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Formulation and in vitro Evaluations of Low Dose Paracetamol Orally Disintegrating Tablets

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Abstract: Orally disintegrating tablets are a solid dosage form compromising medicinal substances which disintegrate rapidly when placed on the tongue. In this study, low dose paracetamol orally disintegrating tablets was formulated and evaluated. Direct compression was used to prepare 350 mg tablets of five formulations (F1- F5) by using a single punch manual tableting machine. Pre-formulation studies were performed on the powder mixture of each formulation to obtain information regarding their flow properties. The tablets from each formulation were also evaluated for weight uniformity, drug content uniformity, thickness, hardness, friability, disintegration and dissolution. The disintegration tests carried out revealed that tablets from F2 showed the shortest disintegration time of 32.67 ± *3.14* seconds followed by tablets from F5, F3, F4 and F1. However, the dissolution results illustrated that tablets from F5 have the best dissolution profile, releasing 84.70 ± 5.31% of drugs within 4 minutes. Hence, F5 is the most optimized formulation of a paracetamol orally disintegrating tablet in this study.

Keywords: paracetamol, orally disintegrating tablets, direct compression

1. INTRODUCTION

There are many routes of drug administration such as intravenous, oral, and pulmonary. The oral route is the most preferred route as it is the most convenient, versatile, and has the highest patient compliance [1]. However, it is estimated that about one-third of the general population suffers from a condition known as dysphagia, difficulties in swallowing [2]. This leads to a high incidence of medication noncompliance and treatment ineffectiveness [3].

Orally disintegrating tablets (ODTs) are one of the solid dosage forms for oral administration, defined as "a solid dosage form containing medicinal substances which disintegrate rapidly, usually within seconds, when placed upon the tongue" according to the Food and Drug Administration (FDA) [4]. As ODTs disperse readily in the mouth before swallowing and without the need of water, it is highly demanded by people with dysphagia [5]. In addition, ODTs are also formulated to have higher bioavailability and a faster onset of action compared to the conventional tablets as the drugs dissolve and disperse in the saliva and are absorbed in oral buccal cavity before reaching the stomach. Side effects caused by the first pass effects of the medication are also reduced as they undergo pregastric absorption [6].

To date, few Paracetamol ODTs such as Calpol® SIXPLUS™ Fastmelts and Febrectol™ have been marketed worldwide, but none are available in Malaysia. In addition, there is also no low dose paracetamol tablet available in the market specifically for the paediatric group. Paracetamol is an

analgesic antipyretic drug which is used to treat common pain and fever that require a rapid onset of therapeutic effect action [7]. Therefore, this study aims to develop better orally disintegrating tablets containing paracetamol as the active ingredient. This study conducted to formulate orally disintegrating tablets of 120mg paracetamol with suitable excipients that targets the paediatric population which requires a lower dose for treatment. Characterization the powder mixture of the formulations is evaluated before tablet formation, by the direct compress method and continued with the evaluation of the pharmacopoeial and non-pharmacopoeial properties.

2. METHODS

2.1. Materials

The materials that were used in this study include Paracetamol (supplied by Euro Pharma Sdn. Bhd.), Xylitol (supplied by Euro Chemo Pharma Sdn. Bhd.), Microcrystalline Cellulose, Avicel® 102 and Sodium Starch Glycolate (manufactured by Sigma Aldrich, USA), Pregelatinized Starch, Sprees® 820 (manufactured in IOWA, USA), Silicon Dioxide (manufactured by Merck, Germany), Magnesium Stearate (supplied by Peter Greven from Netherland), Sodium Hydroxide and Potassium Dihydrogen Phosphate (supplied by R&M Chemicals, UK). All the materials were procured from the Pharmacy Department Lab of Universiti Malaya.

