

Development and Evaluation of Pediatric Orally Disintegrating Paracetamol Tablets

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The limitations of commercially available paracetamol formulations specifically: 1) stability and portability (commercial paracetamol suspensions) and 2) non-pediatric friendly excipients and expensive manufacturing processes (commercially available paracetamol orally disintegrating tablets) were addressed by developing tablets made using generally regarded as safe (GRAS) status excipients and a direct compression process. The aim of this study was to develop pediatric orally disintegrating tablets of paracetamol. Pediatric orally disintegrating tablets with 60-mg and 120-mg paracetamol strengths which disintegrated in less than 30 seconds were successfully prepared by a simple cost effective direct compression process. Tablet disintegration rates were found to correlate well with tablet water absorption ratios and to a lesser extent with tablet wetting times. There was no correlation between tablet disintegration times and tablet mechanical and physical properties such as the tablet breaking force (hardness) or friability.

Keywords: Pediatric formulations, orally disintegrating tablets, paracetamol, drug delivery

INTRODUCTION

It has been widely acknowledged that there is a lack of appropriate formulations available for pediatric patients [1]. This problem is exacerbated for patients below five years of age for whom swallowing of conventional solid dosage forms, such as tablets and capsules, is a challenge. Consequently, most oral pediatric formulations for this age group are formulated as liquid dosage forms. Liquid dosage forms, however have several disadvantages compared to solid dosage forms. Liquid dosage forms have greater stability concerns due to the presence of water which increases the potential for drug degradation, excipient degradation, microbial contamination, drug-excipient and drug-container interactions.

The storage of medicines in tropical countries presents added product stability concerns due to the potentiating effects of higher temperatures on the stability of many active pharmaceutical ingredients. Some reconstituted suspensions require refrigeration which is not universally available in some countries. A further disadvantage of liquid products, even for drugs for which liquid stability is not a concern, is

reduced portability. This is readily apparent for patients who are travelling or flying and have to carry liquid medicines.

Examples of oral dosage forms which provide an alternative to liquid products are sprinkles, chewable tablets, dispersible tablets, mini-tablets, orally dissolving films, and orally disintegrating tablets (ODTs). ODTs have been popular as they combine manufacturability, tablet dosing precision, and ease of swallowing advantages. ODTs may be defined as tablets which rapidly disintegrate in the patient's oral cavity upon contact with saliva. A further advantage of ODTs is the absence of a requirement for administration with water which permits the patient a high degree of flexibility in when and where they take the drug product.

Despite the advantages of ODTs, their use has been limited by certain drawbacks, depending on the specific drug. One of the main challenges results from a need for taste-masking because most active pharmaceutical ingredients have an unpleasant, often bitter taste. This is often addressed by the use of complex manufacturing unit operations such as fluid bed coating or ion-exchange interaction techniques. A major

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drawback of these complex technologies is the use of excipients which do not have generally regarded as safe (GRAS) designation. While such excipients may be acceptable for adult patients, concerns about their use in pediatric patients have arisen because of the differences in physiology, anatomy, organ and tissue development in pediatric patients compared to adult patients [2-3].

The most popular commercially available pediatric oral paracetamol products are liquid dosage forms [4-6]. In addition to dosing accuracy concerns common to liquid products that must have their dose measured prior to administration, all the listed products have an upper storage limitation temperature of 25°C which is a concern for storage in tropical climates. Additionally, these liquid paracetamol products use excipients (parabens, polysorbates and colors) which have had safety concerns for use in pediatric patients.

Four commercially available pediatric paracetamol oral solid dosage form products (ODTs or chewable tablets) were identified [7-10]. Of these four products, three appear to be manufactured using a particle coating process while the fourth product is manufactured by a lyophilization process. Both particle coating and lyophilization processes are specialized unit operations that only companies with specialized equipment can manufacture. These complex processes add to the cost of the finished product. Additionally, the particle coating based products may utilize specialty excipients which do not have a long history of use in pediatric patients.

With pediatric excipient safety as a primary consideration, we sought to develop a pediatric ODT, using paracetamol as a model drug, that would be comprised of GRAS status excipients or excipients used in foods. Furthermore, with cost of goods and unit processes in mind, we investigated whether a pediatric orally disintegrating tablet (PODT) of paracetamol could be manufactured by direct compression which is the most cost effective tablet manufacturing technique. Paracetamol was selected as a model drug because: 1) it is widely used as an antipyretic and analgesic for pediatric patients; and 2) paracetamol is known to be

poorly compactible when subjected to direct compression [11].

