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Influence of the roll compactor parameter settings and the compression pressure on the buccal bio-adhesive tablet properties

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Abstract

Miconazole buccal tablets were prepared via a dry granulation process. By applying a factorial design (2^4), the roll compactor parameters (compaction force, gap between the rolls, type of the rolls (smooth, ribbed) and the sieve aperture) were optimised for the tablet strength. The compaction force and the roll type significantly affected the tablet strength. Afterwards, a quarter fractional factorial design (2^{5-2}) was applied, consisting of the four compactor parameters and additionally the compression pressure, in order to optimise these parameters for the dissolution profile and the buccal bio-adhesion characteristics (bio-adhesive force and energy). In order to evaluate the dissolution profiles properly, the similarity factor between sample and a zero-order release reference profile was used. The compression pressure and the roll type significantly affected the dissolution profile. The sieve aperture had a significant effect on the buccal adhesion properties and the compaction force had a significant effect on the dissolution profile and the bio-adhesive energy. The gap between the rolls affected the bio-adhesive force significantly.

Keywords: Miconazole; Buccal tablet; Dry granulation process; Roll compactor; Experimental design; Factorial design; Similarity factor

1. Introduction

Miconazole nitrate is used in the mouth for topical fungal infections. Buccal application of miconazole is possible as a tablet or a gel (Bouckaert et al., 1992; Bouckaert and Remon, 1992; Bouckaert et al., 1993a,b) or as a chewing gum (Pederson and Rassing, 1990). The tablet adhesion to the mucus in the mouth is explained by several adhesive mechanisms between the tablet polymer and the biological surfaces (Mikos and Peppas, 1990). Duchêne and Ponchel (1989) showed that the bio-adhesive force and the energy are relevant parameters in evaluating the bio-adhesive tablets. Bouckaert et al. (1993b) investi-

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gated the in vitro/in vivo bio-adhesive properties of buccal bio-adhesive miconazole slow-release tablet. They could not conclude which bio-adhesive characteristics have to be considered when evaluating buccal bio-adhesion. Therefore, these bio-adhesive characteristics were used in order to optimise the dry granulation process for the production of buccal tablets.

Bouckaert et al. (1992), Bouckaert and Remon (1992), Bouckaert et al. (1993a,b) prepared the buccal bio-adhesive tablet via direct compression. In the present study, a miconazole buccal tablet was prepared via dry granulation process. Depending on the drug load, dry granulation usually gives better powder flow characteristics and improved compressibility than the direct compression method. In the dry granulation process, the powder mixture is compacted by a roll compactor or a rotary press. Afterwards, the compacted powder or slugging are milled and sieved in order to obtain granules. The granules are further processed into tablets. Several investigators studied the effect of the compaction process parameters on the granule properties (Falzone et al., 1992; Hervieu and Dehont, 1994; Inghelbrecht et al., 1997; Inghelbrecht and Remon, 1998). They have shown that the compactor parameters do affect the granule properties. Sheskey and Cabelka (1992), Sheskey et al. (1994) investigated the effect of the compaction force on the tablet strength of a sustained-release tablet and found that the compaction force had a significant effect on the tablet hardness. However, little is known about the effect of the compaction parameters on the buccal tablet characteristics (tablet strength, dissolution and bio-adhesive characteristics).

The goal of this study was to optimise the roller compactor settings for the buccal tablet characteristics. In order to understand the effect of the compactor parameters on the buccal tablet characteristics better, first the effect of four compactor parameters, namely the compaction force, the gap between the rollers, the roll type (smooth, ribbed) and the sieve aperture was investigated on the granule size. Afterwards, these four compactor process parameters were optimised for the tablet properties (tablet weight variation and the tablet strength) by application of a full factorial design. Furthermore, the settings of the four compactor parameters and additionally of the compression pressure from the tabletting machine were optimised for the dissolution profile and the bio-adhesive characteristics (bio-adhesive force and energy) of the tablets by application of a fractional factorial design.