2.2. Formulation of paracetamol orally disintegrating tablets

Five formulations were prepared (as shown in Table 1) for the production of the paracetamol ODTs by direct compression. The total weight of each tablet was fixed to 350mg with about thirty five percent consisting of the active ingredient, Paracetamol. The excipients used in the formulation were chosen based on their functionality and are compatible with the direct compression method for tablet production. The excipients used were xylitol, as diluent, pregelatinized starch as binder, microcrystalline cellulose as disintegrant, sodium starch glycolate (SSG) as superdisintegrants, magnesium stearate as lubricants and silicon dioxide as adsorbent. In addition, the percentage range of excipients designed for the five formulations was based on the Handbook of Pharmaceutical Excipients and previous literature [8].

Table 1. Formulations of paracetamol orally disintegrating tablets

Ingredient	Formulation				
	1	**2**	**3**	**4**	**5**
Paracetamol (mg/ tab)	120	120	120	120	120
Xylitol (mg/ tab)	63	49	59.5	45.5	50.61
Pregelatinized Starch (mg/ tab)	76.86	90.86	76.86	90.86	87.5
Microcrystalline Cellulose (mg/ tab)	70	70	70	70	70
Sodium Starch Glycolate (mg/ tab)	17.5	17.5	21	21	17.5
Magnesium Stearate (mg/ tab)	0.875	0.875	0.875	0.875	0.875
Silicon Dioxide (mg/ tab)	1.75	1.75	1.75	1.75	3.5
Total Weight (mg/ tab)	350	350	350	350	350

2.3. Powder mixture evaluations

Sieving method were performed to determine distribution of particle size, bulk density determined by densitometer, flow properties of powder determined by angle of repose and compressibility of the powder will be determined by compressibility index and Hausner ratio.

2.4. Preparation of paracetamol orally disintegrating tablets

All the raw materials were passed through an 80-mesh sieve separately, before mixing. Following that, the powder mixture was filled into the 10 mm punch-die cavity of the tableting machine and compressed at a force of about 2500 psi.

2.5. Evaluation tests of prepared paracetamol orally disintegrating tablets

2.5.1. Uniformity of weight

The uniformity of weight test was carried out using the Mettler Toledo College digital weighing balance. Total weight of random 20 tablets was determined and the average weight was calculated.

2.5.2. Drug content uniformity test

Ten randomly tablets were crushed and equivalent to 100 mg of drug was weighed and dissolved into 100 ml of pH 5.8 phosphate buffer in a volumetric flask. 1 ml of the mixture was measured and diluted with pH 5.8 phosphate buffer and the absorbance of the diluted mixture was then measured using UV-spectrophotometer at 243 nm. The percentage of drug content was calculated.

2.5.3. Thickness test, hardness test, and friability test

A digital vernier calliper was used to measure the thickness of the tablets and the results were expressed in mm. The hardness test measured the force that was required to break the tablets in kg/cm^2 by using Monsanto Hardness Tester. ODTs fall under the category uncoated tablets and the satisfactory hardness for uncoated tablets is 3-5 kg/cm^2. Erweka Tar 10 friability tester used for friability test. Tablets were placed inside and rotated for four minutes at 25rpm. Next, the tablets were removed from the tester and brushed to remove any powder on their surfaces. The tablets were then reweighed and the percentage of weight loss was calculated [9].

2.5.4. Disintegration test

Six tablets were chosen randomly and singly placed in each of the six tubes of the basket rack. Discs was then placed over the tubes and the basket rack was immersed in the distilled water. Time taken for the tablets to completely disintegrate without leaving any palatable mass behind were measured.

2.5.5. Dissolution test

900 ml of phosphate buffer with pH 5.8 was used as the dissolution medium and the temperature was maintained at 37 ± 5°C. Six tablets were placed into the six vessels of the apparatus and the paddles were rotated at a speed of 50 rpm for half an hour. At a standard interval of two minutes, 5 ml of the dissolution sample was withdrawn from each vessel and assayed using UV-spectrophotometer at 243 nm. After every sampling, an equal volume of medium which was pre-warmed to 37 °C was replaced into the dissolution apparatus [10].