MATERIALS AND METHODS

Materials

Paracetamol powder and anhydrous citric acid were received as a donation from Regal Pharmaceuticals Limited. Microcrystalline cellulose (100 µm mean particle size), mannitol, colloidal silicon dioxide, magnesium stearate, potassium dihydrogen phosphate and crospovidone were provided by the Pharmaceutics Laboratory, School of Pharmacy at the University of Nairobi. The reagents for the analytical tests were provided by the Pharmaceutical Chemistry Laboratory, School of Pharmacy at the University of Nairobi.

Formulation compositions

The compositions of the formulations that were prepared are shown in Table 1. Drug-excipient compatibility was justified based on prior use of each excipient with paracetamol in commercially marketed solid dosage forms. Powder blends of all the components except the lubricant were mixed manually for 15 minutes in a plastic container. The powder blends were then lubricated with magnesium stearate for 3 minutes.

Evaluation of powder flow properties

The angle of repose was formed by a cone of powder poured through a funnel from a fixed height of 4 centimeters. The height and the radius of the powder cone were measured and used to calculate the angle of repose. The bulk density was determined by dividing the powder mass by the resulting volume obtained after gently filling 25 grams of a powder blend from each batch into a 100 mL graduated measuring cylinder. The tapped density was determined from dividing the same mass of powder by the volume obtained from tapping the powder gently until there was no further change in the volume of the powder. The compressibility index and the Hausner ratio were calculated from the bulk and tapped density values using the equations in the US Pharmacopeial chapter on powder flow [12].

Table 1. Composition of the Pediatric Orally Disintegrating Tablets (% w/w)

Ingredient	PODT -1	PODT -2	PODT -3	PODT -4	PODT -5	PODT -6	PODT -7	PODT -8*
Paracetamol	48.0	48.0	48.0	48.0	48.0	48.0	48.0	48.0
Mannitol	26.0	21.0	16.0	21.0	11.0	31.0	36.0	21.0
Microcrystalline Cellulose	20.0	20.0	20.0	20.0	20.0	0.0	10.0	20.0
Crospovidone	5.0	10.0	5.0	-	-	10.0	5.0	10.0
Sodium Bicarbonate	-	-	5.0	5.0	10.0	5.0	-	-
Anhydrous Citric Acid	-	-	5.0	5.0	10.0	5.0	-	-
Colloidal Silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100.0							

* PODT-8 had the same composition as PODT-2 but the tablets were half the weight to obtain a 60-mg paracetamol dose

Tablet compression and evaluation

The tablets were produced by direct compression using a manually operated single punch tablet compression machine type EP-1 (Erweka, India) equipped with 10-mm round tooling to produce round flat-faced tablets. 250-mg or 125-mg of the powder blends were compressed to yield tablets with paracetamol dose strengths of 120-mg or 60-mg, respectively. The thickness and diameter of ten tablets were individually measured using a pair of vernier calipers.

Breaking force

The tablet breaking force (hardness) was carried out individually on ten randomly sampled tablets from each batch using a Schleuniger-2E tablet hardness tester (Schleuniger & Co., Germany).

Friability test

The tablet friability was assessed using twenty randomly sampled tablets from each batch using an EF2/EF2W friability tester (Electrolab, India) set to rotate at a rate of 25 revolutions per minute for 4 minutes. The tablets were weighed before (initial weight) and after (final weight of

intact tablets) the test. The percentage friability was calculated using Equation 1.

$$\% \text{ Friability} = \frac{\text{Initial wt} - \text{Final wt}}{\text{Initial wt}} \quad \text{Eq. 1}$$

Wetting time and water absorption ratio

The wetting time determination was performed on three randomly sampled tablets from each batch. A piece of tissue paper folded twice was placed in a Petri dish containing 6 mL of water. The tablet was gently placed on the tissue paper to start the test. The time taken for water to rise from the bottom of the tablet to the top surface of the tablet was taken as the wetting time. The wetted tablet was then weighed and the water absorption ratio was determined as per Equation 2.

$$\text{W. A. R.} = \frac{(W_a - W_b)}{W_b} \quad \text{Eq. 2}$$

Where W.A.R. is the Water Absorption Ratio, W_a was the weight of the tablet after water absorption while W_b was the weight of the tablet before water absorption.

