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EFFECT OF DISINTEGRANTS ON THE PROPERTIES OF MULTIPARTICULATE TABLETS COMPRISING STARCH PELLETS AND EXCIPIENT GRANULES

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ABSTRACT

A design of experiments (DOE) approach (2-level full factorial design) was used to investigate the effect of several formulation and process variables on the properties of fast disintegrating tablets comprising starch-based pellets and excipient granules and to optimize and validate the design space. The percentage of starch pellets (30-50% w/w), type of disintegrants (Ac-di-sol, Explotab, Polyplasdone), percentage of external disintegrant (4-8% w/w) and compression force (5-15 kN) were the evaluated factors (24 runs + 9 centre points = 33 experiments), while tablet hardness, friability and disintegration time were the studied tablet properties (responses).

Starch pellets were prepared by extrusion-spheronisation. Excipient granules containing microcrystalline cellulose, lactose, internal disintegrant (8%) and polyvinylpyrrolidone K-30 (4%) were prepared by wet granulation. Pellets, granules (700-1000 μm) and external disintegrant were mixed and compressed into oblong tablets (17.1 mm long, 8.2 mm wide).

Evaluation of the effects calculated from the DOE results showed that a lower concentration of starch pellets and higher compression force were required to yield tablets with a high hardness, a low friability (<1%) and short disintegration time (<3 min). Polyplasdone granules had the lowest porosity and friability which was reflected in the DOE study, where the Polyplasdone-containing tablets were harder, less friable and disintegrated faster compared to Ac-di-sol and Explotab-containing tablets. Monte carlo simulations at the optimal factor settings (30% starch pellets, 4% Polyplasdone and 10 kN compression force) indicated that a robust system was formed as the probability to exceed the limits was low for all responses. Validation of the design

space (at optimal settings) showed that the results predicted via the DOE models correlated well with the observed experimental data.

KEYWORDS

Multiparticulate tablet, starch pellet, disintegrant, design of experiment, granule

1. INTRODUCTION

Multiparticulates have several therapeutic and technological advantages over single-unit dosage forms. Being small (<2 mm), pellets or multiparticulates can distribute evenly in the gastrointestinal tract, resulting in fewer adverse effects. Pellets also reduce the risk of dose dumping compared to single unit dosage forms and result in a reproducible bioavailability (Bodmeier, 1997; Celik, 1994). Pellets can be either filled into capsules or compressed into tablets called multiple unit pellet systems (MUPS), which rapidly disintegrate into smaller units. Compared to capsules, MUPS have a lower production cost (Beckert et al., 1998; Bodmeier, 1997; Nicklasson et al., 1999) and they can contain a higher drug load, leading to improved patient compliance (Bechard and Leroux, 1992). MUPS are also tamper proof and can be divided into smaller units (Abdul et al., 2010; Beckert et al., 1998).

Microcrystalline cellulose (MCC) has been the gold standard for preparing pellets by extrusion-spheronisation. However, MCC pellets show lack of disintegration and incompatibilities, since drug decomposition as well as drug adsorption onto the MCC fibres have been reported (Dukic-Ott et al., 2009). As a result, researchers have been evaluating other excipients as pelletisation aid, which may substitute MCC for extrusion-spheronisation purposes. A resistant and crystalline high-amylose starch grade (VELOX^{TM} MCS) has been reported to be among the promising alternatives for MCC. The starch-based pellets were of high quality (process yield, roundness, surface structure) and had a fast disintegration and drug release (Dukic-Ott et al., 2008; Dukic et al., 2007).

The purpose of this study was to examine the feasibility to compress these starch-based pellets into fast disintegrating multiparticulate tablets (MUPS), by examining the effect of

several formulation (starch pellet percentage, type and concentration of external disintegrant) and process (compression force) parameters on the resulting tablet properties (hardness, friability and disintegration time), using a design of experiments (DOE) approach. DOE was also used to optimize the tablet formulation and to determine and evaluate the design space.

2. MATERIALS

2.1. Starch pellets

Starch-based pellets (710-1000 µm) were prepared by extrusion-spheronisation, using a high amylose, crystalline and resistant starch grade (VELOX™ MCS, Henkel Corporation, New Jersey, USA) as main excipient (83.2%). Hydroxy propyl methyl cellulose (HPMC) (Methocel® E15 LV, Colorcon, Dartford, UK) (4.8%) was used as binder in the pellets and sorbitol (Sorbidex® P16615, Cerestar, Vilvoorde, Belgium) (10%) was added as a plasticizer, to modify the wet mass consistency. Demineralised water was used as granulation liquid. Riboflavin sodium phosphate (2%) (Sigma Aldrich, France) was used as model drug.

2.2. Excipient granules

Microcrystalline cellulose (54.5%) (MCC, Avicel PH 101, FMC Biopolymers, Ireland) and α-lactose monohydrate (33.5%) (Pharmatose® 200M, DMV, Veghel, Nederland) were used as fillers for granulation. Polyvinylpyrrolidone (4%) (PVP, Kollidon® 30, BASF, Ludwigshafen, Germany) was used as binder and crosslinked croscarmellose sodium (Ac-di-sol®, IMCD Limited, Sutton), sodium starch glycolate (Explotab®, JRS Pharma, Rosenberg, Germany) or crospovidone (Polyplasdone® XL, ISP, Germany) were incorporated in the granules as internal disintegrant (8%). Demineralised water (89% w/w of dry mass) was used as granulation liquid. To prepare the multiparticulate tablets, the pellets and granules were mixed with an external disintegrant, colloidal silicium dioxide (1%) (Aerosil®, Alpha Pharma, Belgium) and sodium stearyl fumerate (0.5%) (Lubrisanaq®, Pharmatrans Sanaq, Basel, Switzerland).

