Dimensionless quantities in the evaluation of novel composite disintegrants

O. Adeoye, G. Alebiowu*

Department of Pharmaceutics, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria
*Correspondence: galebiowu@gmail.com; galebiowu@oauife.edu.ng

Composites of native tapioca starch and mannitol were prepared by co-fusion and co-grinding to produce novel excipients. The disintegrant activity of the novel excipients was evaluated using the disintegration efficiency ratio (DER) in a paracetamol tablet formulation with native tapioca starch as control. Two dimensionless quantities DER_N and DER_C were then used to assess the efficiency of the novel excipients in enhancing the quality of the paracetamol tablets. The results indicated that the novel excipients would enhance the balance between the mechanical and disintegration properties of tablets as reflected in the DER values. The results suggested that a particular combination of process and formulation variables is required for the optimum activity of the novel disintegrants. The study concluded that the activity of the novel excipients was dependent on the mode of incorporation, compression load and method of compositing.

Key words: Tapioca starch – Mannitol – Co-fusion – Co-grinding – Disintegration efficiency ratio – Dimensionless quantities.

Tablet disintegration is the first step towards achieving a rapid availability of the drug in systemic circulation for conventional or immediate release tablets [1]. Disintegrants are agents that facilitate the breakup of the compact into smaller fragments by promoting hydration or ingress of water into the tablet when it comes in contact with the liquid or aqueous medium of the gastro intestinal tracts. They are added to the formulation to promote rapid disintegration of tablets and they act by opposing the effect of binders and the cohesive force introduced into the powder mass by compression [2]. Formulation and process variables such as the type and concentration of disintegrant, its mode of incorporation and relative density/compressional force of the tablet; all interact to affect the properties and efficiency of the disintegrant in the formulation [3, 4].

Dimensionless analysis has been proposed as a framework for drawing physical parallels between systems of disparate scale. It affords key insights into the natural phenomena or mechanisms that are too expansive and/or energetic to replicate in the laboratory, which dictates the behaviour of such systems [5]. Vadas *et al*. [6] defined two dimensionless quantities T_N and T_C, to describe the activities of disintegrants and compare the efficiency of different disintegrants in formulations. The dimensionless quantity T_N facilitates the comparison of the disintegration time within a given tablet formulation while T_C evaluates the disintegrant efficiency compared to a standard disintegrant. These dimensionless quantities possess the ability to demonstrate inherent information about the activities of the disintegrants that are not immediately evident from the disintegration time of the tablets.

In this study, the method described by Vadas *et al*. [6] was modified by using disintegration efficiency ratio [DER]; also known as the crushing strength – friability/disintegration time ratio [CSFR/DT] as the test parameter instead of disintegration time. The modification was done because the disintegration efficiency ratio has been described and used effectively as a better index for measuring tablet quality [7]. Apart from measuring the tablet strength [crushing strength] and weakness [friability], it also evaluates the negative effect of these parameters on the disintegration time of the tablet [4, 8]. The disintegrant efficiency ratio can be calculated using the following equation [7]:

$$DER = (CS/FR)/DT \qquad \textbf{Eq. 1}$$

The modification of the Vadas *et al*. [6] method by using the DER was done to enable an effective evaluation of the qualitative and quantitative effect that the co-fused and co-ground disintegrants would have on tablet quality relative to a standard disintegrant. Thus, on the subjection of DER to dimensionless analysis, the dimensionless quantities T_N and T_C described by Vadas *et al*. [6] were redefined as:

$$DER_N = (DER_{sample\ N})/(DER_{sample\ 1}) \qquad \textbf{Eq. 2}$$

where $DER_{sample\ N}$ is the DER of the n^{th} member of the series of tablets all containing the same disintegrants at the same concentration, compressed with different compression pressure, and $DER_{sample\ 1}$ is the DER of the tablet compressed with the lowest compression pressure within the series.

$$DER_C = (DER_{sample})/(DER_{control}) \qquad \textbf{Eq. 3}$$

where DER_{sample} is the DER of a tablet containing a specific disintegrant at a given compression pressure and $DER_{control}$ is the DER of the tablet containing a control disintegrant compressed with the same compression pressure. Both DER_{sample} and $DER_{control}$ must be at the same disintegrant concentration.

The purpose of the present study was to prepare composites of native tapioca starch and mannitol using two methods (co-fusion and co-grinding); to examine the effect of these methods on their disintegrant activity; and to quantitatively and qualitatively optimize the novel disintegrants using the dimensionless quantities DER_N and DER_C. Tapioca starch was used for this study because of its disintegration properties [4] while mannitol, a water soluble polyol, was used because of its dissolution aid properties [9, 10].

I. MATERIAL AND METHODS

1. Materials

The materials used were paracetamol BP (BDH Chemicals Ltd., Poole, United Kingdom), corn starch BP (BDH Chemicals Ltd., Poole, United Kingdom), lactose BP (AB Knight and Co., London, United Kingdom), tapioca starch (prepared in our laboratory from tubers of *Mannihot utilisima* L.), mannitol (BDH Chemicals Ltd., Poole, United Kingdom) and acetone (Sigma-Aldrich Laborchemickalien, Seelze, Germany).

2. Methods

2.1. Extraction of tapioca starch

The tapioca starch was extracted from the root tubers of cassava (*Manihot utilisima* L.) using established procedures [11]. The cassava tubers were peeled, washed and cut into small pieces which were soaked in distilled water for 48 h for softening. The softened tubers were milled to a pulp, and distilled water was added to dilute the slurry which was then sieved using a 100 μm mesh. The procedure was repeated three times until starch was fully extracted from the tubers as confirmed by iodine test on the remaining chaff which was negative. The extracted starch was dried at 50 °C in a hot air oven (Gallenkamp, Model OV-335, Vindon Scientific Ltd, Oldham, United Kingdom) for 72 h. The dried mass was powdered in a Laboratory mill (Christy and Norris Ltd., Chelmsford, United Kingdom) and stored in a screw-capped bottle until needed.

