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Characterising the disintegration properties of tablets in opaque media using texture analysis

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ABSTRACT

Tablet disintegration characterisation is used in pharmaceutical research, development, and quality control. Standard methods used to characterise tablet disintegration are often dependent on visual observation in measurement of disintegration times. This presents a challenge for disintegration studies of tablets in opaque, physiologically relevant media that could be useful for tablet formulation optimisation. This study has explored an application of texture analysis disintegration testing, a non-visual, quantitative means of determining tablet disintegration end point, by analysing the disintegration behaviour of two tablet formulations in opaque media. In this study, the disintegration behaviour of one tablet formulation manufactured in-house, and Sybedia Flashtab placebo tablets in water, bovine, and human milk were characterised. A novel method is presented to characterise the disintegration process and to quantify the disintegration end points of the tablets in various media using load data generated by a texture analyser probe. The disintegration times in the different media were found to be statistically different ($P < 0.0001$) from one another for both tablet formulations using one-way ANOVA. Using the Tukey post-hoc test, the Sybedia Flashtab placebo tablets were found not to have statistically significant disintegration times from each other in human versus bovine milk (adjusted P value 0.1685).

1. Introduction

Tablet disintegration properties are characterised during pharmaceutical development to ensure formulation quality following manufacture. Tablet disintegration is also important to characterise because it is a precursor to dissolution (Anwar et al., 2005). Therefore there is a continuing need to characterise tablet disintegration behaviour in vitro to ensure that safe and reliable dosage forms of active pharmaceutical ingredients (APIs) are produced (Donauer and Lobenberg, 2007).

Conventional tablet disintegration is characterised using methods harmonised across the U.S. Pharmacopeia (USP), the European Pharmacopoeia, and the Japanese Pharmacopeia. As described by the USP, to perform the disintegration test, tablets are placed in the USP apparatus A within a basket-rack assembly, churned in water, and visually examined to determine disintegration completion (U.S. Pharmacopeial Convention, 2014a). In this method tablet disintegration is defined as complete when the tablet appears to have no palpable firm core (U.S. Pharmacopeial Convention, 2014a). The standard method of visual discernment to assess tablet disintegration time could be complemented with additional quantitative measurement techniques, to aid understanding of tablet disintegration behaviour. This is especially true for fast release formulations, such as rapidly disintegrating tablets, whose high speed of disintegration make visual assessment of disintegration using the USP apparatus challenging. Currently there is no designated method of disintegration characterisation specifically for rapidly disintegrating tablets in any of the three mentioned pharmacopoeias (U.S. Pharmacopeial Convention, 2014a).

Experimental quantitative methods for the characterisation of tablet disintegration time has been developed using a texture analyser (Dor and Fix, 2000; el-Arini and Clas, 2002; Szakonyi and Zelkó, 2013). Disintegration testing via texture analysis could be broadly beneficial for disintegration testing in opaque media since the technique does not require visually assessing completion of

Abbreviations: API, Active Pharmaceutical Ingredient; NSDS, Nipple Shield Delivery System; USP, United States Pharmacopeia.

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tablet disintegration. Developing quantitative methods for disintegration testing of tablets in opaque media, such as milk and other mixtures present in the digestive system, could further support existing tablet disintegration characterisation methods. This data could be useful for optimising tablet formulations, like those designed to disintegrate in milks, juices, or other opaque media prior to administration. In the described study, texture analysis is used for a novel application, specifically as a method to quantify disintegration time in opaque media. The specific application of developing rapidly disintegrating and dispersible tablets to be used in a novel breast milk mediated drug delivery system for infants is used as an example for the usefulness of this technique.

During texture analysis disintegration testing, a probe is lowered against a disintegrating tablet in a liquid. In one method, the probe applies a constant load to the tablet and moves at a variable velocity. In another method, the probe moves at a constant velocity while applying a variable load to the tablet. In the constant load technique, the distance travelled by the probe as the tablet disintegrates is recorded (Abdelbary et al., 2005). In the constant velocity technique, a load-displacement curve is generated, from which the in vivo disintegration times have been predicted from an empirical equation (Szakonyi and Zelkó, 2013). Both methods have shown positive correlation with in vivo data (Abdelbary et al., 2005; Dor and Fix, 2000; Szakonyi and Zelkó, 2013). In this study, the constant load technique is used to characterise tablet disintegration in opaque media.

Rapidly disintegrating tablets, also known as fast disintegrating or orally disintegrating tablets, have formulations designed to disintegrate entirely in the mouth prior to swallowing. These tablets are defined by their administration method rather than by a disintegration time specification (U.S. Department of Health and Human Services, 2008). Additionally, dispersible tablets, which are administered after dispersion in liquids such as water or milk, also have very fast disintegration times, typically less than 3 min (UNICEF, 2013). There is therefore high patient compliance associated with the administration of rapidly disintegrating and dispersible tablets to children, elderly, and those with dysphagia because they reduce administration complications for populations with difficulty swallowing (Fu et al., 2004).

