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Research paper

Investigating the effect of processing parameters on pharmaceutical tablet disintegration using a real-time particle imaging approach

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ABSTRACT

Tablet disintegration is a fundamental parameter that is tested *in vitro* before a product is released to the market, to give confidence that the tablet will break up *in vivo* and that active drug will be available for absorption. Variations in tablet properties cause variation in disintegration behaviour. While the standardised pharmacopeial disintegration test can show differences in the speed of disintegration of different tablets, it does not give any mechanistic information about the underlying cause of the difference. With quantifiable disintegration data, and consequently an improved understanding into tablet disintegration, a more knowledge-based approach could be applied to the research and development of future tablet formulations.

The aim of the present research was to introduce an alternative method which will enable a better understanding of tablet disintegration using a particle imaging approach. A purpose-built flow cell was employed capable of online observation of tablet disintegration, which can provide information about the changing tablet dimensions and the particles released with time. This additional information can improve the understanding of how different materials and process parameters affect tablet disintegration. Standard USP analysis was also carried out to evaluate and determine whether the flow cell method can suitably differentiate the disintegration behaviour of tablets produced using different processing parameters.

Placebo tablets were produced with varying ratios of insoluble and soluble filler (mannitol and MCC, respectively) so that the effect of variation in the formulation can be investigated. To determine the effect of the stress applied during granulation and tableting on tablet disintegration behaviour, analysis was carried out on tablets produced using granular material compressed at 20 or 50 bar, where a tableting load of either 15 or 25 kN was used. By doing this the tablet disintegration was examined in terms of the tablet porosity by monitoring the tablet area and particle release. It was found that when 20 and 50 bar roller compaction pressure was used the USP analysis showed almost identical disintegration times for the consequent tablets. With the flow cell method a greater tablet swelling was observed for the lower pressure followed by steady tablet erosion. Additionally, more particles were released during disintegration due to the smaller granule size distribution within the tablet. When a higher tableting pressure was applied the tablet exhibited a delay in the time taken to reach the maximum swelling area, and slower tablet erosion and particle release were also observed, largely due to the tablet being much denser causing slower water uptake. This was in agreement with the USP analysis data. Overall it was confirmed by using both the standard USP analysis and flow cell method that the tablet porosity affects the tablet disintegration, whereby a more porous tablet disintegrates more slowly. But a more in-depth understanding was obtained using the flow cell method as it was determined that tablets will swell to varying degrees and release particles at different rates depending on the roller compaction and tableting pressure used.

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Nomenclature

σ_T	tablet tensile strength [N/mm^2]	ε_T	tablet porosity

1. Introduction

1.1. Tablet disintegration

In the pharmaceutical industry, dissolution and disintegration are essential tablet properties which are thoroughly tested when a new tablet formulation is developed. Firstly, when a tablet is placed into a liquid medium, such as water, the breakage of larger agglomerates into smaller particles is termed as tablet disintegration [1]. Tablet dissolution can be described as the shrinking of solid material due to the solid soluble components dissolving into solution. Disintegration aids dissolution by providing a larger surface area meaning that the rate of dissolution increases, and for this reason it can be assumed that in most cases tablet dissolution is a tablet disintegration dependent process. Tablet dissolution is understood to be limited by the disintegration rate of the tablet, or the dissolution rate of the drug substance [2].

Tablet dissolution and disintegration tests are carried out as an important initial indicator of the probable tablet performance *in vivo*. Standard United States Pharmacopeia (USP) dissolution and disintegration testing apparatus are employed to determine whether a tablet performs suitably [3]. A commonly used dissolution apparatus is the USP II, which comprises a vessel containing a paddle which agitates the solution and a probe (typically ultraviolet-visible spectroscopy) capable of measuring the concentration of active pharmaceutical ingredient (API) in solution. The tablet is placed at the bottom of the vessel [4]. With tablet dissolution the API concentration is measured at regular time intervals to measure the release profile. Disintegration is measured by the time taken for a tablet to fully pass through the mesh while the containment unit is agitated in an upwards-downwards motion.

