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Mechanistic understanding of the link between Sodium Starch Glycolate properties and the performance of tablets made by wet granulation

S.A.C. Wren*, F. Alhusban, A.R. Barry, L.P. Hughes

Product Development, AstraZeneca, Silk Road Business Park, Macclesfield, SK10 2NA, UK

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ABSTRACT

The impact of varying Sodium Starch Glycolate (SSG) grade and wet granulation intensity on the mechanism of disintegration and dissolution of mannitol-based Immediate Release (IR) placebo tablets was investigated. MRI and ^{1}H NMR provided mechanistic insight, and revealed a four-fold range in both tablet disintegration and dissolution rates. MRI was used to quantify the rates of change in tablet volumes and the data fitted to a hydration/erosion model. Reduced levels of cross-linking change SSG from a swelling to a gelling matrix. The tablet hydration and dissolution rates are related to the viscosity at the tablet-solution interface, with high viscosities limiting mass transport.

1. Introduction

The dissolution behaviour of Immediate Release (IR) oral tablets is influenced by the performance of excipients such as the super-disintegrant. Changes to the effectiveness of the disintegrant, for example due to batch and source variation, may alter the disintegration behaviour and so the dissolution of the tablet. It is also recognised that granulation and other high shear processing conditions can alter the effectiveness of the disintegrant (Rudnic et al., 1983).

The development of commercial oral IR tablets typically involves both scale-up and transfer between manufacturing sites. To investigate how robust a formulation might be to these processes, we examined how disintegrant performance might be altered by making large changes in both raw material quality and granulation intensity.

Wet granulation is a widely used processing stage in the manufacture of solid oral dosage forms within the pharmaceutical industry. Although wet granulation is more time consuming than either direct compression or dry granulation it offers advantages, particularly at high drug loadings (Gabbott et al., 2016). Sodium Starch Glycolate (SSG) is a commonly used super-disintegrant in IR tablets made by wet granulation. Starch is chemically modified by the introduction of carboxy methyl groups and phosphate groups to provide cross-linking (Fig. 1). The swelling of SSG upon hydration creates an internal pressure in the tablet matrix, and when the pressure overcomes the strength of inter-particulate forces the tablet disintegrates. Disintegration increases the surface area available for drug dissolution and so may influence both *in-vitro* tablet dissolution and *in-vivo* performance.

SSG has a strong swelling capacity. A strong swelling capability is advantageous since it can ameliorate the deleterious consequences that magnesium stearate over-lubrication or hydrophobic excipients have on the dissolution profiles (Rojas et al., 2012).

The degree of carboxy methyl substitution and phosphate ester cross-linking of SSG is important in determining its effectiveness as a disintegrant (Rudnic et al., 1985). The presence of large and hydrophilic carboxy-methyl groups, attracts water to the polymer. The phosphate ester cross-links reduce water solubility, since their presence limits the exposure of hydrophilic functional groups and assists in trapping water within the polymer (swelling) (Rudnic et al., 1985). Therefore an optimum balance between the degree of substitution and the extent of cross-linking is required for fast and efficient swelling.

SSG is known to be shear-sensitive, as high shear forces can break the phosphate ester bonds that link the starch chains in the SSG polymer. The impact of high shear wet granulation process conditions on the functionality of SSG has been investigated previously. Rudnic et al. reported that increasing the rate of mixing shear adversely affects SSG functionality (Rudnic et al., 1983). Zhao

* Corresponding author.
E-mail address: stephen.wren@astrazeneca.com (S.A.C. Wren).

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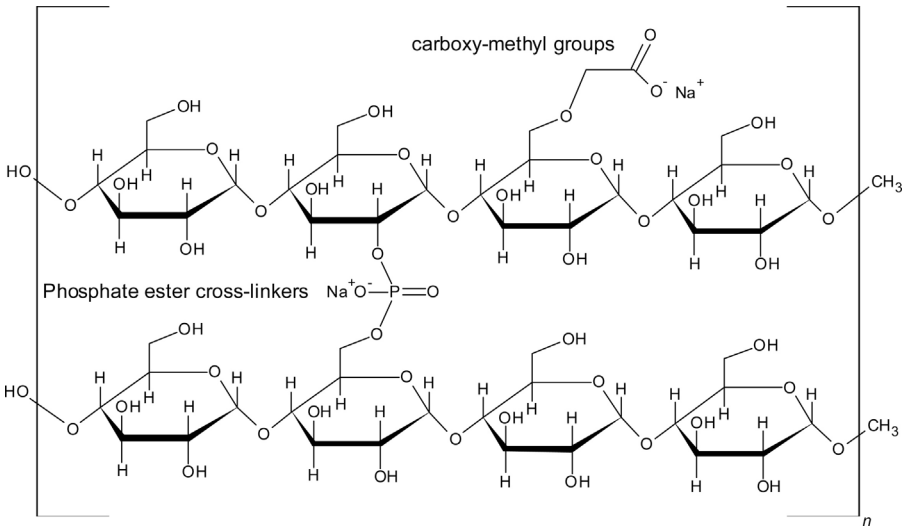