Disintegration test

Disintegration testing was performed on six randomly selected tablets from each batch using a Shimadzu ZT3 disintegration testing machine (Shimadzu, Japan) in distilled water at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

Tablet dissolution

The USP dissolution method for acetaminophen tablets (chewable tablets criteria) was used [12]. A USP dissolution apparatus 2 (Model EDT-08LX, Electrolab, India) was used with 900 mL phosphate buffer at pH 5.8 thermostatically controlled at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ as the dissolution medium. The dissolution tester paddles were set to rotate at 75 revolutions per minute for 45 minutes. The samples were analyzed for paracetamol content at λ max 243 nm using a UV-Visible spectrophotometer (Model G10S UV-Vis, Shimadzu, Japan).

Content uniformity test

Ten tablets from each batch were randomly selected for the uniformity of content test. The tablets were assayed individually as per the BP 2017 to determine their paracetamol content using a UV spectrophotometer at 257 nm [13].

Assay

The assay was carried out based on the BP method for paracetamol tablets [13]. Twenty tablets from each batch were selected randomly for the test. The absorbance of the resulting solution was determined in a UV spectrophotometer with the content of

paracetamol calculated taking 715 as the value of $A_{1\text{cm}}^{1\%}$ at 257 nm.

Statistical analysis

Where applicable, test results were subjected to statistical analysis using analysis of variance (ANOVA) with a p-value of 0.05. Excel (Microsoft Corporation, USA) data analysis and spreadsheets were used to conduct the ANOVA and perform post-hoc (Tukey's HSD) testing, respectively. The null and alternative hypotheses for the ANOVA were:

$$H_0: \mu_1 = \mu_2 = \dots = \mu_k$$

where μ refers to the formulation mean test values and k refers to the number of formulations

H_A : at least two of the mean test values differed

RESULTS AND DISCUSSION

Micromeritic tests

Table 2 shows the results of the micromeritic tests for the eight formulations. Although the Hausner ratio and the compressibility index values for the powders fell in the poor powder flow range, the angle of repose values were in the fair to passable range for powder flow. The angle of repose values for the powder blends in this study ranged from 38 to 44° . The United States Pharmacopoeia indicates that powders with angles of repose up to the $40 - 50^{\circ}$ range have been successfully used in manufacturing [12].

Table 2. Micromeritic test results

Test	PODT -1	PODT -2	PODT -3	PODT -4	PODT -5	PODT -6	PODT -7	PODT -8
Bulk Density (g/cc)	0.40	0.38	0.42	0.46	0.45	0.42	0.42	0.38
Tapped Density (g/cc)	0.65	0.62	0.61	0.73	0.72	0.70	0.69	0.62
Hausner Ratio	1.62	1.63	1.45	1.59	1.60	1.67	1.64	1.63
Compressibility Index (%)	38.5	38.7	31.2	37.0	37.5	40.0	39.1	38.7
Angle of Repose ($^{\circ}$)	42.8	38.5	42.3	43.6	38.0	41.3	42.5	38.5

Tablet characterization

The results for the tablet characterization tests are shown in Table 3. The values for the assay, content uniformity and the dissolution were within acceptable ranges for all the batches.

The breaking force, friability and disintegration times are commonly used tests for ODTs. Of these tests, rapid disintegration (within 30 seconds) [14], is a key factor that influences the *in vivo* performance of an ODT. There are no generally recommended ranges of breaking force values for ODTs. Likewise for friability, very mechanically 'soft' tablets have been marketed commercially with mechanical issues being addressed by appropriate packaging. Therefore, only the disintegration test values were subjected for further statistical analysis.

In order to test the hypothesis that the formulation composition had an effect on tablet disintegration times, a one-way analysis of variance (ANOVA) was performed on the disintegration results for the eight formulations. The between groups ANOVA indicated that there was a statistically significant effect with F

(7, 40) = 9.77, $p < 0.05$. In order to determine which formulations had significantly different disintegration results, Tukey's HSD post-hoc test was performed. The PODT-4 formulation was found to have significantly higher mean disintegration time (51 seconds) than all the other formulations, which all had disintegration times of less than 30 seconds. There were no statistically significant differences between the disintegration times of any of the other formulations.