3. METHODS

3.1. Preparation of starch pellets

Pellets were produced by extrusion-spheronisation according to Dukic et al. (Dukic et al., 2007). Dry mixing was performed in a tumbling mixer (Turbula® model T2A, W.A. Bachofen, Basel, Switzerland) for 15 min. This powder mixture was granulated with demineralised water for 10 min in a planetary mixer (Kenwood Chief, Hampshire, UK), using a K-shaped mixing arm. Water was added during the first 30 s of the wet granulation phase. To ensure uniform mixing, material adhering to the mixing bowl was removed regularly. The obtained wet mass was extruded at an extrusion speed of 50 rpm using a single screw extruder (Dome extruder DG-L1, Fuji Paudal, Tokyo, Japan) equipped with a dome-shaped extrusion screen with 1.0 mm perforations. The resulting extrudates were spheronized for 3 min at a speed of 1000 rpm using a spheroniser having a friction plate with cross-hatched geometry (Caleva Model 15, Caleva, Sturminster Newton, Dorset, UK). The pellets were dried overnight in an oven at 40 °C. Finally the pellets of size fraction 710-1000 µm were separated using a sieve shaker (Retsch, Haan, Germany).

3.2. Wet granulation for preparation of excipient granules

Wet granulation was carried out to prepare placebo granules (containing lactose and MCC) with a particle size matching the size of the pellets. MCC (54.5%), lactose (33.5%) and disintegrant (8%) (either Ac-di-sol, Explotab or Polyplasdone) were mixed in a tumbling mixer for 15 min. Wet granulation was performed by adding an aqueous solution containing 4% PVP as binder to the powder mixture. After mixing for 15 min in a planetary mixer, the wet mass was

passed through a 1480 µm sieve and the obtained granules were dried in an oven at 40 °C for 24 h. The final product was sieved to isolate the 710-1000 µm size fraction.

3.3. Characterization of pellets and granules

3.3.1. Image analysis

The size and shape of the pellets were determined using an image analysis system. Photomicrographs of the pellets were taken with a digital camera (Camedia® C-3030 Zoom, Olympus, Tokyo, Japan), linked with a stereomicroscope (SZX9 DF PL 1.5x, Olympus, Tokyo, Japan). A cold light source (Highlight 2100, Olympus, Germany) and a ring light guide (LG-R66, Olympus, Germany) were used to obtain top light illumination of the pellets against a dark surface. The images were analyzed by image analysis software (AnalySIS®, Soft Imaging System, Munster, Germany). The magnification was set in a way that one pixel corresponded to 5.7 µm and around 300 pellets were analyzed from every batch. Each individual pellet was characterized by its mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°), and the overall average FD value of all pellets analyzed in a batch was calculated (average FD). Each individual pellet was also characterized by the aspect ratio (AR: ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (eR) (Dukic et al., 2007).

3.3.2. Friability

The friability was determined (n=3) using a friabilator (PTFE, Pharmatest, Hainburg, Germany). Pellets and granules (I_{wt}=10 g) were placed in an abrasion wheel together with 200 glass beads (diameter: 4 mm) and the sample was subjected to falling shocks for 10 min at a rotational speed of 25 rpm. Afterwards the fines were removed by sieving through a 250 µm

mesh for 5 min (2 mm amplitude). The fraction above 250 µm (F_{wt}) was used to calculate the friability of pellets according to the following equation (Eq. 1):

$$Friability\ (\%) = [(I_{wt} - F_{wt})/ I_{wt}] \times 100 \qquad Eq\ (1)$$

3.3.3. Bulk and tapped density

The bulk (ρ_b) and tapped density (ρ_t) of pellets and granules were determined using a tapping machine (J. Englesman, Ludwigshafen, Germany) (n=3). A 100 ml measuring cylinder was filled with the sample up to the mark. The volumes at the beginning (bulk volume, V_0) and after 1000 taps (tapped volume, V_{1000}) were recorded. The bulk density was calculated as the ratio of mass and initial volume V_0, while the tapped density was calculated as the ratio of mass and tapped volume V_{1000}. The compressibility index (C%) and Hausner ratio (HR) were calculated according to the following equations (Eq. 2, 3) :

$$Carr's\ Index = (\rho_t - \rho_b/ \rho_t)*100 \qquad Eq\ (2)$$

$$Hausner\ Ratio\ (HR) = \rho_t/\rho_b \qquad Eq\ (3)$$

3.3.4. Porosity

The porosity (ε) of the dried granules and pellets (710-1000 µm) was calculated using the following equation (Eq. 4):

$$E = 100\ (1 - \rho_a/\rho_h) \qquad Eq\ (4)$$

Where ρ_h is the true density (determined by helium pycnometry, Accupyc 1330 Micromeritics, Norcross, USA) and ρ_a is the apparent (granular) density (calculated from the envelope volume

as determined by mercury porosimetry, Autopore III, Micromeritics, Norcross, Georgia, USA) (n=3).