2. Materials and methods

2.1. The roller compactor

The roller compactor we used in this study was a 3-W-Polygran Compactor Type 250/100/3 (Gerteis Maschinen + Processengineering AG, Jona, Swiss). The feeder transported the powder via a horizontal rotating screw and two vertical rotating screws, to the compacting zone. The ratio between the horizontal screw speed and the vertical screw speed was set at 2. The rotational speed of the rolls was kept at 3 rpm. Both rolls were connected to hydraulic jacks. With these hydraulic jacks, it was possible to control the compaction force on the powder. The compactor automatically adjusted the feeding, when the gap or the compacting force exceeded the defined range. The variation of the compaction force was 2–3% and the gap was ± 0.06 mm. This made it possible to control the compacting force and the gap accurately. The rotating rolls produced slugging plates with thickness depending on the gap setting. The milling roll milled the slugging plates to 1–5 mm particles. The same milling roll sieved these particles through a sieve with given aperture. The milling roll surface consisted of transverse furrows, which eased the milling and sieving.

2.2. Design development and analysis

Since minimal settings for the roll speed and the feeding screws speed were optimal for the powder feeding rate (± 200 kg/h), they were not optimised. The four compactor parameters that were to be optimised for the tablet properties were: the compaction force, the gap between the rolls, the roll surface and the sieve aperture. The com-

paction force ranged from 0 to 24 kN and the gap ranged from 0 to 6 mm. The roll surface was either smooth or ribbed. The sieve aperture was either 0.8 or 1.0 mm.

Earlier experiments and experiences showed that the limit settings for the compaction force was between 4 and 8 kN and the gap between 2 and 3 mm were appropriate. The settings of these parameters are given in Table 1.

A full (2^4) factorial design was applied on the four compactor parameters in order to optimise the tablet properties (tablet weight variation and tablet strength). Also, the granule size of the runs were measured and the effect of the four compactor parameters were investigated in order to explain the obtained tablet properties.

The dissolution profile and the bio-adhesive characteristics were also optimised for the four compactor parameters and additionally the compression pressure of the tabletting machine. The compression pressure was included, because it is known that this parameter has a significant effect on the dissolution profile (Van Aerde and Remon, 1988).

Due to limited resources, only reduced number of experiments could be performed for the optimisation of the dissolution profile and the bio-adhesive characteristics. Therefore, a quarter fractional factorial (2^{5-2}) design was applied on the five parameters.

The runs were randomised, in order to minimise the effect of extraneous parameters. The full factorial design enabled us to determine the main effects and all the interaction effects. The quarter fractional factorial design was a resolution III fractional factorial design, where the main effects were confounded with second order effects (Montgomery, 1991). Also, some second order effects were confounded with each other, so from the eight runs performed, five main effects and two second order effects were calculated (see Section 3). In fact, when a main effect is significant, we cannot say whether this significant effect is as a consequence of the main effect or of the second order effect. Arujo and Brereton (1996) described a method to separate second order interaction effects confounded with each other. Interaction effect diagrams were drawn of the confounded second order interaction effects. The interaction diagrams provided preliminary suggestions which interaction effect distributed most to the significant effect. The residual error in the analysis of variance (ANOVA) was calculated stepwise by including the effects with the largest P-value in the residual, until the remaining effects were significant (P-value < 0.05). The designs were developed and analysed by the graphic software 'STATGRAPHICS PLUS' version 2.1 (STSC Inc., Rockville, MD, USA). It enabled the ANOVA and the calculation of the parameter effects.

Table 1
The investigated roll compactor parameters and their settings

Parameter	Settings	
	−1	+1
Compaction force (kN)	4	8
Roll type	Smooth	Ribbed
Sieve aperture (mm)	2	3
Gap (mm)	0.8	1

2.3. The dry granulation process

Three 30 kg batches containing 1.0% (w/w) miconazole nitrate (Janssen Chimica, Geel, Belgium), 93.9% (w/w) drum-dried waxy starch (Cerestar, Vilvoorde, Belgium) and 5.1% (w/w) carbopol 974P (BF Goodrich Co, Cleveland, OH) were prepared by mixing in a Collette MP 90 blender (Collette Machines, Wommelgem, Belgium) for 5 min at speed 1. The powder mixture was compacted on the roller compactor using different setting combinations of the four compactor parameters proposed in the factorial design (Table 2). The sieved granules were collected and sampled for the determination of the granule properties.