The breaking force, thickness and friability of the tablets were dependent on the compression force applied during tablet formulation. The compression force was adjusted to attain a targeted breaking force in the range of 20 to 60 N. The tablets from the different batches had friability values ranging from between 1.5 to 5.4%. While the typical limit for the friability of conventional tablets is 1%, this issue can be addressed in ODTs by careful packaging and in cases of extremely soft tablets (e.g., lyophilized products) specialized blister packaging is an option.

Table 3. Tablet Characterization test results (mean values with the standard deviation in parentheses)

Ingredient	PODT -1	PODT -2	PODT -3	PODT -4	PODT -5	PODT -6	PODT -7	PODT -8
Thickness (mm)	2.54 (0.05)	2.75 (0.16)	2.71 (0.23)	2.47 (0.08)	2.56 (0.08)	3.11 (0.11)	2.56 (0.05)	1.36 (0.05)
Breaking Force (Newtons)	47.3 (3.47)	45.8 (5.77)	46.2 (14.68)	42.4 (3.63)	53.0 (6.41)	<10	33.2 (4.24)	29.0 (5.75)
Friability (%)	1.53	1.63	4.62	2.84	4.87	Failed*	5.42	1.57
Wetting time (s)	5.33 (0.58)	5.33 (0.58)	11.33 (3.21)	56.0 (3.00)	48.33 (2.89)	13.33 (1.52)	6.00 (0.00)	2.67 (0.58)
Water absorption ratio	2.22 (0.590)	2.27 (0.310)	2.28 (0.69)	5.51 (0.16)	3.68 (0.29)	2.51 (0.31)	1.61 (0.51)	1.57 (0.14)
Disintegration time (s)	12.5 (3.21)	11.83 (3.37)	11.17 (3.06)	51.00 (29.65)	21.00 (6.99)	9.50 (1.05)	18.00 (6.10)	6.50 (0.55)
% Drug dissolved at 45 min	94.62 (3.54)	90.70 (2.30)	110.90 (5.51)	102.39 (3.43)	91.30 (1.16)	90.11 (0.65)	93.30 (1.95)	104.65 (2.50)
Uniformity of content (%)	97.94 (1.90)	97.47 (2.16)	95.78 (1.43)	98.90 (3.82)	95.20 (1.15)	94.79 (0.53)	99.04 (2.86)	100.55 (4.72)
Assay (%)	98.49 (1.35)	101.20 (6.10)	95.76 (0.59)	111.79 (9.48)	104.60 (8.14)	94.97 (6.09)	100.39 (6.53)	99.29 (6.55)

* Tablets cleaved or broke during the test

In Figures 1 to 4, the tablet disintegration times for the various batches are plotted as a function of tablet breaking force, friability, wetting time, and water absorption ratio. PODT-6 was not included in the graphs in figures 1 and 2 as continuous numeric values were not obtained for its breaking force and friability (Table 3). The correlation coefficient (R^2) was used to assess the strength of the relationship between the disintegration time and the four tests.

The R^2 values obtained were 0.022, 0.018, 0.696, and 0.829 when the disintegration times were plotted as a function of tablet breaking force, friability, wetting time, and water absorption ratio, respectively. Therefore of these four tests, the water absorption ratio had the strongest correlation with the tablet disintegration times. Interestingly, the tablet breaking force and tablet friability values did not show a correlation with the disintegration times. In general, it is expected that tablets with higher breaking force values will usually have longer disintegration times as their increased density (due to the increased solid fraction) leads to a delay in the penetration of water into the tablet core. Similarly, tablet friability would be expected to correlate with disintegration times as tablets with weaker inter-particulate bonding (higher friability) would be expected to have faster disintegration times.

It was observed that the tablet water absorption ratios had a stronger correlation with tablet disintegration times than the wetting times, even though their measurement methods are somewhat related. Indeed, there was a strong correlation ($R^2 = 0.887$, graph not shown) between the wetting time and the water absorption ratio values. It may be concluded that the tablet-water interaction rate (wetting time) and amount of water taken up by the tablets (absorption ratio) have a greater influence on disintegration times than tablet mechanical properties (breaking force and friability). Other authors have reported that wetting rate and water absorption have been found to relate to disintegration times of ODTs [15]. Furthermore, the work of Pabari and Ramtoola found that rapid wetting and

disintegration of ODTs was not necessarily related to tablet porosity [16].

