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Application of face centred central composite design to optimise compression force and tablet diameter for the formulation of mechanically strong and fast disintegrating orodispersible tablets

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ABSTRACT

A two factor, three level (3^2) face centred, central composite design (CCD) was applied to investigate the main and interaction effects of tablet diameter and compression force (CF) on hardness, disintegration time (DT) and porosity of mannitol based orodispersible tablets (ODTs). Tablet diameters of 10, 13 and 15 mm, and CF of 10, 15 and 20 kN were studied. Results of multiple linear regression analysis show that both the tablet diameter and CF influence tablet characteristics. A negative value of regression coefficient for tablet diameter showed an inverse relationship with hardness and DT. A positive value of regression coefficient for CF indicated an increase in hardness and DT with increasing CF as a result of the decrease in tablet porosity. Interestingly, at the larger tablet diameter of 15 mm, while hardness increased and porosity decreased with an increase in CF, the DT was resistant to change. The optimised combination was a tablet of 15 mm diameter compressed at 15 kN showing a rapid DT of 37.7 s and high hardness of 71.4 N. Using these parameters, ODTs containing ibuprofen showed no significant change in DT (ANOVA; $p > 0.05$) irrespective of the hydrophobicity of the ibuprofen.

1. Introduction

The demand for orodispersible tablets (ODTs) has grown over the last decade with the number of commercial over-the-counter and prescription ODT products now reaching over 450 (Aubrey, 2011). This expansion is attributed to the convenience the ODTs offer to the patient population. While originally developed for specific patient groups such as the paediatric, geriatric, patients with dysphagia as well as travelling patients, ODTs have since gained popularity amongst the wider patient population (Abdelbary et al., 2005). To allow this expansion in ODT application, the number of ODT technologies has increased with a major shift from lyophilisation towards conventional tableting. Depending on the process used therefore, the resultant ODTs vary in their key properties of disintegration time (DT) and mechanical strength (Fu et al., 2004; Sandri et al., 2006). In general ODTs produced by lyophilisation tend to have the most rapid DT of 2–3 s due to their high porosity; however these have poor mechanical strength requiring specialised packaging (Corveleyn and Remon, 1997; Seager, 1998). Conventional processing produces ODTs with higher mechanical strength but as these are inherently less porous, they show slower disintegration.

Ideally, the ODT should disintegrate rapidly, be pleasant tasting and of sufficient mechanical strength to withstand handling, packaging, transport and more importantly should be easy to handle by the patient (Okuda et al., 2009). It is interesting that European Pharmacopoeia (PhEur, 2008) describes an ODT as a tablet which disperses readily and within 3 min before swallowing while according to the FDA (FDA, 2008); ODTs should have an in vitro DT of 30 s or less.

Considerable efforts have been applied to modify conventional tableting formulation and/or the process in order to produce ODTs with rapid DT while maintaining sufficient mechanical strength. Wehling and Schuehle (1996) and Wehling et al. (1993) report the addition of effervescent excipients and use of low compression force to increase the disintegration rate of ODTs. However, they report that the resultant ODTs had a low mechanical strength requiring specialised packaging. To improve the mechanical strength of these ODTs, other researchers have subjected directly compressed tablets to post compaction treatment. Various post compaction treatments used include exposure to humidity and/or heat, to effect a solid-state transition of amorphous sugars (such as maltose) to its crystalline form (Mizumoto et al., 2005) or heating to attain phase transition of sugar alcohols such as xylitol (Kuno et al., 2005, 2008). Mizumoto et al. (2005) reported an

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Table 1
Commercially available orally disintegrating tablets.

Name	Tablet diameter (mm)	Active and dosage strength	Process	DT
Zofran Zydis®	9	4 mg, 8 mg Ondansetron	Lyophilisation	2.2 s
Alavert™ (CIMA)	10	10 mg Loratadine	Direct compression	32.8 s
Xilopar Zydis®	11	1.25 mg Selegiline	Lyophilisation	2.8 s
Elan	13.0	100 mg Nimesulide	Wet granulation/compression	25 s
Calpol® fastmeltsFlashtab®	14.3	250 mg Paracetamol/808.2 mg	Dry granulation/compression	<60 s
Nurofen® Meltlets	15	200 mg Ibuprofen	Dry granulation/compression	31 s
Excedrin® Quicktabs™	17.5	500 mg Acetaminophen	Dry granulation/compression	25.8 s

increase in the hardness by approximately 4-fold to 4 kp, without causing any change in the DT at 10–15 s, whereas Kuno et al. (2005) reported that after 12 h treatment, an approximately 4.5-fold increase in the hardness to 4.5 kp and a 5-fold increase in the DT to about 30 s was observed.