Fig. 1. The chemical structure of Sodium Starch Glycolate (SSG) showing the phosphate ester cross-links.

and Augsburger found that the rate of water being absorbed into the tablet matrix was decreased following wet granulation (Zhao and Augsburger, 2006). Because of this shear sensitivity, low viscosity grades of SSG are available for wet granulation which have a higher degree of phosphate cross-linking.

The aim of this work is to provide insight into the mechanisms by which the input SSG grade, and the wet granulation intensity, affect tablet disintegration and dissolution behaviours. We prepared a range of mannitol-based IR placebo tablets to explore the impact on *in-vitro* performance of some of the more extreme tablet variants that might be encountered during product development.

The *in-vitro* performance of tablets is normally determined using the pharmacopeial dissolution and disintegration tests (Azarmi et al., 2007; Donauer and Löbenberg, 2007). Whilst these tests are satisfactory for comparing the performance of different formulations, batches, or stability samples, they give little information on the causes of any differences. If the objective is to obtain a good understanding of how and why variations in the manufacturing processes affect *in-vitro* tablet performance, more informative *in-vitro* tests are required. Improved understanding can be achieved by using measurement techniques which give insight into the disintegration of the tablet, and the dissolution of soluble components. In addition a more mechanistic approach to tablet dissolution can provide a valuable alternative perspective. For example tablet disintegration may be more usefully considered, not as a single discrete event, but in terms of the rate of generation of particles (Wilson et al., 2012). For a general summary of disintegration phenomena and measurement techniques the reader is directed to recent reviews (e.g. Markl and Zeitler 2017; Desai et al., 2016).

A range of spectroscopic and other techniques are available which mean that the physical and chemical changes occurring during tablet dissolution can be followed. These techniques are especially valuable when used along with hydrodynamic conditions which approximate to those which the tablet experiences during the pharmacopeial dissolution tests. Previously solution state ^{1}H NMR was employed for the first time to follow the release of lactose and three different drugs from a combination tablet in a USP II dissolution experiment (Coombes et al., 2014). Proton NMR had not been used in this way before and the ability to quantify the release of small sugars such as lactose and mannitol means that the dissolution of placebo tablets can be measured.

Conventional dissolution testing follows only the extent of drug release. This is problematic mechanistically as the observed rate will be a complex convolution of tablet disintegration and drug dissolution processes. If drug dissolution is rate limiting then any changes to tablet disintegration behaviour may remain unnoticed. In this study we minimise complexity by following the dissolution of a highly soluble excipient, and so reveal the mechanistic link between product processing and product performance.

Previously we used Magnetic Resonance Imaging (MRI) to measure rates of hydration and erosion in amorphous solid dispersions using USP IV style flow cells (Langham et al., 2012; Tres et al., 2015). The attraction of MRI is that it enables the determination of molecular mobility at different spatial locations within the tablet during the course of dissolution. We can therefore follow *in-situ* important dissolution process such as hydration, gelation, and erosion, which are not readily accessible by other techniques.

With extended release polymer based formulations containing fluorinated drugs, advanced MRI techniques have been used to study matrix and drug mobilities and release behaviour (Chen et al., 2014). This provides significant insight into the mechanisms controlling drug dissolution, for example the relative contributions of Fickian diffusion and Case II relaxation. MRI has been used by others to study the behaviour of binary compacts made from different disintegrants using small and static volumes of water (Quodbach et al., 2014). Other work on compacts made with SSG from different sources has shown a link between the extent of phosphate cross-linking and the rate of water uptake and compact disintegration (Abraham et al., 2016).

In this paper we use MRI and NMR to show how the dissolution rates of IR placebo tablets based on mannitol are affected by the processing conditions used during the granulation step. In this study we considered entire tablet formulations rather than SSG compacts. We also carried out tablet dissolution under conditions very similar to those used for pharmacopieal testing as this is of more direct interest to pharmaceutical scientists. We model tablet disintegration as a hydration/erosion process, with our results being broadly consistent with literature models treating disintegration as a continual loss of layers of particles (Caramella et al., 1988).

We show how the changes to SSG quality alter the performance of the whole tablet even though SSG is present at only 5%. MRI and NMR revealed the mechanistic link between changes in tablet