3.4. Preparation of multiparticulate tablets

The composition of the multiparticulate tablets is given in Table 1. Pellets, granules (710-1000 µm), external disintegrant, silicium dioxide and sodium stearyl fumerate were mixed in a tumbling mixer for 1 h. From this mixture oblong tablets (length 17.1 mm, width 8.2 mm, weight 800 mg) were manufactured on a single punch tablet press (Korsch EK0, Berlin, Germany) at a production rate of 1000 tablets per hour.

3.5. Design of Experiments

The influence of several formulation and process parameters on the properties of the multiparticulate tablets was studied using Design of Experiments (DOE). The effects of three formulation variables (percentage of starch pellets, type of disintegrant, percentage of external disintegrant) and one process variable (compression force) were studied by applying a 2-level full factorial design. The experimental space within which the factors were studied, are detailed in Table 2. The disintegrant type was a qualitative factor. Design centre point experiments combining each type of disintegrant and the centre points of the other factors (40% starch pellets, 6% each disintegrant, 10 kN compression force) were performed, resulting in 3 centre point experiments. Each centre point experiment was performed in triplicate. Hence, in total 2^3 * 3 + 9 = 33 experiments were performed (Table 3). All experiments were performed in a randomized order. Tablet hardness, friability and disintegration time were included as response variables. The results were analyzed using Modde software (Version 9.0, Umetrics, Umea, Sweden).

3.6. Tablet characterization

Tablet hardness was determined from the force required to fracture the tablets along their longest axis using a tablet hardness tester (PTB 311 Pharma Test, Hainburg, Germany) (n=6).

The tablet friability was determined in a friabilator (PTFE Pharma Test, Hainburg, Germany), described in the European Pharmacopoeia, at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

The disintegration time was determined (n=6) using the apparatus described in the European Pharmacopoeia (PTZ-E Pharma Test, Hainburg, Germany) (Eur. Pharm. 2009). These tests were performed in distilled water at 37.0 ± 0.5 °C using disks.

Scanning Electron Microscopy (SEM) was used to visualize the surface morphology of the tablets, pellets and granules. Samples were coated with platinum by means of a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan) to assure conductivity. Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan). Digital microscope (KH 7700, Hirox, Japan) was used for visual inspection (qualitative study) of the effect of the compaction process on pellet integrity.

The content uniformity of selected formulation was determined by crushing 10 tablets and dissolving the powder in 100 ml of distilled water. After filtration through a 0.2 µm cellulose acetate filter (Sartorius, Gottingen, Germany), the riboflavin content was determined via UV-analysis (Perkin-Elmer UV/VIS λ12, Norwalk, CT, USA) at 445 nm.

Drug release from selected formulations was performed according to the USP paddle method (VK 8000, Vankel, New Jersey, USA) at a rotational speed of 100 rpm and at a temperature of

37.0 ± 0.5°C. Demineralised water (900 ml) was used as dissolution medium. Samples of 5 ml were withdrawn from the dissolution vessel at different time intervals. The samples were analyzed using double-beam spectrophotometer (Perkin-Elmer UV/VISs λ12, Norwalk, CT, USA) at a wavelength of 445 nm. Each batch was analyzed in triplicate.

4. RESULTS AND DISCUSSION

4.1. Development of MUPS tablets

As the first step of the development of multiparticulate tablets, starch pellets were mixed with 0.5% sodium stearyl fumerate as preliminary experiments with magnesium stearate resulted in a too low tablet hardness. After compression at 25 kN the resulting compacts were easy to de-aggregate and the original pellets could be retrieved by gently shaking the tablet in a petri dish. Although the pellets deformed (Figure 1) there was not sufficient binding between the pellets to produce a coherent tablet. When only die wall lubrication (with 1% sodium stearyl fumerate suspension in ethanol) was used, the binding properties did not improve although there was a higher tendency of the pellets to fragment. These results were confirmed via image analysis: the mean aspect ratio increased from 1.1 to 1.3 and 1.4 after lubrication with 0.5% sodium stearyl fumerate and in-die lubrication, respectively, while the average feret diameter decreased from 1.30 to 1.18 and 0.90 mm.

It was essential to use suitable inert compression diluents to improve the compactibility of starch-based pellets. These diluents should have minimal segregation propensity, cushion the pellets during compression, have a high dilution potential, disintegrate rapidly to release the starch-based pellets and have minimal effect on the drug release kinetics.

The effect of excipients on compression of multiparticulates has been the subject of many publications, the excipients varying from powders to placebo beads/granules. Lundqvist et al. evaluated the effect of diluents on tablet properties using a mixture of drug pellets (MCC/lactose/drug, ratio: 50/48/2), cushioning pellets (barium sulphate/MCC/glyceryl monostearate, ratio: 50/20/30) and disintegrating pellets (MCC/disintegrant, ratio: 50:50)

(Lundqvist et al., 1997). Beckert et al. compressed coated MCC pellets into disintegrating tablets using powders and granules of various excipients along with disintegrants (Beckert et al., 1996, 1998). Ghanam et al. formulated MUPS tablets by embedding κ-carrageenan pellets in a silicified microcrystalline cellulose powder (SMCC HD 90) (Ghanam et al., 2010). Habib et al. developed placebo beads containing different MCC/lactose ratios and different levels of super disintegrants by extrusion–spheronization, followed by freeze drying and examined the effects of these variables on water requirement, porosity, compactibility, compressibility and disintegration of MUPS tablets. High levels of MCC and different superdisintegrants, especially croscarmellose sodium, increased the granulation liquid requirement, thus producing freeze-dried beads with higher porosity and compactibility (Habib et al., 2002).