Compression force (CF) is known to affect tablet properties and in general an increase in CF results in an increase in tablet hardness and is accompanied by an increase in DT. Bi et al. (1999) reported that for 8 mm tablets, a 5-fold increase in the CF to 4.9 kN caused approximately an 11-fold increase in the tensile strength to 23 kg/cm^2 and a 2.4-fold increase in DT of tablets to 31 s. The increase in CF resulted in a decrease in tablet porosity to 16%. Similarly for tablets of diameter 10 mm, Schiermeier and Schmidt (2002) reported an approximately 5-fold increase in the tablet crushing strength to 71 N when the CF was increased by 2.5 times to 10 kN. The authors reported a corresponding increase in the DT and tablet wetting time. Late et al. (2009) reported that an increase in tablet hardness resulted in an increase in the DT of tablets of 11 mm diameter.

Studies of the impact of CF on tablet hardness, porosity and DT for the ODTs have been carried out predominantly for tablet of diameters in the range of 8–11 mm. Tablets of these diameters are generally applicable to a limited weight and dose range. A larger tablet diameter of 25 mm was studied by Schiermeier and Schmidt (2002). The authors reported that a 2-fold increase in CF caused approximately a 5-fold increase in the tablet crushing strength to 130 N, and a 2-fold increase in DT to 78 s. Commercially available ODT tablets have diameters ranging from 9 mm to 17.5 mm and at the larger diameters of 13 mm and greater, they can accommodate higher drug dosage of $\geq$100 mg (El-Arini and Clas, 2002; Klancke, 2003; McLaughlin et al., 2009) (Table 1).

Tablet diameters have also been reported to influence the characteristics of tablets. Kiekens et al. (2004) reported a decrease in tablet tensile strength from 3.99 to 3.68 MPa when the tablet diameter increased from 4 mm to 9.5 mm whereas, Rawas-Qalaji et al. (2007) reported a non-significant increase in hardness from 6.8 $\pm$ 0.4 to 7.2 $\pm$ 0.3 kg for directly compressed tablets when tablet diameter increased from 7.94 mm to 8.73 mm. DT of the tablets was found to be $\leq$10 s.

In the present study the influence of increasing compressional force and tablet diameter on the mechanical strength, porosity and DT of tablets prepared by direct compression was examined. A two factor, three level (3^2) face centred, central composite design (CCD) was used and response surface methodology was applied to determine the interaction of compression force and tablet diameter for ODT formulations with optimal hardness and DT. Statistical models with interaction terms were derived to investigate the relative significance of the two variables, tablet diameter (X1) and compression force (X2) and their interaction on the responses, i.e. hardness (Y1), disintegration time (Y2) and porosity of tablets (Y3). The water soluble sugar-alcohol, mannitol was used as the filler in combination with sodium starch glycolate (SSG) and calcium silicate (CS) as disintegrants. The two disintegrants were chosen for their complimentary mechanism of disintegration to optimise disintegration process. CS was added for its capillary action (Late et al., 2009) in order to maximise the uptake of the disintegration medium into the tablet and swelling of SSG and hence facilitating disintegration of the tablet. The optimum parameters of tablet diameter and compression force were applied to formulate ODTs containing ibuprofen at increasing content to a paediatric dose of 50 mg. Ibuprofen is a non steroidal anti-inflammatory drug (NSAID) widely used in both adults and children for the treatment of analgesia and pyrexia. Paediatric doses of ibuprofen at 100 mg and below are available commercially as oral liquid preparations (100 mg/5 ml) and more recently as an oral ODT preparation at 100 mg dose. A low dose of ibuprofen at 50 mg formulated as an ODT would represent a convenient alternative dose form.

2. Materials and methods

2.1. Experimental design

The face centred, central composite design contains an imbedded factorial design with centre points. It is used to find the best set of values, for a set of factors, giving an optimal response. In this mathematical approach the design helps in exploring quadratic surface responses where each experimental response (Y) can be represented (Late and Banga, 2010). A polynomial model developed based on the regression analysis of the statistically significant variables enables the study of the effects of each factor (X) and their interaction over the considered responses (Y) and hence can be used to predict responses of hardness (Y1), disintegration time (Y2) and porosity (Y3) values for orodispersible tablets. Comparison of predicted values for Y1, Y2 and Y3 with experimental data was used to test validity of the models. The independent factors, their levels and the analysed dependent responses are shown in Table 2.

The matrix of the face-centred central composite design (CCD) is outlined in Table 3. Each row in the matrix represents an experiment and each experiment presents a set of results, which include the 3 responses or dependant variables studied. The selected levels are within practical use and were chosen to have a measurable effect on the responses. For the purpose of CCD, 13 mm was taken as 12.5 mm, the centre point for the tablet diameters of 10 mm and 15 mm. The statistical experimental design was generated, evaluated for the quality of fit of the model and the constant and

Table 2
Variables in 3^2 central composite design.