Afterwards, the sieved granules (97.8% (w/w) were mixed with sodium stearyl fumarate 2.0% (w/w) and colloidal anhydrous silica, 0.2% (w/w) (Wacker Chemie, München, Germany) in a Collette MP 20 (Collette Machines, Wommelgem, Belgium) blender for 5 min at speed 1. Each run consisted of a 5-kg batch.

Table 2
Full factorial (2^4) design of the roll compactor parameters on the granules and the tablet properties

Run	Roll compactor parameters				Response		
	Compaction force (kN)	Roll type	Sieve aperture	Gap (mm)	Granule size (μm)	Tablet properties	
						R.S.D. weight	Strength
1	4	Smooth	0.8	2	162.00	1.01	32.7
2	4	Smooth	1	2	170.00	1.11	34.9
3	4	Smooth	0.8	3	165.00	1.08	36.7
4	4	Smooth	1	3	169.00	0.97	35.1
5	8	Smooth	0.8	2	189.00	0.88	24.5
6	8	Smooth	1	2	201.00	1.16	27.5
7	8	Smooth	0.8	3	181.00	1	26.0
8	8	Smooth	1	3	192.00	1.16	26.9
9	4	Ribbed	0.8	2	154.00	1.11	32.7
10	4	Ribbed	1	2	167.00	0.9	30.6
11	4	Ribbed	0.8	3	160.00	1.51	32.69
12	4	Ribbed	1	3	158.00	1.56	31.9
13	8	Ribbed	0.8	2	180.00	0.87	24.8
14	8	Ribbed	1	2	176.00	1.18	23.4
15	8	Ribbed	0.8	3	165.00	1.27	28.2
16	8	Ribbed	1	3	177.00	0.76	24.8

2.4. Sieve analysis

The sieve analysis was carried out in order to determine the geometric mean granule size. A set of sieves (75, 150, 250, 500, 850 and 1000 μm) in combination with the Retsch VE 1000 sieve shaker (Retsch, Haan, Germany) were used for this analysis. A 100-g of granule sample was transferred to the pre-weighed sieves and allowed to shake at amplitude of 1.5 mm for 5 min. The sieves were then re-weighed to determine the weight fraction of granules retained on each sieve.

These weights were converted in mass percentage. The geometric mean granule size was calculated from these mass fractions according to the equation given by Fonner et al. (1981a).

2.5. Compression

The granules were compressed on a Korsch type PH 100/6 tabletting machine (Korsch, Frankfurt, Germany). Tablets of 100 mg with diameter of 6.5 mm were compressed on flat punches. The compression pressure in the full factorial design (2^4) was kept constant at 160 MPa. The compression pressure in the quarter fractional design (2^{5-2}) was set at low and high level (Table 1). The other compression settings were held constant during the experiments. The tabletting speed was 10 800 tablets per h.

Tablet strength ($n = 10$) and tablet weight ($n = 100$) were measured on a Pharma Test equipment (Pharma Test WHT-1, Pharmatest Apparatebau GmbH, Hamburg, Germany) and the relative standard deviation (R.S.D.) of the tablet weight was calculated.

2.6. Dissolution

The tablet dissolution was determined according to the paddle method in 550 ml 0.1 N HCl, 37°C, containing three tablets in each vessel in Hanson dissolution equipment (SR8, Hanson Research Co., Chatsworth, Ca, USA). The rotational speed of the paddle was set at 50 rpm. All dissolution media in the dissolution vessel were connected to an UV-spectrophotometer (Hewlett-Packard 8450a, Palo Alto, CA, USA) with tubes.

A peristaltic pump transported the media through tubes to the UV-spectrophotometer. The media was filtered (Millipore Millex-LCR hydrophilic PTFE 0.5 μm, Millipore Co., Bedford, MA, USA) before the measurement took place. The media was transported back to the dissolution vessel after the measurement. The absorbance was measured at 220 nm and the dissolved miconazole in the media was determined. The dissolved miconazole (% (w/w) of the active compound in the tablet) in the media was determined after 60, 120, 240, 480, 840, 1080 and 1440 min.