As starch-based pellets with a narrow size distribution were used, excipient granules of similar size and shape were considered as the best choice, as compression diluents in order to minimize the risk of segregation during compression and in order to ensure content uniformity of the drug incorporated into the pellets (Beckert et al., 1998; Ivic et al., 2009). These placebo granules should deform/fragment during compaction with pellets, in order to fill the voids between the pellets and also to surround them so that the tablet is held together by excipient-excipient interactions. Ideally these placebo granules should fracture into progeny primary powder particles thus facilitating maximum tablet bonding (Aulton et al., 1994).

Similar to Habib et al., this study used granules consisting of MCC and lactose as compression aids; however these granules were prepared via wet granulation and oven drying. Combining these granules with starch-based pellets yielded tablets with an acceptable hardness and low friability, but a long disintegration time. To enhance the disintegration, an internal disintegrant phase was added to the placebo granules, either Polyplasdone, Explotab or Ac-di-sol

were combined with MCC and lactose. These granules in combination with starch pellets and an extragranular disintegrant phase yielded acceptable multiparticulate tablets (Figure 2). The deformation of the starch-based pellets was limited as tablet cohesion was due to the deformation of the MCC/lactose granules (Figure 3).

The Carr's index and Hausner ratio indicated that the different granule formulations had a good flowability. The friability of Polyplasdone granules was less than 1%, while the Ac-di-sol and Explotab-based granules were more friable (Table 4).

4.2. Experimental design

From the experimental results (Table 3), the effects of all studied variables and the variable interactions were graphically and statistically interpreted for all responses. Figure 4 show the effect plots for hardness, disintegration time and friability, where negative values indicate a negative effect of a specific variable on the response factor. In these plots the effects are sorted from largest to smallest, and. Replicate plots (data not shown) were used to evaluate per response whether the variability of repeated experiments was smaller than the overall variability. Next, normal distribution of the experimental results per response (hardness, disintegration time and friability) was evaluated using the histogram plots. In case of disintegration time and friability, logarithmic transformation was needed to obtain a normal distribution of the experimental results. This transformation improved the model fit for these responses. Based on the DOE experimental results, models describing the factors/response relationship were calculated for each response. Model refinement was done by excluding the non-significant model terms, hence improving the model predictability.

4.2.1. Hardness

Increasing the compression force significantly increased the hardness, yielding stronger tablets (Figure 4A). A high percentage of starch pellets resulted in reduced bonding forces within the tablets, confirmed by a lower hardness. Polyplasdone had a positive effect on hardness, irrespective of the concentration used in external phase. In contrast, Explotab as disintegrant in the granules reduced the hardness significantly and Ac-di-sol had a negligible effect. These results are similar to the results obtained by Habib et al. (Habib et al., 2002), where Polyplasdone as external phase during compression of MCC pellets yielded stronger tablets compared to formulations with Ac-di-sol and Explotab as external disintegrant. The disintegrant concentration had a limited effect on hardness. Kornblum et al. demonstrated that Polyplasdone acted both as binder and disintegrant in tablets made by wet granulation (Vankamp et al., 1983). This was confirmed in the current study, as granules containing Polyplasdone had a low porosity and friability compared to Explotab and Ac-di-sol granules (Table 4). Furthermore, this was also reflected in the DOE as Polyplasdone-containing tablets were harder and less friable, probably due to the binding properties of Polyplasdone acting as an adhesive. The interaction effect between percentage of starch pellets and Ac-di-sol or Explotab increased the hardness whereas the use of Polyplasdone decreased the hardness.

4.2.2. Disintegration time

In the present study, the disintegrant was incorporated in both the intra (8%) - and extra-granular (4-8%) phase. Increasing the compression force significantly increased the disintegration time of MUPS tablets (Figure 4B). Mainly the compression force affected the disintegration time, whereas the other factors had a limited effect. As all tablets disintegrated very rapidly (within 5 min), the multiparticulate behaviour of the compressed system could be maintained in all formulations. Increasing the percentage of starch pellets significantly reduced

the disintegration time. Polyplasdone lowered the disintegration time, whereas the other two disintegrants did not have a significant effect on tablet disintegration. Polyplasdone has a porous particle morphology which enables it to rapidly absorb liquids into the tablet by capillary action and generate rapid volume expansion and hydrostatic pressure, which induce tablet disintegration, without forming a gel at higher concentrations (Polyplasdone® Superdisintegrants). On the other hand, Ac-di-sol and Explotab show a disintegration effect mainly via swelling (Gorman et al., 1982).

The effect plot for disintegration time suggested an increase at higher compression force, whereas the interaction of Polyplasdone as disintegrant with a higher compression force prolonged disintegration time. This might be related to tablet hardness, as Polyplasdone improved binding within the tablets.