	Levels used		
	Low (−1)	Middle (0)	High (1)
Independent variable, factor			
X1 = tablet diameter (mm)	10	13	15
X2 = compression force (kN)	10	15	20
Dependent variable, response			
Y1 = hardness (N)			
Y2 = disintegration time (s) Y3 = porosity (%)			

Table 3
Matrix of 3^2 central composite design.

Exp. no	Tablet diameter (X1)	Compression force (X2)
1	−1	0
2	0	1
3	1	−1
4	1	1
5	−1	−1
6	0	0
7	0	−1
8	1	0
9	−1	1

regression coefficients were calculated using the Design-Expert® software (Version 8.0.1, Stat-Ease Inc., Minneapolis, USA).

2.2. Materials

Mannitol 200 was a gift from Parteck®, Merck KGaA; Norman Lauder, Dublin, calcium silicate (RxCIPIENTS™ FM1000) was a gift from Huber Engineered Materials, Finland, sodium starch glycolate (Explotab®) was a gift from JRS Pharma, Germany. Magnesium stearate was a gift from JMB, UK.

2.3. Formulation of orodispersible tablets (ODTs)

Mannitol 200 and the disintegrants were weighed and blended together for 5 min in a resealable plastic bag. The disintegrants, calcium silicate and sodium starch glycolate, were added at 10% (w/w). Magnesium stearate at 0.5% (w/w) was added to the sugar and disintegrant blend and blended gently for 1–2 min. Tablets were compressed at a compression force ranging 10–20 kN and speed of 7 rpm using an 8 Station rotary tablet press (Riva Piccola, Hampshire, UK) fitted with flat faced bevelled edge (FBE) tools of diameter 10–15 mm as described by Ramtoola et al. (2008). Tablets were compressed to a target weight of 300 or 500 mg ± 10% depending on the tablet diameter. To limit the effect of compression force on varying volumes/heights of powder to be compressed, a lower weight of powder of 300 mg was selected for the 10 mm tablet diameter. Powder weight (w) is directly proportional to volume (v) of the powder to be compressed and volume is defined by $v = \pi r^2 h$ where r is the tablet radius and h is the height of powder to be compressed. The height of powder to be compressed is therefore proportional to v/r^2 or w/r^2. At 500 mg weight, this ratio would range from 20 to 9 for 10–15 mm diameters, respectively, which is a 2-fold difference in height. To keep the height (or w/r^2) in a narrow range, a lower weight of 300 mg for the 10 mm diameter was used to give a height (or w/r^2) in the range of 12–9 for 10–15 mm diameters, respectively.

2.4. Characterisation of tablets

2.4.1. Uniformity of weight (mass) and thickness

Uniformity of tablet weight was carried on $n = 5$ tablets, taken randomly and weighed individually on a Sartorius balance, Model CP225D, Bradford, MA, USA. The average weight of the tablets ± standard deviation was calculated. The thickness of each ODT ($n = 5$) was measured using a pair of calibrated digital Vernier callipers (Digital Caliper Workzone, UK).

2.4.2. Mechanical strength of tablets

Hardness or crushing strength of the tablets was carried out individually on $n = 5$ tablets using a pre-calibrated PTB 411E Tablet hardness tester (PharmaTest Germany). The average hardness ± standard deviation was calculated. The tensile strength ($\sigma_{tensile}$) which takes into account dimensions of the compact, was calculated from the measured hardness/crushing strength ($F_{failure}$), using Eq. (1) (Heinz et al., 2000):

$$\sigma_{tensile} = \frac{2F_{failure}}{\pi A_{cross\text{-}sectioned\ area}} \quad (1)$$

For bevelled edge flat faced tablets,

$$A_{cross\text{-}sectional\ area} = 2 \times (cup\ \ area) + 2\pi rh$$

where r is the radius of tablet and h is the height of tablet edge.

Cup area was provided by Natoli Engineering Company, Inc., MO, USA.

2.4.3. Friability test

Friability test on tablets was performed on $n = 10$ tablets using a pre-calibrated PTFE Friability tester (PharmaTest Germany). If tablets cracked, cleaved, or broke after testing, the sample was recorded as 'Failed' for failed friability test.

2.4.4. Disintegration test

The disintegration tests were performed using deionised water maintained at a temperature between 37 ± 2°C, using a pre-calibrated Pharmatest PTZ Auto, PTFE Disintegration Tester (PharmaTest Germany). Only one ODT at a time was placed into the disintegration apparatus and the time taken (seconds; s) for the tablet to fully disintegrate was recorded. The test was repeated with 4 additional ODTs and the average DT ± standard deviation was calculated.

2.4.5. Porosity of tablets

The porosity of the tablets (ε) was calculated using Eq. (2) (Sugimoto et al., 2005):

$$\varepsilon = \left(1 - \frac{m}{\rho_{true} v}\right) \times 100 \quad (2)$$

where ρ_{true} is the true density of the tableting mixture, m is the weight of the tablet, and v is the volume of the tablet.