2.7. In-vitro determination of bio-adhesion

The tablet bio-adhesion characteristics were determined according to the method earlier described by Bouckaert and Remon (1992). The maximum detachment force and the work of adhesion necessary to break the bond between tablet and mucosa were calculated. The mean bio-adhesion characteristics were determined from five tablets.

3. Results and discussion

3.1. Granule size

Table 2 shows the applied factorial design (2^4) and the obtained results for the geometric mean granule size, the R.S.D. of the tablet weight and strength.

Fig. 1 shows d50-values for all the combinations of the investigated parameters. The d50-values were smaller at low compaction force than at high compaction force. At 1.0 mm sieve aperture size higher d50-values were obtained than at 0.8 mm sieve aperture size. Smaller d50-values were observed at large gap compared with the small gap, but not as obvious as for the other parameters.

Table 3 shows the compaction force has the largest effect on the granule size.

The ANOVA of the compactor parameter effect on the granule size is summarised in Table 3. Effects with P-value less than 0.05 are considered significant in the ANOVA table. Significant effects on the d50-value were obtained by the compaction force (P-value = 0.000), the roll type (P-value = 0.001) and the sieve aperture (P-value = 0.032). During compaction the powder particle bond formation is characterised by several stages in the following order — particle rearrangement, particle deformation, particle fragmentation and particle bonding (Miller, 1997; Van der Voort Maarschalk and Bolhuis, 1998). In this study drum dried waxy starch was used, which has plastic deformation properties (Inghelbrecht et al., 1997). When high compaction force is used, the starch particles will be deformed at a higher degree than at low compaction force. Inghelbrecht et al. (1997) found reduced friability of drum dried starch granules at high compaction force, indicating the formation of robust granules. The granules compacted at high compaction force will be stronger which, when subsequently milled, produces coarser granules (Sheskey et al., 1994).

The slugging with ribbed roll has a grid-like surface, whereas the smooth roll produced a smooth slugging surface. The milling of the grid-like surface slugging was more extensive than the smooth surface slugging, resulting in smaller granules.

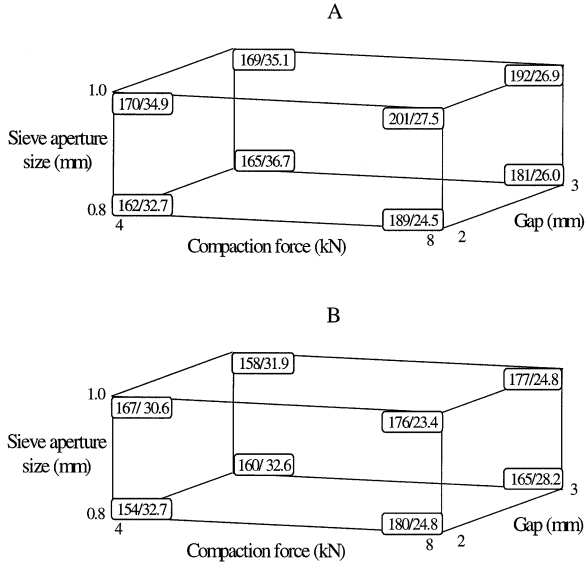

Fig. 1. Cube plots of the granule size (μm)/tablet strength (N) at smooth (A) and ribbed (B) rolls for the full factorial design.

Table 3
Scaled significant effects of the roll compactor parameters on the granule size and the tablet strength in the full factorial (2^4) design

Source	Estimated effects		Significance[a]	
	Granule size	Tablet strength	Granule size	Tablet strength
Average	172.88	29.58	0.000	0.000
A:compaction force	19.50	7.64	0.000	0.000
B:roll type	−11.50	−1.91	0.001	0.008
C:sieve aperture	6.75	−0.39	0.032	
D:gap	−4.00	1.39		0.04
AB	−4.75	0.99		
AC	1.00	0.16		
AD	−3.75	0.04		
BC	−2.00	−1.51		0.028
BD	−0.25	0.11		
CD	−0.50	−0.81		
R-squared (%)			85.7	94.4

[a] Significance at $\alpha = 0.05$, obtained from analysis of variance by stepwise regression.

