity.

Controlled crystallization can produce particles with desired morphological features such as size, shape and surface texture. Crystallization process can be carried out using various techniques such as batch cooling crystallization (Mullin, 2001; Kaialy et al., 2012b), antisolvent crystallization (Garside, 1985; Kaialy and Nokhodchi, 2012), in situ crystallization (Rasenack and Müller, 2002), crystallization by changes in pH (Al-Jibbouri and Ulrich, 2002) and sonocrystallization (Dhumal et al., 2009). Cooling crystallization technique has the disadvantage of being slow (Kapil et al., 1991), and this was attributed to the large width of metastable zone that requires a high supersaturation degree in order to induce

Abbreviations: BCS, biopharmaceutics classification system; CI, Carr's consolidation index; DSC, differential scanning calorimetry; DE, dissolution efficiency; FT-IR, Fourier transform infrared spectroscopy; GRAS, generally recognized as safe; HSD, Honestly Significant Difference; MD, mean diameter; MC, methylcellulose; MW, molecular weight; ANOVA, one way analysis of variance; Copt, optical concentration; PA, paracetamol; PEG, polyethylene glycol; PVA, polyvinyl alcohol; SEM, scanning electron microscopy; SD, standard deviation; SM, supplementary material; MDT, the mean dissolution time.

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the induction of crystal growth. The antisolvent crystallization process is a purification technique by which a nonsolvent is added to a concentrated solution in order to induce crystallization of the solute (O'Grady et al., 2007). This technique is suitable for thermo-labile compounds. The quality of the crystals obtained via nonsolvent technique is dependent on several processing parameters such as type of antisolvent (Kaialy et al., 2011; Oosterhof et al., 1999), saturation degree (Kitamura and Sugimoto, 2003), agitation intensity (Yu et al., 2005), the rate of addition of the antisolvent (Beckmann, 1999) and type of additive in the crystallization medium (Davey, 1982).

About 40% of pharmaceutical compounds are recognized as poorly water-soluble, and their poor solubilities lead to poor bioavailability (Blagden et al., 2007). Additionally, pharmaceutical compacts are required to possess sufficient mechanical strength to withstand handling yet remain bioavailable. The strength of a compact is a reflection of the bonding that has occurred during compaction.

Paracetamol (acetaminophen) is a popular analgesic and currently, more than 90 products, spanning various dosage forms, containing paracetamol are available over-the-counter in the UK (Ellis et al., 2002).

Paracetamol exists in different polymorphic forms. Form *I* (monoclinic) is the commercially available form; it is thermodynamically stable at room temperature and pressure. However, this polymorphic form has poor flowability, compactibility and wettability. In contrast, the metastable polymorphic form *II* (orthorhombic) undergoes plastic deformation during compression and is suitable for tablet direct compression; however, this form is unsuitable for scaling-up (Giordano et al., 2002). Form *III* is unstable at ambient temperature and pressure and its crystal structure has not been determined. This form is not suitable for direct compression and requires the use of a binder solution to make granules before tableting, such process is costly and time-consuming (Di Martino et al., 1996). The poor compression behaviour of paracetamol powders is due to reduced plastic deformation during compression, resulting in the formation of soft tablets with a high capping tendency (Hong-Guang and Ru-Hua, 1995). The poor tablet quality of paracetamol tablets produced via direct compression has made pharmaceutical companies to use wet granulation. Direct compression is cost effective and avoids the use of heat and moisture associated with wet granulation. As the monoclinic polymorphic form of paracetamol shows poor mechanical properties under the compaction process, therefore, the aim of this research was to produce paracetamol monoclinic crystals with improved compaction properties and dissolution rates using generally recognized as safe (GRAS) additives, i.e., polyvinyl alcohol (PVA), Avicel PH 102, Brij 58, methylcellulose (MC) and polyethylene glycols (PEG 1500, PEG 6000 and PEG 8000). The effect of the concentration of additives on the physicomechanical properties of crystallized paracetamol was also investigated.

PEG (á-Hydro-ù-hydroxypoly(oxy-1,2-ethanediyl) has the advantage of being commonly used for example in solid dispersions and PEGylated liposomes and well tolerated orally and parenterally. PEG (e.g. PEG 400 and 8000) can be easily frozen and thus it has been widely used as a cryoprotectant during freeze-drying (MacKenzie, 1976). Avicel (microcrystalline cellulose) is a purified cellulose widely used as diluent/dry binder and

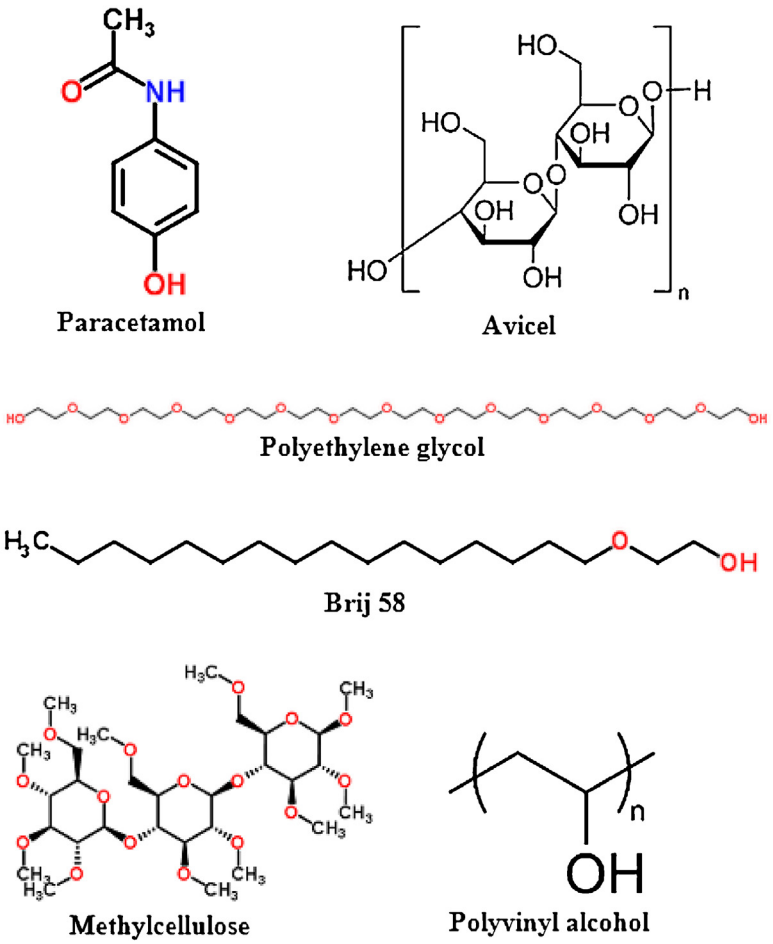

Fig. 1. Chemical structure of paracetamol and different additives used during crystallization, i.e., Avicel, polyethylene glycol, Brij 58, methylcellulose and polyvinyl alcohol.