The true density of the materials was determined using helium pycnometer (Accupyc 1330, V3.03, Micrometrics, Norcross, USA) and v is given by:

$$v = 2 \times (cup\ \ volume) + \pi r^2 h$$

where r is the radius of tablet, h is the height of tablet edge, and cup volume as provided by Natoli Engineering Company, Inc., MO, USA.

2.5. Statistical analysis

The results obtained are expressed as a mean ± standard deviation calculated using Microsoft Excel (Redmond, WA, USA) software. Statistical analysis was performed using SPSS version 15.0 for windows (SPSS, Inc, Chicago, IL, USA). One-way ANOVA followed by the Tukey multiple comparisons were used to compare the results. A p value of less than 0.05 was considered as statistically significant.

3. Results and discussion

Tablet weight showed very low variability of less than 1% as was expected from the excellent flow of the direct compression grade mannitol used (Table 4). The tablet thickness also showed low variability related to the formulation flow and consistency of compression force. A decrease in tablet thickness was observed with increasing compression force (CF) at each tablet diameter studied, signifying an increase in tablet density. The low variability observed for both parameters support the reproducibility of the formulation

Table 4
Characteristics of orodispersible tablets. Data is expressed as mean ± SD ($n = 3$).

Exp. no	Diameter (X1)	CF (X2)	Weight (mg)	Thickness (mm)	Hardness (N)	Friab[a] (%)	DT (s)
1	−1	0	298.4 ± 3.5	3.06 ± 0.04	80.3 ± 3.3	0.00	91.3 ± 3.5
2	0	1	492.1 ± 2.9	3.15 ± 0.01	73.5 ± 5.3	0.00	70.7 ± 7.0
3	1	−1	551.1 ± 4.8	2.78 ± 0.03	37.5 ± 1.2	0.00	37.3 ± 3.8
4	1	1	541.9 ± 1.8	2.52 ± 0.02	97.0 ± 6.9	0.00	42.0 ± 8.9
5	−1	−1	301.3 ± 2.7	3.33 ± 0.01	45.2 ± 2.5	0.17	49.0 ± 2.7
6	0	0	495.8 ± 3.8	3.31 ± 0.06	54.7 ± 2.6	0.00	61.7 ± 5.0
7	0	−1	490.4 ± 3.3	3.34 ± 0.04	29.8 ± 0.8	0.36	37.7 ± 2.1
8	1	0	546.7 ± 0.5	2.68 ± 0.03	71.4 ± 10	0.00	37.7 ± 3.8
9	−1	1	293.5 ± 0.7	2.88 ± 0.03	100.9 ± 1.7	0.00	117.3 ± 2.1

[a] Friability (% weight loss).

and tableting process used for the study. The responses, hardness, DT and porosity are presented in Table 4.

3.1. Statistical analysis and mathematical modelling of experimental data

The values for the responses hardness (Y1), disintegration time (Y2), and porosity (Y3) of the ODTs were analysed using the Design-Expert® software and the mathematical model for each response was generated. Results of the multiple linear regression analysis for each response variable derived by the best fit method are shown in Eqs. (3)–(5) below.

$$Y1\,(\text{Hardness}) = +457.91286 - 81.12971 \times X1 + 9.78295 \times X2 + 0.077600 \times X1 \times X2 + 3.14423 \times X1^2 - 0.18194 \times X2^2 \quad (3)$$

$$Y2\,(\text{DT}) = -25.11369 - 11.68062 \times X1 + 25.41755 \times X2 - 1.27260 \times X1 \times X2 + 0.85577 \times X1^2 - 0.19926 \times X2^2 \quad (4)$$

$$Y3\,(\text{Porosity}) = +14.87367 + 1.56467 \times X1 - 0.70267 \times X2 \quad (5)$$

Eqs. (3)–(5) reflect the quantitative influence of process variables; X1 (tablet diameter) and X2 (compression force (CF)) and their interactions on the responses; Y1 (hardness), Y2 (disintegration time), and Y3 (porosity).

Analysis of variance (ANOVA) for the responses indicated that the quadratic regression model was significant and valid for each of the responses Y1 ($p = 0.0008$) and Y2 ($p = 0.0003$) and hence was appropriate to represent the observed data for hardness and DT, respectively. For the response Y3, linear regression model was significant ($p < 0.0001$). The statistical analysis for the response surface quadratic/linear model showed that the standard error of estimate was 2.51 for Y1, 2.11 for Y2 and 0.42 for Y3.

From the regression equations (3)–(5), both factors, X1 (tablet diameter) and X2 (CF) influence the hardness (Y1), disintegration time (Y2) and porosity (Y3) of the tablets. The negative regression coefficient of variable X1 in Eqs. (3) and (4) suggests a decrease in hardness and disintegration time (DT) with an increase in tablet diameter, while a positive regression coefficient of variable X1 in Eq. (5) suggests an increase in porosity with an increase in tablet diameter. A positive sign was observed for regression coefficient X2 (CF) in Eqs. (3) and (4), and a negative sign for X2 was observed in Eq. (5), showing that an increase in CF results in an increase in hardness and DT and a decrease in porosity.