The effect of the sieve aperture on the granule size is obvious. The larger the sieve aperture will be, the more coarse particles will be produced.

3.2. R.S.D. of the tablet weight and tablet strength

Table 2 shows the R.S.D. of the tablet weight in the applied factorial design. The R.S.D. was $< 1.57\%$ for all runs, which was acceptable. None of the parameters seemed to have an effect on the R.S.D. ANOVA results confirmed these findings. The R.S.D. is mainly affected by the granule quality (granule size, angle of repose etc.) (Fonner et al., 1981b). The geometric mean granule size in the design ranged between 158 and 201 μm. The angle of repose in the design ranged between 40.7 and 51.5° (not shown). Although the roller compactor produced granules with different granule quality, the tablet weight RSD was not affected by the granule quality.

From Fig. 1, we clearly see that the compaction force of the roller compactor has the largest effect on the tablet strength. The tablet strength was significantly higher at low compaction force than at high compaction force. The roll type also shows an effect on the tablet strength, but not as large as the compaction force. The ribbed roll results in slightly lower tablet strength than the smooth roll. The gap also shows a small effect on the tablet strength. The larger gap results in a small increase of the tablet strength. The sieve aperture does not show any significant effect on the tablet strength. The observed results are confirmed in Table 3, the ANOVA table. From the ANOVA table, we conclude that the compaction force (P-value = 0.000), the roll type (P-value = 0.008) and the gap between the rolls (P-value = 0.040) have a significant effect (P-value < 0.05).

The effect of the compaction force on the tablet strength is confirmed by Sheskey and Cabelka (1992) and Malkowska and Khan (1983). The robust granules produced at high compaction force exhibit increasing resistance to fragmentation at tablet compressing compared with the granules produced at low compaction force. This phenomenon is known as the working hardening principle (Malkowska and Khan, 1983; Kochhar et al., 1995). Brittle granules are necessary to form new surfaces for bonding and influence, therefore, the tablet strength (Nyström and Karehill, 1996; Hiestand, 1997). This may explain the increased tablet strength at low compaction force of the compactor.

As seen in the earlier section, the smooth roll produce larger granules than the ribbed roll. Due to the rough slugging surface obtained from the ribbed roll, smaller granules were obtained from

the milling process. However, the ribbed roll did not produce stronger tablets than the smooth roll, as would be expected from the granule size. The function of the ribbed rolls is to drag the material to be compacted with greater friction force into the roll nip zone compared with the smooth rolls, resulting in increased particle arrangement and deformation before compaction compared with the smooth rolls. This may change the contact pressure distribution within the roll at constant compaction force. The smooth roll tends to have a contact pressure distribution in a narrow region whereas the ribbed roll may have a more uniform pressure distribution within a wider region, at constant compaction force. Therefore, the maximum contact pressure is larger with smooth rolls than with ribbed rolls (Johanson, 1965). The more uniform pressure distribution should increase the compressibility (Johanson, 1984) and, therefore, result in robust granules. The robust granules obtained with the ribbed roll produce weaker tablets, which explains the effect of the roll surface on the tablet strength. By changing the gap, the powder drawn-in conditions were changed, because the speed and the torque of the tampering auger were changed, which may cause alteration in the density profile of the slugging. The slugging will consist of a sinus-shaped profile of hard compacted slugging and other parts with soft compacted slugging. By increasing the gap, this phenomena is more pronounced, resulting in partially less robust granules and, therefore, in stronger tablets.

From the above results, we can conclude that although some compactor parameters affected the granule size, none of the compactor parameters affected the R.S.D. of the tablet weight. This means we do not have to optimise the roller compactor for the R.S.D. of the tablet weight. As seen in Section 3 above, high compaction force, ribbed roll and small gap resulted in weaker tablets. As the tablet strength is important for the packaging process and the granule quality did not affect the tablet weight during the tabletting process, low compaction force, smooth roll and large gap was preferred for high tablet strength.