2.5.6. Statistical data analysis

All the data in this study were presented using Mean ± Standard Deviation. One way analysis of variance (ANOVA) was used to determine the significant differences of profile between formulations. Level of statistical significance was set at $p < 0.05$ [11].

3. RESULTS AND DISCUSSION

3.1. Powder mixture evaluation

In all five formulations, the bulk and tapped densities were calculated using powder mixtures of mass 22.05 g. As for tapped density, the maximum number of taps carried out was 1250 and the results presented were calculated using the data obtained after 1250 taps. As shown in Table 2, tapped densities do not vary much between formulations. F1 has the highest tapped density (0.58 g/mL) followed by F3 (0.56 ± 0.02 g/mL) while F2, F4 and F5 have the lowest tapped density (0.55 g/mL). The higher bulk density and lower tapped density will lead to a lower compressibility index and Hausner's ratio which show better flow character of the powder mixture [9]. Moreover, based on Table 2, the angles of repose of all the formulations range from 41 - 45° with the largest value being 43.63 ± *1.33*° of F2 which has the best flow characteristics while the smallest being 41.27 ± *1.33*° of F1. According to USPC 2013, angle of repose ranging from 41 - 45° shows passable flow of powder mixture [9]. As shown in Table 2, the compressibility index of all the formulations range either from 16 – 20 % or from 21 – 25 %. According to USPC 2013, compressibility index ranging from 16 – 20 % shows fair flow of powder mixture while compressibility index ranging from 21 – 25 % shows passable flow of powder mixture. The powder mixture of F4 has the best flow character as it has the smallest compressibility index (19.96%) while the powder mixture of F1 has the worst flow character as it has the largest compressibility index (23.97%). This could be attributed due to high content of xylitol (63 mg/tab) in F1 that can reduce compatibility and compressibility of powder mixture due to its hygroscopic properties [12]. Based on Table 2, the Hausner's ratio of all the formulations range either from 1.19 - 1.25 or from 1.26 - 1.34. According to USPC 2013, Hausner's ratio ranging from 1.19 - 1.25 shows fair flow of powder mixture while Hausner's ratio ranging from 1.26 - 1.34 shows passable flow of powder mixture. The powder mixtures of F4 and F5 have the best flow character as they have the smallest Hausner's ratio (1.25) while powder mixture of F1 has the worst flow character as it has the largest Hausner's ratio (1.32).

Table 2. Evaluation of powder mixtures of the formulations (F1 - F5) (Mean ± *SD*)

Formulation	F1	F2	F3	F4	F5
Bulk Density (g/mL)	0.44 ± *0.00*	0.42 ± *0.00*	0.45 ± *0.01*	0.44 ± *0.00*	0.44 ± *0.02*
Tapped Density (g/mL)	0.58 ± *0.00*	0.55 ± *0.03*	0.56 ± *0.02*	0.55 ± *0.00*	0.55 ± *0.00*
Angle of Repose (°)	41.27 ± *1.33*	43.63 ± *1.33*	42.33 ± *1.94*	42.33 ± *1.54*	41.97 ± *0.76*
Compressibility Index (%)	23.97 ± *0.00*	23.06 ± *3.83*	20.26 ± *0.52*	19.96 ± *0.00*	20.93 ± *3.67*
Hausner's Ratio	1.32 ± *0.00*	1.30 ± *0.07*	1.25 ± *0.01*	1.25 ± *0.00*	1.27 ± *0.06*

3.2. Evaluation tests of prepared paracetamol orally disintegrating tablets

3.2.1. Uniformity of weight

Not more than two tablets from each formulation should deviate ± 5 % from the average weight for the tablets to have passed the test. Table 3 shows the average weight of twenty tablets

from formulations one to five (F1 - F5). All the tablets have weight variations ranging from 99.1 – 101 % which are within the acceptance limit (95 – 105 %).