4.2.3. Friability

Friability of the tablets compressed at lower compression force and having a higher percentage of starch pellets was significantly higher (Figure 4C). Mainly Polyplasdone-containing tablets had a low friability, whereas the friability of tablets formulated with Ac-di-sol and Explotab increased. These results are correlated with the granule friability (Table 4) as Polyplasdone granules were less friable compared to agglomerates prepared with Ac-di-sol and Explotab, due to the increased binding properties of Polyplasdone. During friability testing some tablet formulations disintegrated into the individual pellets. This was related to the amount of external disintegrant in the tablet, which significantly increased the friability.

4.3. Process optimization

To optimize the final tablet formulation and process conditions, the required limits of the response values were clearly defined, and the combinations of variables which resulted in tablets meeting the required specifications were calculated using the Modde optimizer software to obtain tablets with the following properties: a hardness between 80 and maximum 200 N, a friability below 1% and a disintegration time below 3 min. The sweet spot plots (Figure 5) show those regions where the combinations of variables resulted in tablets having the required specifications (green area). These response criteria are mainly met when Polyplasdone is used as external disintegrant, irrespective of the concentration used. Ac-di-sol containing formulations still meet the criteria at higher compression force, whereas Explotab offered limited opportunities to meet the requirements. It is obvious that the obtained design space is more robust when Polyplasdone is used as disintegrant, compared to Ac-di-sol and Explotab. Strict control of these optimum settings is clearly needed to result in a high hardness, low friability and short disintegration time.

Sweet spot plots are limited by the number of dimensions and the lack of probability estimation in the predicted surface (i.e. design space). Therefore, the values of the response factors (hardness, disintegration time, friability) were predicted via Monte Carlo simulations (using Modde software) by randomly varying the settings around their optimum value (but within the lower and upper limits). The resulting distribution of each response factor (presented as a histogram) allows to determine the probability that the accepted limit of a response factor is exceeded when the settings fluctuate around their optimum. Monte Carlo simulations at the optimum factor settings (4% crospovidone, 10 kN compression force and 30% starch pellets) showed that there is a 0% probability for hardness and disintegration time and a 0.1% probability for friability to exceed the specification limit values (Figure 6). At the above-mentioned

optimum settings validation of the design space outlined via the DOE was performed, and the results predicted based on the DOE model correlated well with the observed experimental data (Table 5).

4. 4. Content uniformity and drug release

When processing the optimized tablet formulation (contained 30% starch pellets and 4% Polyplasdone in the external phase and is compressed at 10 kN) in automatic mode (i.e. filling the pellets into the tablet die from a feed hopper by gravity), the weight variation and content uniformity were within the acceptable limits, confirming the absence of segregation between granules and pellets. The entire riboflavin content was released within 15 min from pellets and MUPS tablets, confirming the suitability of starch-based pellets to formulate fast-disintegrating MUPS.

5. CONCLUSION

The compression of starch-based pellets as such was not possible. However, the addition of excipients granules (formulated with MCC, lactose and a disintegrant) yielded fast disintegrating MUPS tablets. Via DOE, it was determined that selection of the proper formulation (disintegrant type, concentration of starch pellets, concentration of external disintegrant) and process (compression force) parameters was of paramount importance to obtain MUPS tablets with optimum hardness, friability and disintegration time.

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Table 1. Composition of the multiparticulate tablets

Ingredient	Concentration (% w/w)
Starch pellets	Variable
Disintegrant	Variable
Silicium dioxide	1
Sodium stearyl fumerate	0.5
Excipient granules	q.s. ad 100 %

Table 2. DOE factors with their experimental space

Variables	Units	Levels	
		-	+
Starch pellets	% w/w	30	50
Concentration of external disintegrant	% w/w	4	8
Compression force	kN	5	15
External disintegrant type		Ac-di-sol, Explotab, Polyplasdone	

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Table 3. 2-level full factorial design with 4 variables: A. type of disintegrant (at 3 levels); B. compression force (kN); C. percentage of starch pellets (%); D. percentage of external disintegrant (%). The quantitative variables A, B and C were evaluated at 2 levels. 3 replicates of the central point for each type of disintegrant were performed. The experiments were performed in randomized order.

Exp. No.	Variables B	C	D	Hardness (N)	Disintegration time (sec)	Friability (%)
Variable A: Ac-di-sol						
1	5	30	4	34.9	37	9.2
2	15	30	4	156.6	125	0.12
3	5	50	4	10.0	38	19.2
4	15	50	4	107.6	162	2.1
13	5	30	8	31.4	56	24.5
14	15	30	8	133.7	178	0.9
15	5	50	8	18.9	59	22.9
16	15	50	8	68.7	79	4.5
25	10	40	6	54.9	55	4.7
26	10	40	6	73.7	55	4.7
27	10	40	6	75.3	65	5.8
Variable A: Explotab						
5	5	30	4	36.7	21	6
6	15	30	4	114.7	314	0.4
7	5	50	4	12.0	22	15.4
8	15	50	4	70.7	151	2.4
17	5	30	8	42.3	25	12.6