3.3. Dissolution profiles

Table 4 shows the fractional factorial design (2^{5-2}) applied on the four roller compactor parameters and the compression pressure of the tabletting machine. The response parameters in this design were the dissolution profile, the bioadhesive force and energy.

The release of miconazole during 24 h for each run is shown in Fig. 2. The figure shows the dissolution profiles are not equal for all runs. If the release at certain time was taken as a response, then the effect of the parameters on the release would depend on the release time considered. In this case, the comparison of the complete dissolution profiles between the runs is a better response for the dissolution. We decided to do this by comparison with a reference dissolution profile. A linear dissolution profile representing a zero-order release profile was chosen as a reference dissolution profile for each run, since for controlled drug formulations, a constant release per time unit is recommended (Lordi, 1986; Robinson and Eriksen, 1966). The exact nature of this reference release profile is not important. We chose the simplest one. The (linear) dissolution profile of drugs is affected by process and formulation parameters (McGinity et al., 1981). In this study, the effect of the four roller compactor parameters and the compression pressure on the dissolution profile was investigated. Fig. 3 shows the dissolution profiles of runs 5 and 6 and their optimal linear dissolution profile (straight line between release at 0 and 24 h). The degree of linearity of the dissolution profiles is determined as the deviation from the linear dissolution profile, defined by the similarity factor, f_2. The similarity factor, f_2, was calculated (according to the method described by Moore and Flanner (1996)) for all dissolution profiles compared with their optimal linear dissolution profile as the reference dissolution profile. The f_2 varies between 0 and 100. A f_2 of 0 means that the dissolution profiles are dissimilar to each other and a f_2 of 100 means they are similar. Moore and Flanner (1996) have shown that for an average difference of 10% between sample and reference, a f_2 of 50 is obtained. Therefore, one can say that a dissolu-

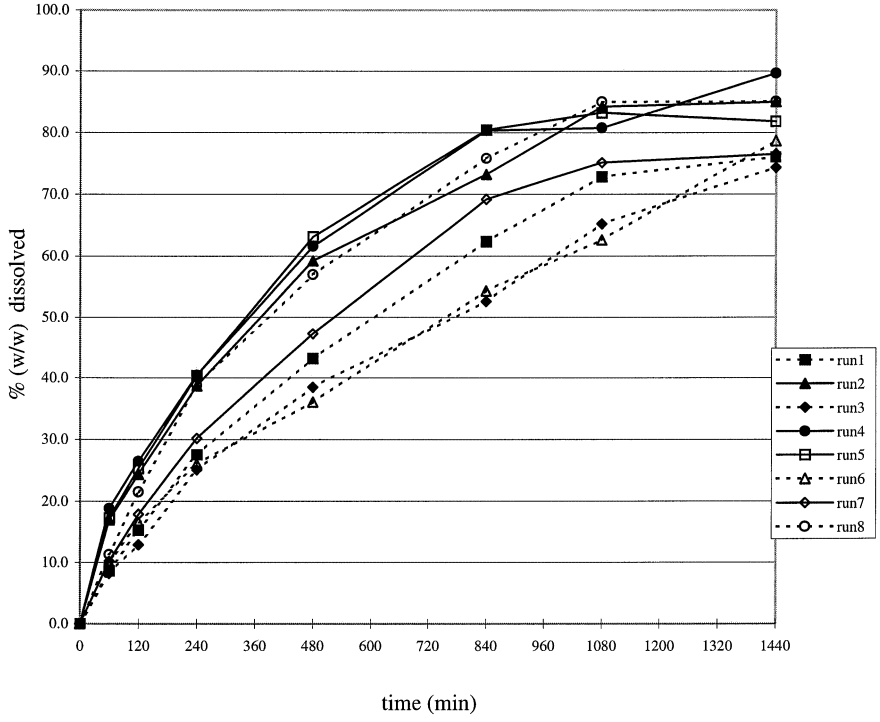

Fig. 2. Dissolution profile of the runs in the fractional factorial (2^{5-2}) design.

tion profile with f_2 of ≥ 50 is 'similar' to the reference and tends to have a zero order release profile.