In Eqs. (3) and (4), factors at higher order (i.e. $X2^2$) denote quadratic relationships, while coefficient containing both factors (i.e. X1X2), indicates an interaction effect of factors studied on the responses. The positive regression coefficient for the quadratic term $X1^2$ in Eqs. (3) and (4) indicates that the hardness (Y1) and DT (Y2) decreased with increasing tablet diameter to a minimum after which it increased, whereas a negative sign observed for the quadratic term $X2^2$ indicates that as CF increased, both hardness and DT increased to a maximum, after which it decreased. The interaction of tablet diameter (X1) and compression force (X2) had a positive impact on the hardness (Y1) but a negative impact on the disintegration time (Y2) as observed by the respective coefficients in Eqs. (3) and (4), respectively.

Quality of fit of the model for each response was carried out. The R^2 values for the observed responses were 0.97 and 0.98 for Y1 and Y2, respectively. Corresponding linear regression analysis gave an r^2 value of 0.91 for Y3. Corresponding "Predicted R^2 or Q^2" values for responses Y1, Y2 and Y3 were 0.85, 0.92 and 0.83, respectively. Hence the model was found statistically excellent for all three responses of Y1, Y2 and Y3.

The relationship between the dependent variables hardness (Y1), disintegrating time (Y2) and porosity (Y3) and the independent variables tablet diameter (X1) and CF (X2) is demonstrated on the surface response plots in Fig. 1a–c. The plots also show the region of maxima (region in red) and minima (region in blue) for each of the 3 responses investigated.

3.2. Analysis of the fitted data – hardness (Y1) and porosity (Y3)

The response surface plot for the effect of tablet diameter (X1) and CF (X2) and their interaction effects on the hardness of orodispersible tablets (ODT) (Y1) and porosity (Y3) are illustrated in Fig. 1a and c. An increase in the tablet diameter from 10 mm to 15 mm resulted in a significant decrease in the tablet hardness from 45 to 37 N at 10 kN (ANOVA; post hoc, $p < 0.002$). This was related to the 2-fold decrease in the CF per unit surface area, from 0.127 to 0.062 kN/mm^2. A 2-fold increase in the compression force from 10 to 20 kN led to a 2.2-fold increase in tablet hardness to 100 N for 10 mm tablets and about 2.5-fold increase in hardness at the larger diameter of 15 mm. Schiermeier and Schmidt (2002) reported a 5-fold increase in the crushing strength to 71 N for a 2.5-fold increase in CF to 10 kN for 10 mm orodispersible tablets. Fig. 1a also illustrates the quadratic relationship of effect of tablet diameter on tablet hardness. An increase in tablet diameter resulted in a decrease in hardness to a minimum after which hardness increased.

Fig. 1c shows the linear relationship of effect of compression force and tablet diameter on tablet porosity. Compression decreases the intermolecular voids resulting in densification, interparticle bonding to enhanced binding and densification of tablets (Van Veen et al., 2000). Both enhanced binding and densification result in increased tablet hardness and tensile strength. This relationship in our experiments is shown in Fig. 2 which describes the linear relation between the tensile strength and porosity of tablets at all diameters studied, r^2 values of 1.0, 0.94 and 0.94 for 10, 13 and 15 mm tablets, respectively. The ODTs at all the tablet diameters passed the friability test showing a percent weight loss of less than 1%.