Effervescent forming combinations of alkali metal carbonates salts and organic acids may contribute to tablet disintegration from the generation of carbon dioxide and consequent volumetric air expansion [16]. In the current study, the use of sodium bicarbonate and citric acid to facilitate disintegration by effervescence in the PODT-3, PODT-4, PODT-5 and PODT-6 formulations did not provide any added benefit to the tablet properties that were studied. Interestingly, the PODT-4 and PODT-5 formulations had the highest water absorption ratios. This indicates that while effervescence may facilitate high water uptake in ODTs, it does not necessarily lead to fast disintegration rates compared to croscopovidone, which acts by capillary action, wicking and strain recovery.

The incorporation of the effervescent sodium bicarbonate and citric acid pair (PODT-3, PODT-4, PODT-5 and PODT-6 formulations) also appeared to have a negative effect on the tablet friability as these formulations had friability values greater than 2%. The PODT-7 tablets, which had half the level of microcrystalline cellulose (MCC) compared to the other formulations, showed the highest friability while PODT-6 (which lacked MCC) failed the friability test suggesting that MCC was functioning as a dry binder in the formulations. The friability of the PODT-1, PODT-2 and PODT-8 formulations was less than 2%, which may be considered manageable for further optimization or specialized ODT packaging techniques as previously mentioned. Consequently, PODT-1 and PODT-2 were selected as the most appropriate formulations for further development. PODT-8 was similar to PODT-2 in terms of percentage composition, but the tablets were prepared at half the total weight to yield 60-mg paracetamol tablets. The use of a common blend or granulation to manufacture tablets of different dose strengths is advantageous as it does not require a separate manufacturing process prior to the tablet compression step.

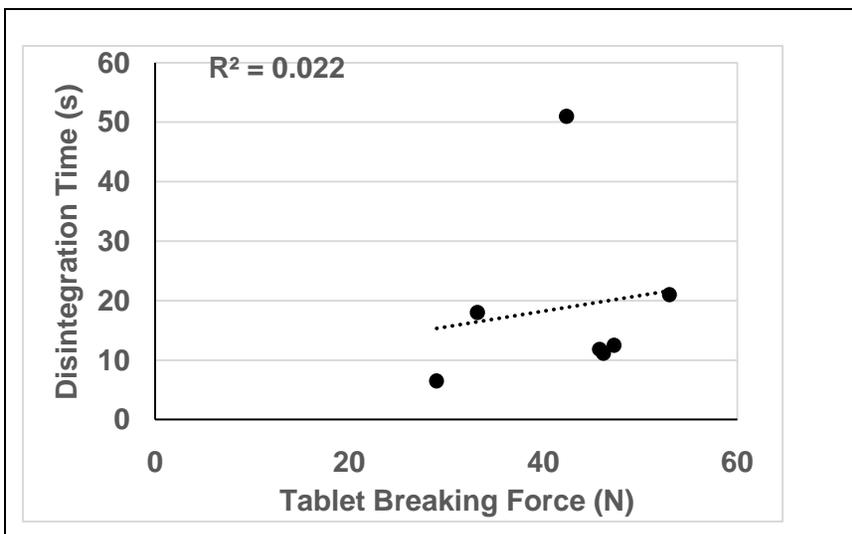


Figure 1. Disintegration time plotted as a function of tablet breaking force.