Tablets must conform to the standards set by the United States Pharmacopeia [5]. The data are analysed and if the tablet does not behave as expected then the tablet formulation is altered to try and improve performance. This cycle may occur repeatedly until an ideal formulation is reached which can go onto the next testing stage. However this "data-driven", pass or fail approach does not provide comprehensive knowledge as to why the tablet failed or insight into the mechanisms involved during disintegration. A more knowledge-based approach to tablet design would be beneficial as fewer tablets would fail during initial testing, making it more time and cost effective.

While the various processes, such as wicking, wetting and penetration, occurring during dissolution and disintegration have been investigated, they are relatively poorly understood [6–8]. Pharmaceutical tablets can contain numerous excipients, each of which behaves differently in solution (e.g. hydrophobic or hygroscopic powders) [8,9]. However, during USP analysis the tablet is analysed as a whole entity, and little knowledge is gained as to how each excipient alters the tablet dissolution-disintegration profile. Research has been conducted to investigate how various materials affect the disintegration behaviour of tablets [9–11]. However, the pharmaceutical industry continues to utilise the USP apparatus even though limited information is gained regarding the mechanisms of disintegration.

In addition to the tablet formulation, the processing parameters used to produce the tablet can also affect the dissolution-disintegration behaviour [9,12,13]. Granulation is a widely used technique in the pharmaceutical industry for the conversion of primary excipient powder into larger, agglomerated granules. Granules, rather than powders, are preferred for use in the food, pharmaceutical and detergent industries due to the improvement in bulk granule properties such as flowability, wettability, bulk density and homogeneity [14]. Various methods, each with their own advantages, can be used to granulate powders. Generally the techniques used to produce granules are characterised as either wet granulation, such as high shear or fluidised bed [15], or dry granulation, such as roller compaction [15,16]. The granules produced will have different properties, such as size, size distribution, strength, porosity, disintegration and dissolution, depending on the granulation technique used. The granules are then compacted into solid oral dosage tablets or in some cases encapsulated [17].

Dry granulation relies on using an applied load to bond primary particle powders together into a denser compact, also known as a ribbon. Roller compaction is a predominantly dry granulation technique used in the pharmaceutical industry as it allows for continuous granulation, which means that a constant and uniform end granule product is obtained throughout [16]. In addition, materials that are sensitive to moisture or shear are able to be granulated successfully using roller compaction. Roller compaction also offers the potential to control various parameters during granulation, such as screw feed rate, roller speed and crusher speed and mesh size [18,19]. During roller compaction it is possible to control the thickness, strength and porosity of the ribbon and the size of the granules produced via variation of the process parameters [20–23].

While roller compaction is a preferred technique for the production of granules, there are inherent issues that can occur, such as a loss in material deformability due to over-compression [24]. The stress applied to the material can not only affect the deformability properties but also the disintegration behaviour of the subsequent tablets [25,26]. A study was carried out to establish the link between the effect of the stress applied during granulation and tableting on the final tensile strength of the material [27]. It was found that two stages of stress applied to a material can have a negative effect and reduce the overall tensile strength of a material.

Tablet porosity is regarded as a reliable indicator of the disintegration behaviour that will be exhibited by a tablet [28–30]. The porosity of a tablet is dictated by the excipients, the granulation technique and tablet compression [31,32]. Dense, low porosity tablets are typically seen when high stress is applied during granulation or compression. When considering the effect of tablet porosity on tablet disintegration, it has been established that tablets with higher porosity disintegrate at a faster rate as more void space within a tablet allows faster saturation by water during disintegration [29,33]. In this paper this concept will be investigated further using the flow cell method.

Extensive research has been carried out to develop alternative methods to analyse and model tablet disintegration for various materials. Colombo et al. investigated the parameter of disintegration force, which is the force which develops within a tablet which dictates the rate of the breakage of particle-particle bonds [34]. The relationship between the maximum force developed (y_0) and the time of the half maximum force development (b) was elucidated for varying formulations. It was determined that for rapid disintegration of a tablet a significant y_o value must develop relatively