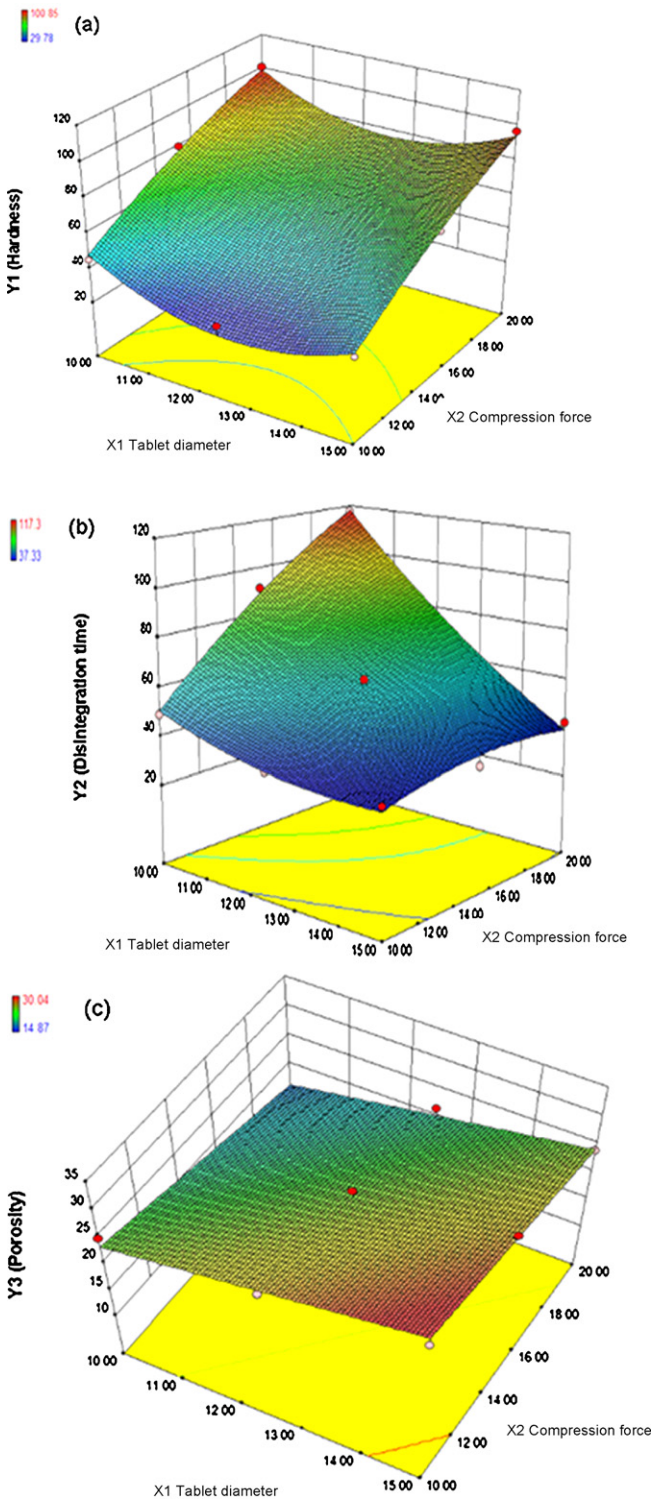

Fig. 1. Response surface plot showing the effect of X1 (tablet diameter) and X2 (compression force) on (a) Y1 (hardness of ODT), (b) Y2 (disintegration time of ODT), and (c) Y3 (porosity of ODT) (the region in red is the maxima while the region in blue is the minima). (For interpretation of the references to colour in text, the reader is referred to the web version of this article.)

3.3. Analysis of the fitted data – disintegration time (Y2) and porosity (Y3)

The response surface plot for effect of tablet diameter and CF on disintegration time (Y2) of ODTs is illustrated in Fig. 1b. The DT (Y2) of the tablets was found to be inversely proportional to the tablet diameter (X1). An increase in tablet diameter from 10 mm to 15 mm resulted in a significant decrease in the DT from 49 to 37 s at CF of 10 kN (ANOVA; post hoc, $p < 0.004$). At the higher CF of 20 kN, increasing tablet diameter showed a larger decrease in DT from 117 to 42 s for a diameter increase from 10 to 15 mm. Increasing the tablet diameter resulted in an increase in tablet porosity (Y3) as a result of the reduction in applied CF per unit surface area. An increase in porosity of tablets generally facilitates the rate of water uptake into the tablet core resulting in faster tablet wetting and disintegration time. The decrease in DT with increasing tablet diameter is demonstrated in Fig. 3 a–c.

At a constant diameter, an increase in CF (X2) by 2-fold to 20 kN caused a significant increase in DT (Y2) from 49 to 117 s for 10 mm tablets (ANOVA, post hoc, $p < 0.0001$). Schiermeier and Schmidt (2002) reported a 1.6-fold increase in the wetting time of 10 mm tablets to 23.7 s when CF was increased from 4 to 10 kN. Interestingly in our study, at 15 mm tablet diameter, a 2-fold increase in the CF did not result in a significant increase in DT (ANOVA, post hoc, $p > 0.05$), despite a decrease in tablet porosity. This occurrence can be related to the larger surface of the 15 mm tablets which facilitates wetting and disintegration when in contact with the disintegration medium.

3.4. Validation of the model

Theoretical (predicted) values of Y1 (hardness), Y2 (disintegration time) and Y3 (porosity) for the 9 experiments were calculated from the response surface models; Eqs. (3)–(5), respectively, by substituting values of X1 (tablet diameter) and X2 (compression force). Good correlation between theoretical (predicted) values and the observed (actual) values was observed for responses Y1 (hardness), Y2 (disintegration time) and Y3 (porosity) (Table 5).

In order to validate the model, the centre points, i.e. 13 mm were compressed at two compression forces not selected for the central composite design, i.e. at 12 kN and 18 kN. At 12 kN, the actual hardness, DT and porosity values were found to be 34.6 ± 5.0 N, 50.3 ± 2.5 s and 26.1%, respectively, which were in close agreement with the values predicted by the model of 37.9 N, 47.3 s and 26%, respectively. Similarly, at 18 kN, the actual hardness, DT and porosity values measured were 68.4 ± 4.7 N, 63.7 ± 3.1 s and 23.2% and were in close agreement with the model predicted values of 69.7 N, 69.2 s and 21.8%, respectively.