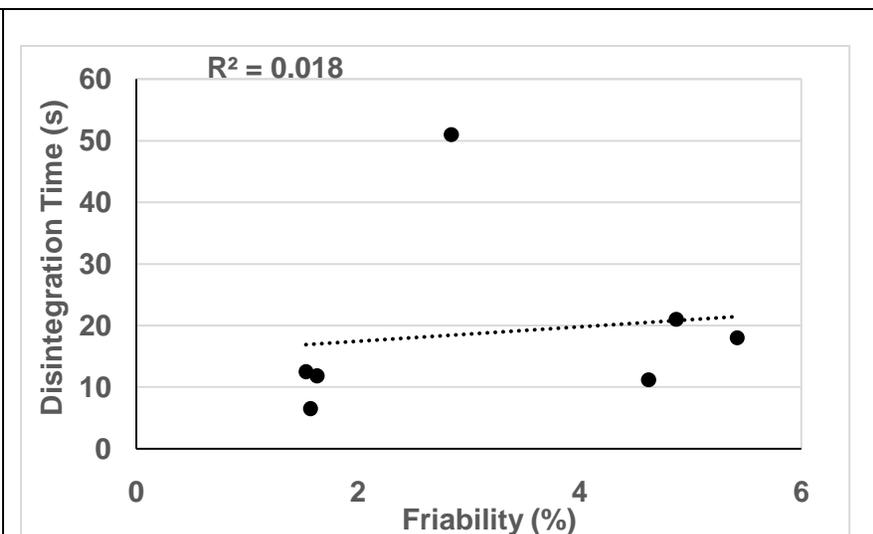


Figure 2. Disintegration time plotted as a function of tablet friability.

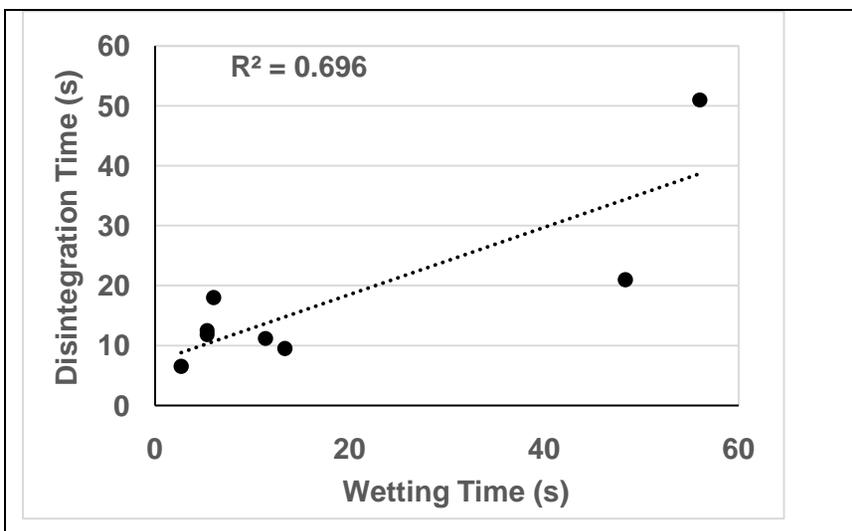


Figure 3. Disintegration time plotted as a function of tablet wetting time.

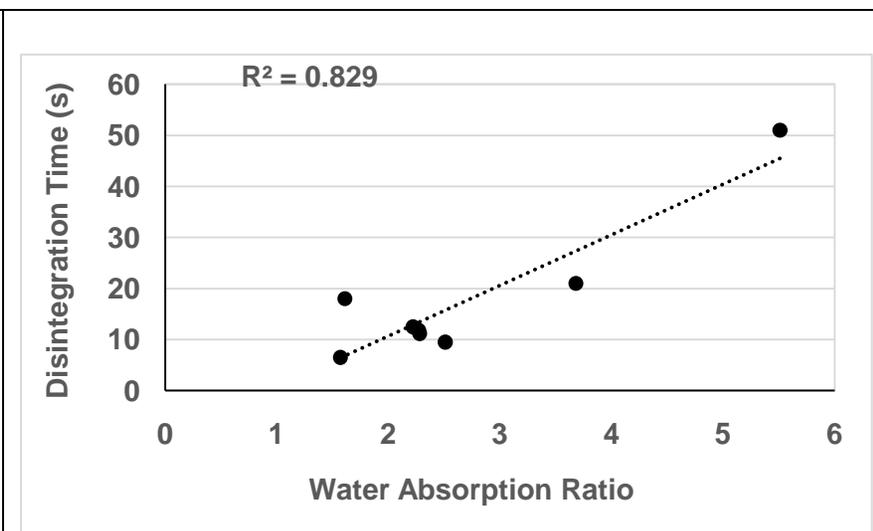


Figure 4. Disintegration time plotted as a function of tablet water absorption ratio.

CONCLUSIONS

Paracetamol (60-mg and 120-mg) PODTs were successfully prepared by a direct compression process using excipients with minimal safety concerns. The direct compression process avoided the complex steps associated with many marketed ODT products. The designed tablets had disintegrating times of less than 30 seconds. Further work is ongoing to optimize the taste of the PODTs.

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