Table 4 lists the f_2-values for the runs, compared with the reference run with their zero order release profile.

Run 3 and 6 were the only runs with f_2-values larger than 50, indicating a zero-release profile. High f_2-values were obtained at high compression pressure (compare runs 1, 3, 6, 8 and runs 2, 4, 5, 7). The largest f_2-values (runs 3 and 6) were found at high compression pressure and ribbed roll, indicating an interaction between these parameters.

An ANOVA was applied in order to detect significant effects of the parameters on f_2-value. In the applied design, the second order effects between the roll type and the sieve (BC) and between the gap and the compression pressure (DE) were confounded with each other. Also, the second order effects between the roll type and the compression pressure (BE) and between the sieve and the gap (CD) were confounded with each other. The main effects were confounded with some other second order interaction effects (see

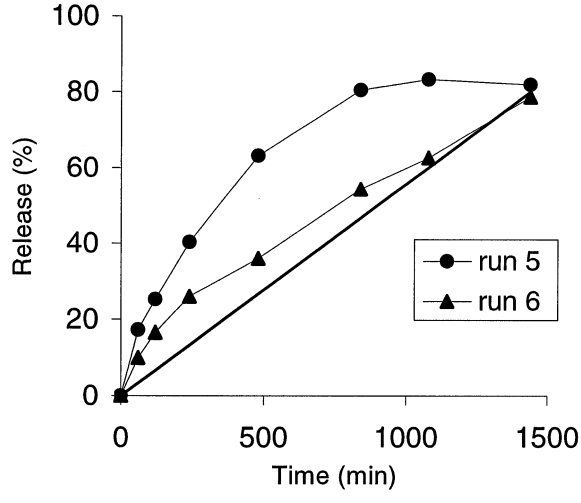

Fig. 3. Comparison of non-linear dissolution profiles of run 5 and 6 with linear dissolution profile (straight line).

Table 4
Fractional factorial (2^{5-2}) design of the roll compactor parameters and the compression pressure on the bioadhesive tablet properties

Run	Roll compactor parameters			Tabletting parameter		Response		
	Compaction force (kN)	Roll type	Sieve aperture (mm)	Gap (mm)	Compression pressure (MPa)	Bioadhesive force (N)	Bioadhesive energy (mJ)	Similarity factor, f_2
1	4	Smooth	0.8	2	160	2.76	0.44	43.9
2	4	Smooth	1	2	120	2.17	0.36	34.1
3	4	Ribbed	0.8	3	160	2.77	0.45	51.7
4	4	Ribbed	1	3	120	2.33	0.36	33.4
5	8	Ribbed	0.8	2	120	2.42	0.40	30.8
6	8	Ribbed	1	2	160	2.22	0.40	53.7
7	8	Smooth	0.8	3	120	2.79	0.41	39.3
8	8	Smooth	1	3	160	2.39	0.39	34.8

Table 5
Effects of the roll compactor parameters and of the compression pressure and their significance on the similarity factor (f_2) and the bioadhesive tablet properties in the fractional factorial (2^{5-2}) design

Source	Estimated effects			Sigificance[a]		
	f_2	Bioadhesive force	Bioadhesive energy	f_2	Bioadhesive force	Bioadhesive energy
Average	56.8	2.481	0.401			
A:compaction force, BD+CE	−1.1	−0.053	−0.003			
B:roll type, AD	4.4	−0.093	0.003			
C:sieve aperture+AE	−2.4	−0.408	−0.048		0.004	0.000
D:gap, AB	−0.8	0.178	0.003		0.073	
E:compression pressure+AC	11.6	0.108	0.038	0.014		0.000
BC–DE	4.7	0.088	0.003			
BE–CD	9.0	0.013	0.008	0.036		0.040
R-squared				81.4	86.6	99.3

[a] Significance at $\alpha = 0.05$, obtained from analysis of variance.