18	15	30	8	113.6	240	1.2
19	5	50	8	7.9	23	20.8
20	15	50	8	49.3	184	5.1
28	10	40	6	81.0	98	6.7
29	10	40	6	66.1	108	6.2
30	10	40	6	53.0	91	4.5
Variable A: Polyplasdone						
9	5	30	4	59.3	16	3.1
10	15	30	4	214.7	224	0.1
11	5	50	4	20.4	16	10.2
12	15	50	4	84.1	159	1.2
21	5	30	8	64.0	15	8.9
22	15	30	8	203.6	275	0.1
23	5	50	8	7.5	15	17.5
24	15	50	8	80.9	*	1.6
31	10	40	6	91.2	90	0.9
32	10	40	6	88.1	66	1.3
33	10	40	6	83.2	63	1.6

* Outlier

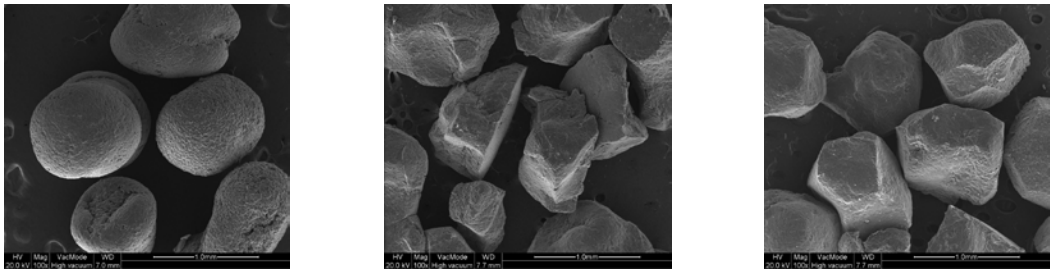
Table 4. Characterisation of placebo granules formulated with MCC (54. 5%), lactose (33.5%), disintegrant (8%) and PVP (4%)

Evaluation parameters	Granules with different disintegrants		
	Ac-di-sol	Explotab	Polyplasdone
Carr's index (%)	13.0	14.2	14.9
Hausner ratio	1.15	1.17	1.18
Porosity (%)	65.8	60.8	52.1
Friability (%)	12.9	12.2	0.2

Table 5. Process validation of the DOE model: predicted response values via DOE model vs. observed response values. The following settings of the different factors were defined: compression force 10 kN, starch pellets concentration: 30%, external disintegrant concentration: 4%, disintegrant type: Polyplasdone

Response	Predicted	Observed
Hardness (N)	153	143
Friability (%)	0.41	0.39
Disintegration time (sec)	90	81

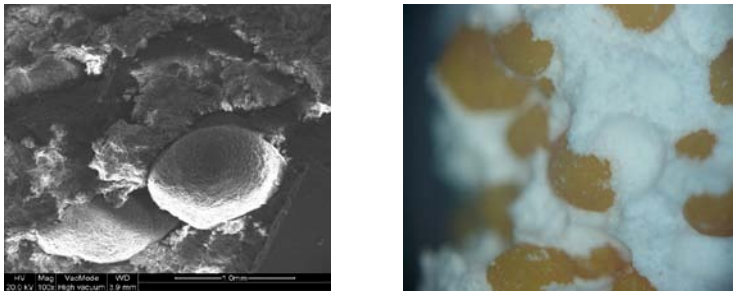
Figure 1. SEM pictures of starch based pellets



(a) **(b)** **(c)**

Figure 2. Appearance of multiparticulate tablets

Figure 3. SEM and optical microscopy pictures of the fracture plane of multiparticulate tablets