3.2.2. Drug content uniformity test

The uniformity of drug content of all the formulations are shown in Table 3. The drug content of all the tablets assayed in each formulation are within 85 – 115 % of the required drug amount of 120 mg. Hence, in accordance with the BPC 2011, all the tablets pass the drug content uniformity test.

3.2.3. Thickness, hardness, and friability test

According to Table 3, the thickness of the tablets in all the formulations are about the same and only vary from 3.73 ± *0.01* mm to 3.77 ± *0.03* mm. The thickest tablets are produced by F2 and F3 which caused by high contents of pregelatinized starch and SSG respectively. However, F4 has lower thickness of tablet compared to F2 and F3 despite has highest content of pregelatinized starch (90.86 mg) and SSG (21 mg). It remains unclear to which factor contribute to this, but it can be due to lower content of xylitol in F4 compared to F2 and F3. Xylitol, pregelatinized starch and SSG are hygroscopic excipients that may have led to an increase in moisture absorption by the tablets, thus causing increased thickness. The hardness of the tablets in all the formulations range from 2.20 ± *0.35* - 3.20 ± *0.35* kg/cm^2, Table 3 Since ODTs fall under the category uncoated tablets, the satisfactory hardness is 3-5 kg/cm^2 [13]. Therefore, it can be said that only tablets from F4 and F5 pass the hardness test with hardness of 3.20 ± *0.35* kg/cm^2 and 3.00 kg/cm^2 respectively. This is because of the high concentrations of pregelatinized starch used in F4 and F5 which are 25.96 % and 25 % of each tablet respectively. On the other hand, the tablets from F1, F2 and F3 do not have hardness within satisfactory range which may be caused by low concentration of pregelatinized starch and SSG. Pregelatinized starch is acts as a binder, an increase in its concentration leads to increased tablet hardness while increase in the concentration of SSG increases the hardness of tablets [14]. The friability test results of all the formulations are shown in Table 3. The weight loss of the tablets in all the formulations range from 0.76 - 0.99 %. As shown in the table, tablets from F4 show the lowest friability (0.76 %) while tablets from F2 show the highest friability (0.99 %). This is in relation to the hardness of the tablets. The harder the tablet, the greater the pressure it can withstand without breaking thus, the lower the friability.

3.2.4. Disintegration test

The results of the disintegration tests for all the formulations are shown in Table 3. The disintegration time of all the tablets from all the formulations range from 32.67 ± 3.14 - 39.17 ± 5.12 seconds which have passed the requirements of both the USPC and the European Pharmacopoeia, and are thus considered to be orally disintegrating tablets. Besides that, the use of SSG, which is a super-disintegrant, at its optimum concentration of 5 % has reduced the disintegration time of the tablets as it causes rapid uptake of water which is followed by rapid and enormous swelling [8]. This is because SSG swells 7 - 12 folds in less than 30 seconds [6].

Table 3. Evaluation of prepared Paracetamol orally disintegrating tablet formulations (F1 - F5) (Mean $\pm SD$)

Formulation	F1	F2	F3	F4	F5
Weight variation[a] (mg)	350.1 ± *0.98*	350.7 ± *1.14*	350.10 ± *0.98*	350.43 ± *1.83*	349.90 ± *1.03*
Drug content[b] (%)	85.0 ± *0.15*	86.07 ± *3.50*	86.57 ± *2.02*	86.27 ± *2.63*	85.30 ± *3.96*
Thickness[c] (mm)	3.73 ± *0.01*	3.77 ± *0.02*	3.77 ± *0.03*	3.74 ± *0.05*	3.76 ± *0.05*
Hardness[d] (kg/cm²)	2.30 ± *0.26*	2.20 ± *0.35*	2.75 ± *0.26*	3.20 ± *0.35*	3.00 ± *0.00*
Friability[e] (%	0.98 ± *0.00*	0.99 ± *0.00*	0.89 ± *0.00*	0.76 ± *0.00*	0.79 ± *0.00*
Disintegration[f] (seconds)	39.17 ± *5.12*	32.67 ± *3.14*	35.50 ± *3.27*	36.67 ± *5.16*	33.00 ± *3.35*