Table 5). The ANOVA results are summarised in Table 5. From this table, it is concluded that the compression pressure ($P < 0.05$) and the confounded second order effects (BE–CD) ($P < 0.05$) affected the dissolution profile significantly. Using the interaction diagrams, the interaction effect BE contributed mostly to the significance of the confounded interaction effects, indicating an interaction effect between the ribbed roll and the compression pressure (Fig. 4). From the similarity results, we can conclude that the compression pressure and the ribbed roll tend to make the dissolution profile more linear.

Probably, the compression pressure changes the tablet matrix during tablet compression and, therefore, also the release mechanism. Indeed, in Fig. 2 we can see that run 5 tends to have a Higuchi like release profile (Senel et al., 1991) and run 6 tends to have a more zero order release profile. The effect of the roll type on the dissolution profile was mainly determined by the interaction with the compression pressure.

3.4. Bio-adhesive energy and bio-adhesion force

In this study, the bio-adhesion characteristics are used to optimise the adhesive potential of the buccal tablets in the mouth.

From the results of the fractional factorial design in Table 4, it can be observed that high bio-adhesion forces were obtained (runs 1, 3, 5, 7) at small sieve aperture compared with large sieve aperture (runs 2, 4, 6, 8). This result was confirmed in Table 5, where the sieve aperture had the largest effect (-0.41 ± 0.062) on the bio-adhesion force with a P-value < 0.05. The gap can be considered important with a P-value $= 0.073$. The other parameter did not have a significant effect on the bio-adhesion force.

Table 4 also showed larger bio-adhesive energy was obtained at small sieve aperture (runs 1, 3, 5, 7) than at large sieve aperture. The compression pressure at 160 MPa (runs 1, 3, 6, 8) resulted also in larger bio-adhesion energy than the compres-

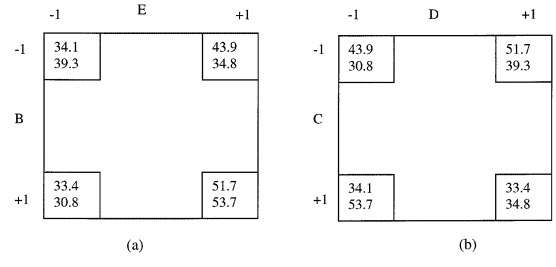

Fig. 4. Interaction diagrams of (a) the interaction between the roll type (B) and the compression pressure (E) and of (b) the interaction between the sieve aperture (C) and the gap (D).

sion pressure at 120 MPa. These two parameters showed a significant effect on the bio-adhesion energy (P-value < 0.05) in Table 5. Also, the second order interaction effects (BE–CD) were significant on the bio-adhesive energy. The interaction diagrams did not reveal which interaction effect contributed to the most part of the significant effect.

The development of a strong adhesive bond requires wetting of the polymer (Mikos and Peppas, 1990) and the wetting of the tablet is stimulated by the capillary effect of the tablet surface. Therefore, the tablet surface area plays an important role in the bio-adhesive process. The small sieve aperture produced smaller granules with higher granule surface area compared with the large sieve aperture and this external granule surface tends to increase the tablet surface (Alderborn and Wikberg, 1996; Armstrong, 1996). The increased tablet surface increases the capillary force and subsequently, also the bio-adhesive force.

The higher compression force increases the tablet pore radius (Kawashima et al., 1993; Alderborn and Wikberg, 1996) and, therefore, also the wettability of the tablet. The increased wettability promotes the binding between the polymer and the mucus and, therefore, increases the bio-adhesive energy. These phenomena may explain the effect of the sieve aperture and the compression pressure on the bio-adhesion characteristics.

4. Conclusions

In this study, the compaction process was optimised for the buccal tablet characteristics by application of factorial designs. From the tablet strength results, low compaction force, smooth rolls and large gap was preferred. From the dissolution profile and the bio-adhesive characteristic results, high compression pressure, ribbed rolls and small sieve aperture was preferred. Smooth roll was optimal for tablet strength, but ribbed roll was optimal for the dissolution profile. As the dissolution profile was considered more important than tablet strength, ribbed rolls was chosen as optimal for the buccal tablet characteristics. In order to produce buccal tablets with desired quality, these roll compactor parameter settings should be considered. This study showed that the compaction process parameters are important for optimal buccal tablet characteristics.

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