2.2. Composite preparation by co-fusion

Equal amounts of dried mannitol (MNT) and tapioca starch (TPS) were fused together by dispersing the TPS in distilled water already heated to 50 °C. The dispersion was then stirred for 5 min at the same temperature to form a paste. The dry MNT powder was then added to the TPS paste and mixed together for 10 min. The resulting paste (fused MNT and TPS) was then dried at 50 °C in a hot air oven (Gallenkamp, Model OV-335, Vindon Scientific Ltd., Oldham, United Kingdom) for 24 h before it was milled and sieved using a 250 μm sieve. The resulting product (FTM) was stored in a screw-capped bottle until needed.

2.3. Composite preparation by co-grinding

An equal amount each of mannitol (MNT) and tapioca starch (TPS) was used. The MNT and dry TPS were triturated together using a porcelain mortar and pestle for 10 min to ensure uniform size reduction and mixing of the two powders [12]. The resulting product (GTM) was then sieved using a 250 μm sieve and stored in a screw-capped bottle until needed.

2.4. Determination of physicochemical properties

The particle size and shape of each excipient was determined by optical microscopy (Leica DM 750 Research Microscope with an integrated icc50 camera, Leica Microsystems GmbH, Germany) on 500 particles randomly selected from the optical field. The photomicrographs taken were analyzed using the Image-pro Premier software (MediaCybernetics, Bethseda, MD, United States). The size and shape descriptors used in this study are defined below [13, 14]:

$$\text{Equivalent circle diameter (ECD)} = 2 \times \sqrt{(A/\pi)} \qquad \textbf{Eq. 4}$$

$$\text{Aspect ratio (AR)} = b/l \qquad \textbf{Eq. 5}$$

where b is the minimum Feret diameter, l the maximum Feret diameter, and A the projected area of the particle.

The particle density was determined using a solvent pycnometric method [15] with acetone as the displacement fluid. The bulk density of each powder was determined by pouring 30 g of the sample at an angle 45° into a 100 mL measuring cylinder with a known internal diameter. The quotient of the weight and volume was taken as bulk density. The relative density (D_o) of each excipient was obtained from the ratio of its loose bulk density to its particle density. Porosity was obtained by calculation from the knowledge of the relative density ($\varepsilon = 1 - D_o$). The result used was the average of three determinations [11].

The moisture content of 10 g of each excipient was determined on a wet weight basis using an Ohaus infrared moisture analyzer (Ohaus Scale Corporation, New Jersey, United States).

The angle of repose which is the maximum angle that can be obtained between the self-supporting cone of the powder mound and the horizontal plain was determined according to the relationship:

$$\theta = \tan^{-1}(h/r) \qquad \textbf{Eq. 6}$$

where h is the height of powder pile or cone (cm), r the radius of the cone base (cm), and θ the angle of repose.

Table I - Basic formulation table.

Ingredients	Formula (%)		
	I	III	V
Paracetamol	90	90	90
Corn starch (binder)	3	3	3
Lactose (diluent)	6	4	2
Disintegrant	1	3	5

2.5. Preparation of binder mucilage

Corn starch mucilage was prepared by weighing the amount required (*Table I*). The starch powder was suspended in the required amount of distilled water in a beaker and heated with continuous stirring until mucilage was formed. The mucilage was then used while hot to facilitate an effective binding of the powder mass.

2.6. Preparation of granules

Paracetamol granules containing different concentrations of the disintegrants added as intra-granular or extra- granular disintegrants were prepared by the wet granulation method of massing and screening. The granules containing intra-granular disintegrant were prepared by dry mixing the required quantities of paracetamol, lactose and the disintegrant for each batch for 5 min in a Hobart planetary mixer (Hobart Canada Inc., Don Mill, ON, Canada) and then moistening them with the corn starch binder mucilage. Wet massing continued for 5 min before the resulting wet masses were granulated by passing them through a sieve size 1400 μm, dried at 60 °C for 2 h in a hot air oven (Gallenkamp, Model OV-335, Vindon Scientific Ltd, Oldham, United Kingdom) the dried granules were then re-sieved through a sieve size 1000 μm after which they were stored in airtight containers [3].

Granules containing extra-granular disintegrants were prepared by dry mixing the required quantities of paracetamol and lactose for each batch for 5 min in a Hobart planetary mixer (Hobart Canada Inc., Don Mill, ON, Canada). The blend was then moistening with the corn starch binder mucilage. Wet massing was carried out for 5 min after which the wet masses were granulated by passing them through a sieve size 1400 μm, dried at 60 °C for 2 h in a hot air oven (Gallenkamp, Model OV-335, Vindon Scientific Ltd, Oldham, United Kingdom) and then re-sieved through a sieve size 1000 μm. The required amount of disintegrant was added and adequately mixed with the granules before storage in an airtight container [3].

2.7. Preparation of tablets

Quantities (555 mg) of granules from each batch were compressed for 30 s into tablets with predetermined loads (104.04, 121.38, 138.72, 156.06 and 173.40 MNm^{-2}) on a Carver hydraulic hand press (Carver, United States) using a 12 mm die and flat-faced punches lubricated with a 2 % w/v dispersion of magnesium stearate and talc (1:1) in acetone before each compression. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening, and to prevent falsely low yield values during analysis.

2.8. Determination of tablet crushing strength and friability

Erweka digital hardness tester (GB Caleva, Dorset, United Kingdom) was used at room temperature to determine the force required to diametrically break the tablets (crushing strength) into two equal