The response surface optimisation was carried out to derive the optimum combination of tablet diameter (X1) and compression force (X2) to formulate tablets with hardness (Y1) greater than 40 N and DT (Y2) of below 40 s. The combination of tablet diameter of 15 mm compressed at 15 kN was found to give a desirability value of 1, showing a high hardness of 71.4 N and rapid disintegration time of 37.7 s. Reformulation using these parameters resulted in ODTs of reproducible hardness and DT values of 65.1 ± 7.1 N and 39.3 ± 2.9 s, respectively.

3.5. Application of the optimum process parameters to formulate paediatric ibuprofen ODT

The optimum tableting process parameters of 15 mm and 15 kN were used to formulate ODTs containing increasing dose of ibuprofen from 10 to 50 mg. A decrease in tablet hardness was observed with increasing ibuprofen content (Fig. 4) although this decrease in hardness was not statistically significant at the low ibuprofen content of 10 mg. No significant change in the DT was observed regardless of the ibuprofen concentration (ANOVA; $p > 0.05$) (Fig. 4). The characteristics of small diameter tablets have been reported to be influenced by the addition of actives. Hydrophobic actives generally tend to increase the tablet disintegration time. Yang et al. (2004) reported a large increase in DT by 8.8-fold to 219.5 s

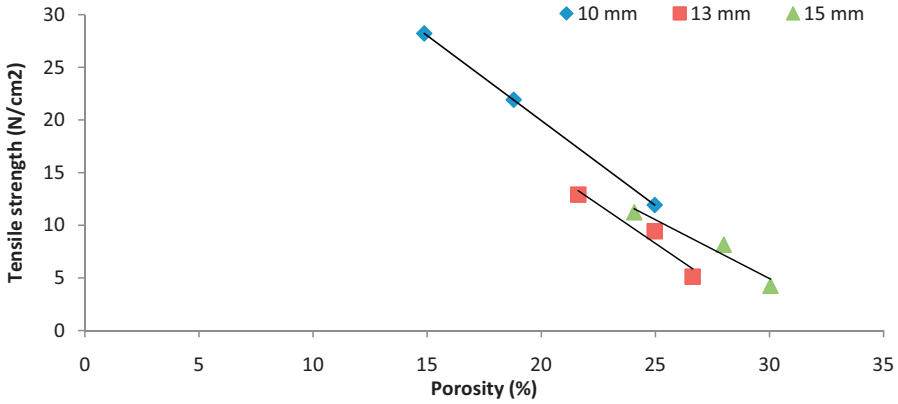

Fig. 2. Correlation of tablet tensile strength (N/cm^2) and tablet porosity (%) of ODTs of increasing tablet diameters.

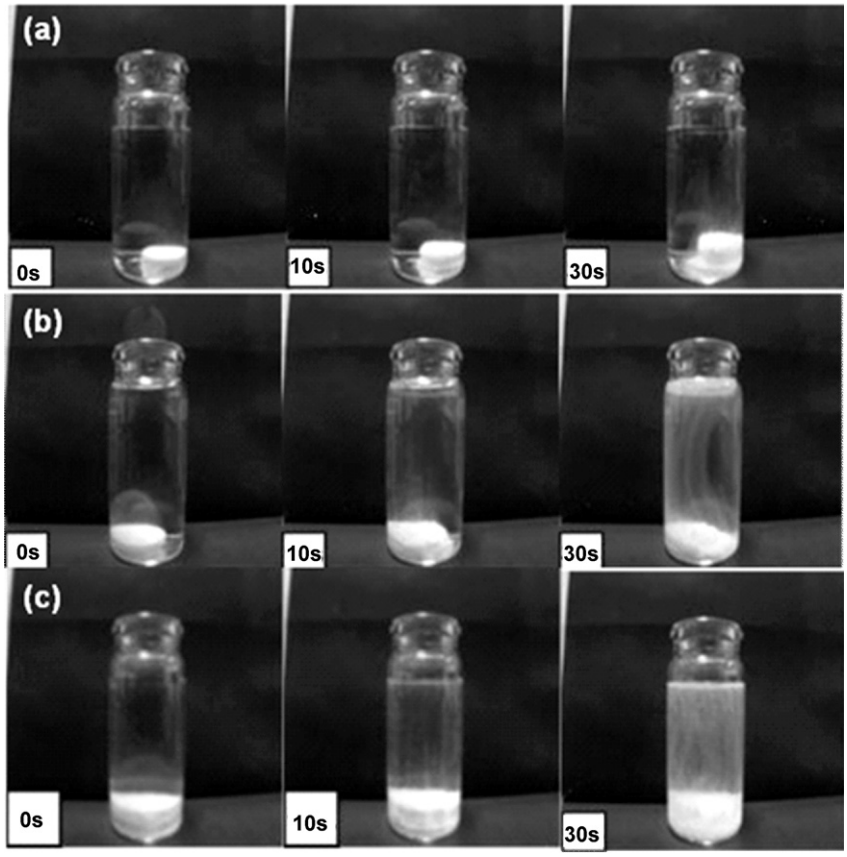

Fig. 3. Disintegration profile of ODT of increasing tablet diameters. (a) 10 mm, (b) 13 mm and (c) 15 mm.