(a) **(b)**

565 **Figure 4.** Effect plots

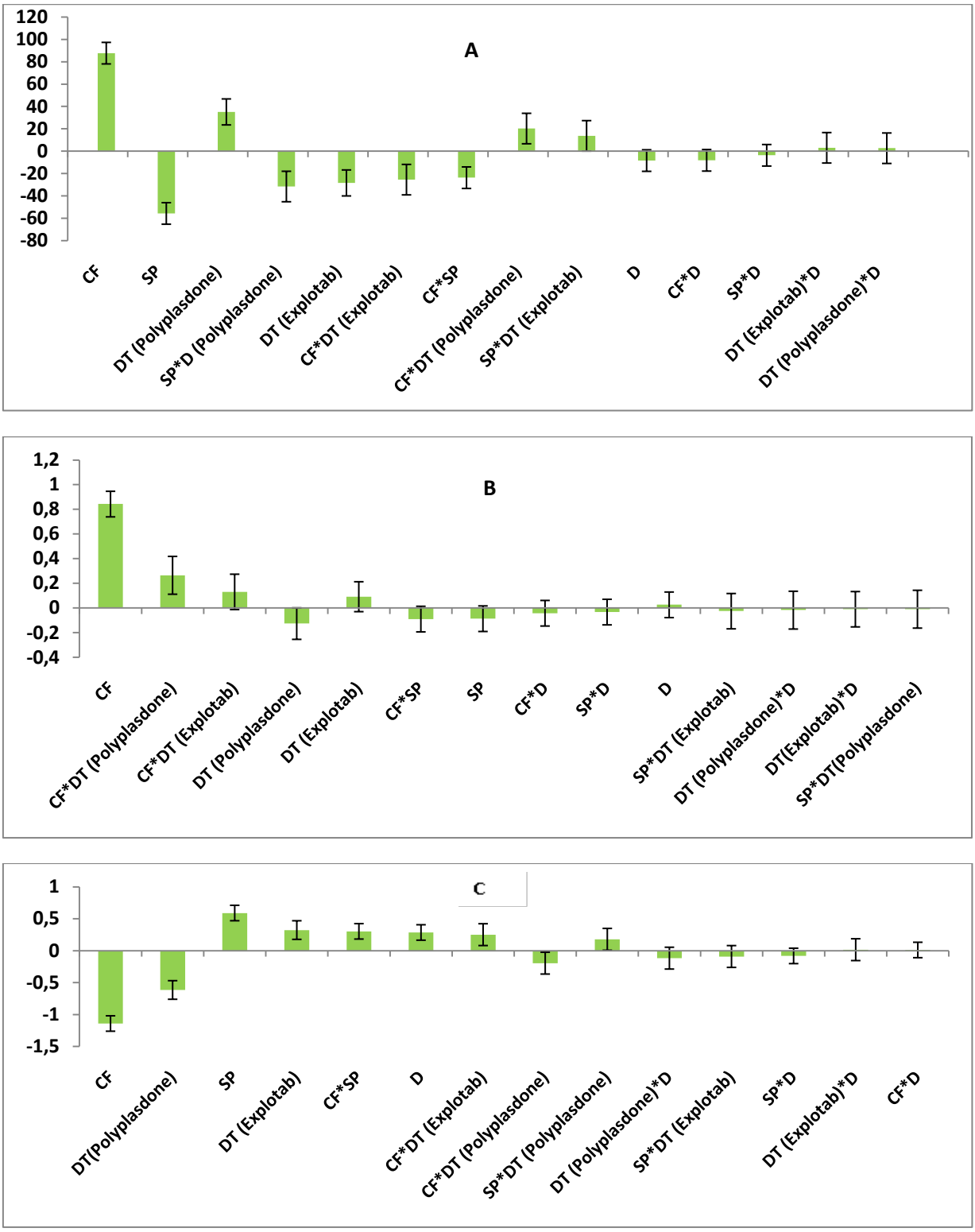


Figure 5. Sweet spot plots

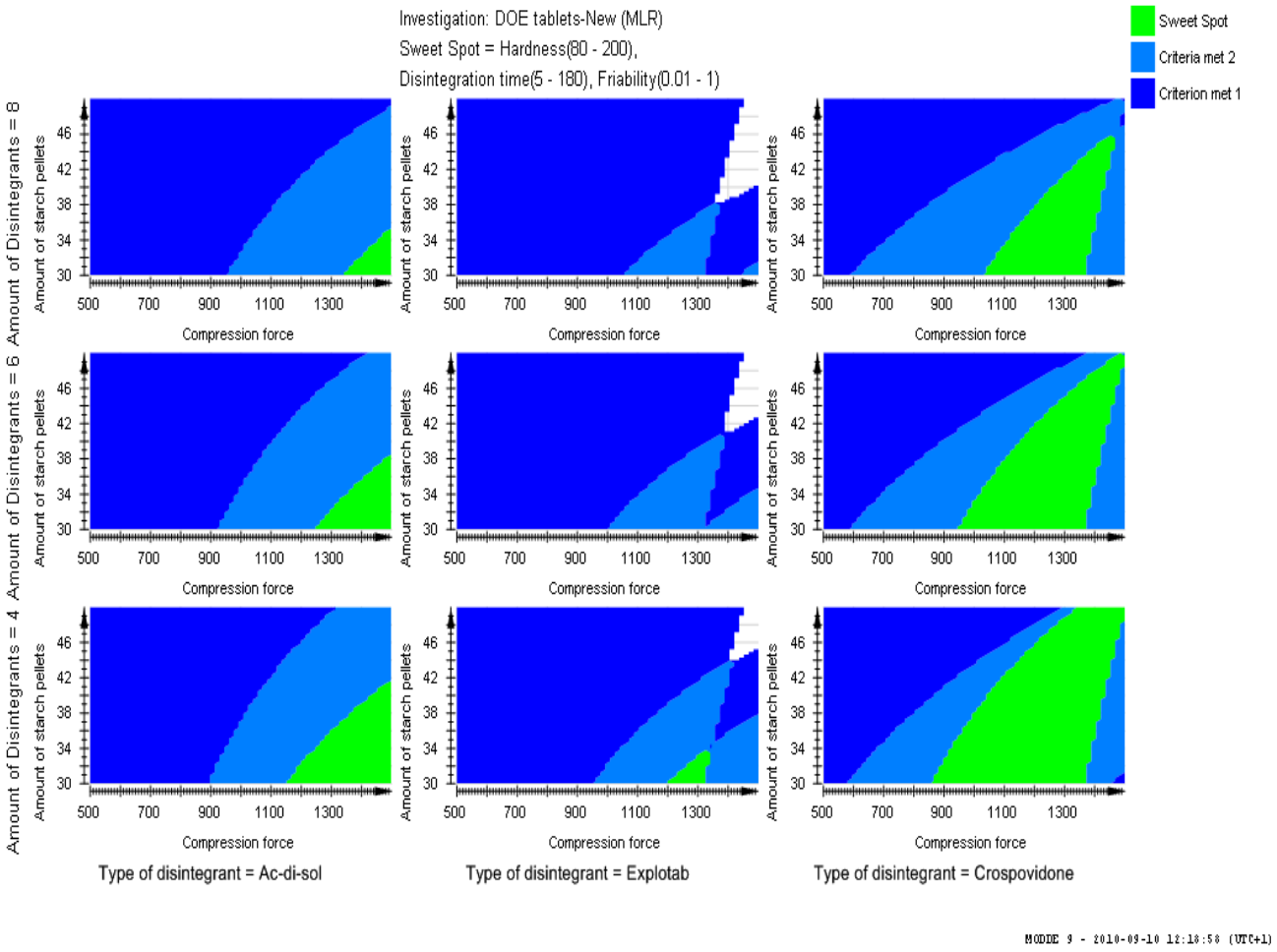


Figure 6. Monte carlo simulations

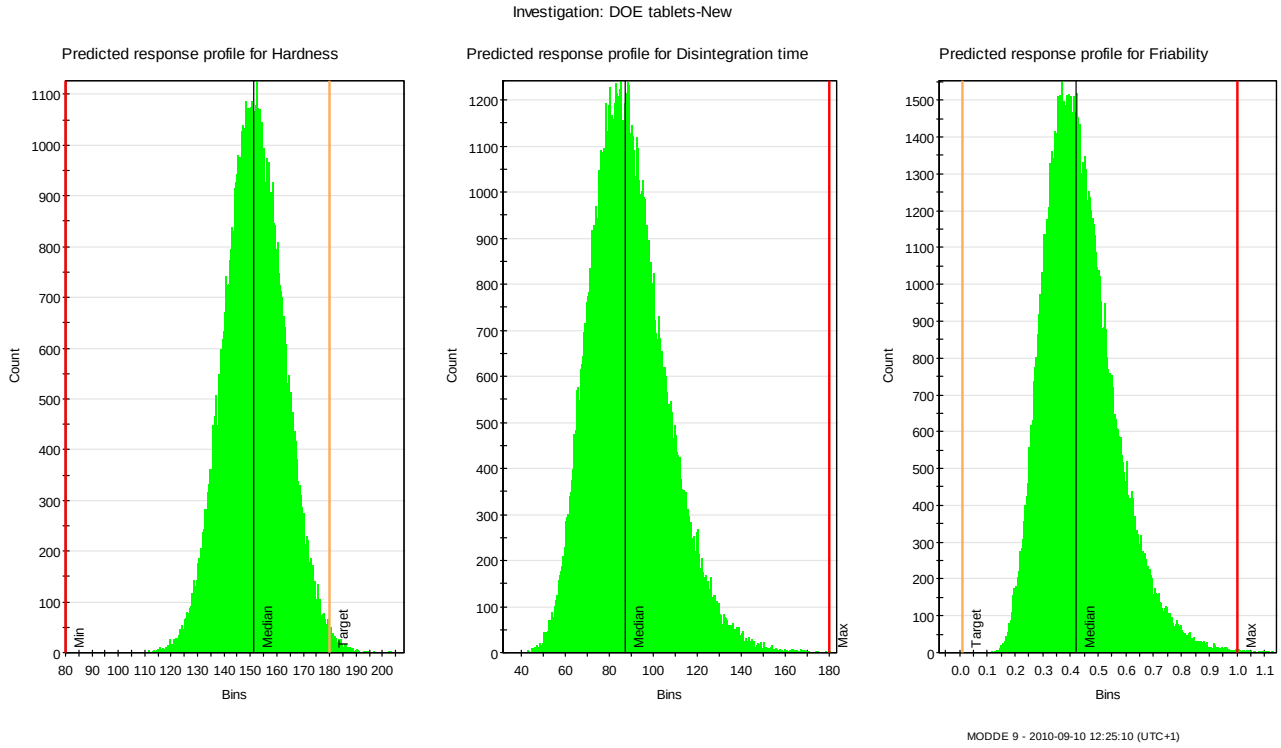


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FIGURE LEGEND

Figure 1:

SEM pictures of starch-based pellets before (a) and after compression using die lubrication (b) and 0.5% sodium stearylfumerate as lubricant (c).

Figure 2:

Appearance of multiparticulate tablets containing 30% starch pellets and 64.5% MCC/lactose granules. Riboflavin (2%) was added as a marker to the starch-based pellets, resulting in yellow-colored pellets.

Figure 3:

SEM (a) and optical microscopy (b) pictures of the fracture plane of multiparticulate tablets formulated with starch-based pellets (30%) and MCC/lactose (64.5%) granules

Figure 4:

Effect plots for hardness (A), disintegration time (B) and friability (C). Studied factors: compression force (CF), disintegrant type (DT), percentage of starch pellets (SP), percentage of disintegrant (D).

Figure 5:

Sweet spot plot highlighting the combination of factors (green areas) resulting in tablets having the required properties (i.e., hardness: 80 - 200N, disintegration time: <180 sec, friability <1%).

Dark blue and light blue area represents combinations of factors resulting in 2 and 1 responses within the desired ranges, respectively. The white area represents combinations where none of the responses met the specifications.

Figure 6:

610 Predicted response profiles for the response variables. The yellow line represents the target value for the responses here. The red lines are the specification limits for each response residual. The green region represents the probability of a prediction when the optimum process settings are used.