An administration method for delivering rapidly disintegrating and dispersible tablets specifically to infants has been proposed using a novel nipple shield delivery system (NSDS) (Gerrard et al., 2013a,b; Hart et al., 2015; Sokal et al., 2013). When worn by a mother during breastfeeding, an insert, such as a tablet, is held within the NSDS and releases an API into breast milk consumed by the infant (Gerrard et al., 2013b) (see Fig. 1).

The NSDS could potentially provide a simple method for infant drug delivery and a hygienic and natural means of administering medications to infants. To understand the dosing and drug delivery of potential tablet formulations using the device, their disintegration behaviour in human milk needs to be characterised. A critical design specification for tablets used in the NSDS is that the entirety of the API is released into the breast milk within one breastfeed; therefore, disintegration characterisation of the tablets is especially important.

Characterisation of tablet disintegration in human milk via texture analysis provides a novel method of screening potential tablet formulations for the NSDS. In addition, disintegration testing in bovine milk serving as a fed-state gastric fluid model (Anwar et al., 2005) could prove widely applicable in pharmaceutical development.

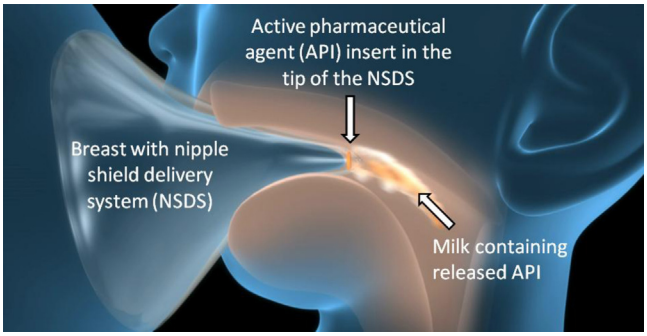

Fig. 1. An illustration of the nipple shield delivery system (NSDS) during use delivering an active pharmaceutical ingredient (API) into an infant during breastfeeding – provided courtesy of justmilk.org.

2. Materials and methods

Characterisation of tablet disintegration was performed through analysis of position and load data of a texture analyser probe applying constant load to tablets disintegrating in various media.

2.1. Media

Disintegration was characterised in a variety of media including deionised water, human milk, and bovine milk. The three media used in the study were chosen due to their relevance in previous disintegration characterisation literature and their applications in facilitating tablet disintegration in numerous applications.

Water was selected because it is the media used in USP disintegration characterisation, and has been used in the literature for texture analysis disintegration testing previously (Abdelbary et al., 2005; Dor and Fix, 2000). It is frequently used to dissolve and disintegrate tablets in a variety of applications including drug delivery, by facilitating reconstitution of dispersible tablets prior to administration.

Human milk was selected because thorough understanding of tablet disintegration behaviour in this fluid is critical to formulation development of tablets to be used in the NSDS. Other methods of characterising tablet disintegration behaviour in human milk is challenging since human milk is not transparent, obstructing visual observation. Therefore, to determine if texture analysis could be applied to screening tablets for development of dosage formulations appropriate for the NSDS, human milk was tested as one of the media.

The human milk was obtained from 10 healthy donors (screened negative for HIV 1 and 2, HTLV I and II, hepatitis B and C, and syphilis) who had consented for their milk to be used for research. The Cambridge Human Biology Research Ethics Committee at the University of Cambridge provided ethical approval for all human milk sample use. All of the milk was centrifuged (Sigma-Zentrifugen, Osterode, Germany) for 15 min at 5500 rpm, from which the fat later was removed and into which the protein layer was resuspended to produce fat-free milk. Milk batches of various fat compositions were produced through mixing various proportions of fat and fat-free milk, from which one composition was selected for use in this study (3.4 wt% fat, 1.8 wt% protein, Queen Charlotte's and Chelsea Hospital Milk Bank). Protein content was measured using a standard Bradford Agent (Sigma Aldrich, Dorset, UK) assay (Bradford, 1976).

Human milk fat content is highly variable, with average fat content varying between colostrum, transitional, and mature milk. The averages range from 2.6 w/v% to 4.1 w/v% depending on the time of day, the number of days post-partum, the time within the feed, and the mother (Emmett and Rogers, 1997). The composition of human milk for the study was chosen such that the fat content fell within this physiologically relevant range. Prior to the experiments, the human milk was thawed from −80 °C storage in a 3 °C refrigerator for 2 days.