Note: (*a*: n= 20, *b*: n= 10, *c*: n= 10, *d*: n= 10, *e*: n= 19, *f*: n= 6)

3.2.5. Dissolution test

The dissolution results of all the formulations are shown in Figure 1. Based on the results, it is shown that the tablets from F5 have released the greatest amount of drug (84.70 ± 5.31 %) while tablets from F2 have released the least amount of drug (63.20 ± 4.53 %). This is mainly caused by higher content of silicon dioxide in F5 compared to F2 as silica particles have a very high surface area, which increases the available surface area for dissolution and allows for more efficient release of the active ingredient [15]. Besides, high content of pregelatinized starch in F2 can reduce drug dissolution rate by absorbing water, forming gel-like matrix subsequently creating barrier around drug particle [16]. Tablets from F1 and F3 took higher time to release the maximum amount of drug. It is suspected that this may be due to low content of pregelatinized starch in the formulation causing higher disintegration time. It is known that pregelatinized starch improves the disintegrability of tablets through its ability to swell prior contact with water [17].

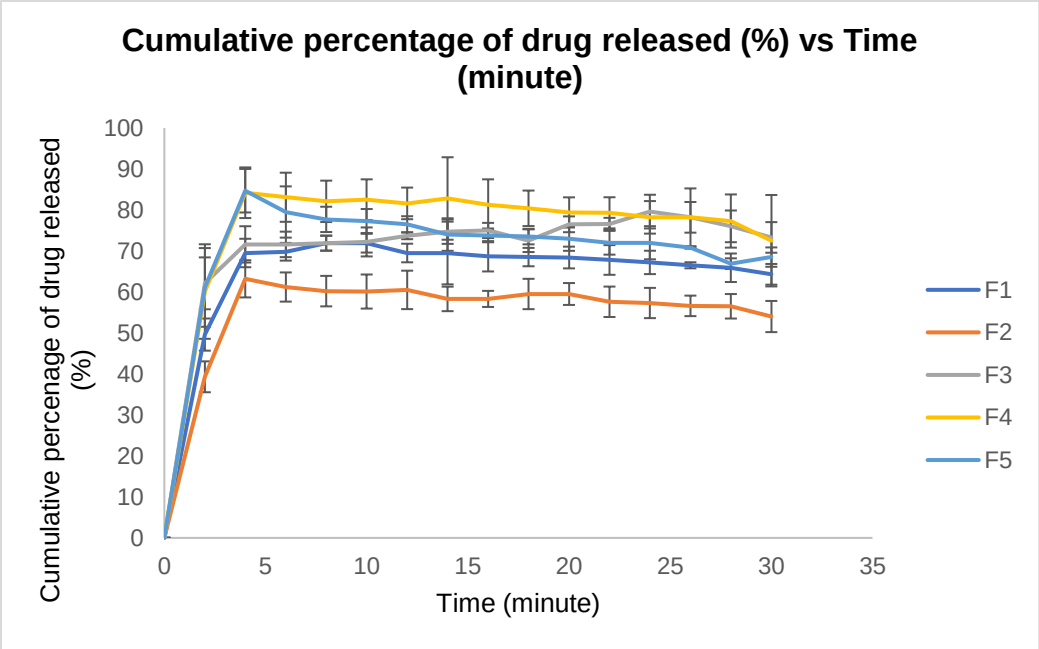

Figure 1. Drug release profile of F1 to F5 paracetamol orally disintegrating tablets

4. CONCLUSION

In conclusion, F5 is considered the most optimised formulation with uniformed weight and drug content, good hardness and reduced friability, good disintegration time and dissolution profile. The results of the study have proven that changing the concentrations of certain excipients such as pregelatinized starch and sodium starch glycolate, can affect the physicochemical properties of the formed orally disintegrating tablets.

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