Table 5
Theroetical (predicted) values and the observed (actual) values observed for responses Y1 (hardness) and Y2 (disintegration time).

Exp.	Y1 (Hardness (N))			Y2 (DT (s))			Y3 (Porosity (%))		
	Predict.	Act.	Resid.	Predict.	Act.	Resid.	Predict.	Act.	Resid.
1	78.5	80.3	1.8	89.2	91.3	2.1	20.0	18.8	−1.2
2	77.4	73.5	−3.8	73.1	70.7	−2.4	20.4	21.6	1.2
3	39.7	37.5	−2.2	35.6	37.3	1.7	31.3	30.0	−1.3
4	94.6	97.0	2.4	39.1	42.0	2.9	24.3	24.1	−0.2
5	48.4	45.2	−3.2	50.7	49.0	−1.7	23.5	25.0	1.5
6	55.4	54.7	−0.8	60.4	61.7	1.3	23.9	25.0	1.1
7	24.4	29.8	5.4	37.8	37.7	−0.10	27.4	26.6	−0.8
8	71.7	71.4	−0.3	42.3	37.7	−4.7	27.8	28.0	0.2
9	99.4	100.9	1.4	117.8	117.3	−0.5	16.5	14.9	−1.6

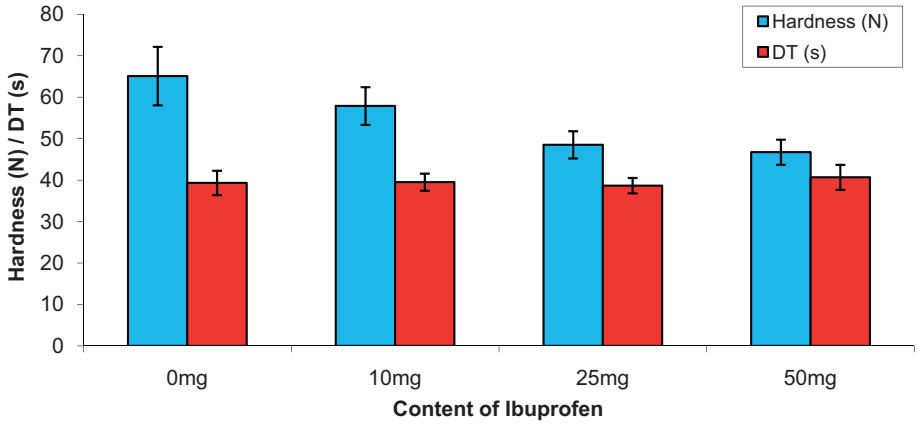

Fig. 4. Influence of increasing ibuprofen content on the hardness and disintegration time of ODTs formulated using the optimised tablet diameter of 15 mm and compression force of 15 kN.

when the tablet content of ketoprofen was increased from 0 to 100 mg although no significant increase in the tensile strength was observed. In contrast Rawas-Qalaji et al. (2006) reported that increasing the epinephrine bitartrate content of tablets of diameter of 8.73 mm from 0 to 36 mg caused a 6-fold decrease in hardness to 2 kg and a 7-fold decrease in DT to 5.6 s was observed. Epinephrine bitartrate is hydrophilic while ketoprofen is hydrophobic and the change in the tablet properties reported was related to the physicochemical properties of the active. In our study, ibuprofen is hydrophobic with a higher log *P* value compared with ketoprofen and therefore the decrease in hardness may be a result of decrease in bonding due the higher hydrophobic nature of ibuprofen.

4. Conclusions

In this study compression force and tablet diameter were observed to have a profound and interactive effect on the characteristics of orodispersible tablets as shown by the models obtained using a central composite design and response surface methodology. The data observed showed this experimental design was successfully applied to optimise the combination of tablet diameter and compression force to formulate ODTs with desirable properties of high mechanical strength and low DT. The optimised combination in this study was a tablet diameter of 15 mm compressed at 15 kN. Using this combination of process variables, ODTs formulated were resistant to a change in the DT despite an increase in hardness. The optimised process parameters were successfully applied to formulate rapid disintegrating and mechanically strong ODTs at increasing dose of the analgesic non-steroidal anti-inflammatory agent ibuprofen. These process combinations may have wider application to other actives to achieve ODTs with desirable qualities of rapid disintegration and high mechanical strength.

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