

FORMULATION OF ORODISPERSIBLE TABLETS CONTAINING MELOXICAM AND THEIR *IN VITRO* AND *IN VIVO* CHARACTERIZATION

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Abstract

The aim of this experimental work was to evaluate the influence of formulation variables on the characteristics of orodispersible tablets, using a statistical method, in order to reach a balance between their properties: fast disintegration, convenient hardness and good palatability. 26 formulations were obtained, according to a D-Optimal experimental design. The formulation factors were the disintegrate ratio, compression force, sweeteners ratio and diluents ratio. For the response variables, the tablets were characterized *in vitro* and *in vivo*.

The obtained results showed that the two most important factors were the diluents ratio and the compression force. Choosing well balanced formulation factors and technological variables enables the obtaining of tablets with convenient mechanical strength, water absorption capacity, oral disintegration time, *in vitro* dissolution time and palatability. The conditions for the obtaining of the highest crushing strength, shortest disintegration time and best palatability were generated. Taking into account the results for the chosen variables' influence, an optimal formulation was obtained.

Rezumat

Obiectivul acestui studiu a fost evaluarea influenței factorilor de formulare asupra caracteristicilor comprimatelor orodispersabile, prin intermediul unei metode statistice, în vederea atingerii unui echilibru între o dezagregare rapidă, rezistență mecanică suficientă și palatabilitate bună. S-au preparat 26 tipuri de comprimate conform unui plan experimental D-Optimal. Factorii de formulare au fost: raportul dintre dezagreganți, forța de comprimare, raportul dintre diluanți și dintre îndulcitori. Pentru obținerea variabilelor de răspuns, comprimatele au fost caracterizate *in vitro* și *in vivo*.

Rezultatele au arătat că cei mai importanți factori au fost raportul dintre diluanți și forța de comprimare. Alegerea echilibrată a factorilor de formulare și a variabilelor tehnologice, a dus la obținerea de tablete cu rezistență mecanică suficientă, timp de dezagregare *in vitro* și *in vivo* scurt, capacitate de absorbție a apei și palatabilitate convenabile. Ținând cont de rezultatele privind influența variabilelor luate în calcul, a fost determinată o formulare optimă.

Keywords: meloxicam, orodispersible tablets, superdisintegrant, experimental design, palatability

Introduction

In the last years, patient's lack of compliance to treatments has drawn the attention of the researchers. One of the reasons is related to the swallowing dysfunctions and dysphagia, more frequently met with the geriatric and paediatric patients [20]. As a result, the pharmaceutical industry started developing patient-friendly solid oral dosage forms (SODF), like orodispersible tablets [11, 19]. In 2008, Food and Drug Administration's (FDA) Guidance for Industry mentioned orally disintegrating tablets as solid dosage forms which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue. The conditions they have to meet are: fast disintegration, appropriate crushing strength to allow conventional packaging and convenient organoleptic properties [5, 18]. One of the most common methods to obtain orodispersible tablets is by using superdisintegrants [11].

The aim of this research study was the formulation and characterisation of orodispersible tablets containing meloxicam, using highly available excipients and a conventional method – direct compression. Sodium starch glycolate (SSG), a highly swellable disintegrant, with increased water absorption capacity, is generally used in percentages that range from 2% to 10% [9, 19]. Croscarmellose sodium (CCS) is usually used in percentages between 0.5 and 5%, has high capillary activity and hydration capacity [9, 19]. The total percentage of superdisintegrants was 15%, higher than usual, in order to accelerate meloxicam dissolution [13]. The diluents were mannitol (Man) – for its high water solubility and sweetness, and microcrystalline cellulose (MCC) – for its disintegration capacity [12, 19]. The tablets were evaluated *in vitro* and also *in vivo*, for a better characterization of the disintegration process and organoleptic properties [10, 13, 15].

Materials and Methods

Apparatus. Tablet press (Korsch EK-0 Germania), analytical balance (Sartorius, Switzerland); tablet hardness test apparatus Dr. Schleuniger (Dr. Schleuniger, Germany); tablet disintegration test apparatus ZT 2 (Erweka, Germany); tablet friability test apparatus TA (Erweka, Germany), dissolution test apparatus (PharmaTest, Germany).

Materials. Meloxicam (Uquifa, Spain), Mannitol – Pearlitol 200M (Merck, Germany); Microcrystalline cellulose PH102 – (JRS, Germany); Sodium starch glycolate (SSG) (JRS Pharma, Germany); Croscarmellose sodium (CCS) – Ac-Di-Sol (FMC BioPolymer, Belgium); sodium

saccharine (Sach) (Foodchem, China), sodium cyclamate (Foodchem, China), aspartame (Asp) (Ajinomoto, Japan), Magnesium stearate (Merck, Germany).

Methods. Experimental Design. The study was performed according to a D-Optimal experimental design. Modde 9.0 optimization program, Umetrics, Sweden, was used for the experimental design construction, coefficients and statistical parameters computation and fitting of the experimental data in order to evaluate the results. Table I presents the independent variables (formulation and process variables) and their level of variation. X_1 represents the ratio between CCS and SSG – 0:3, 1:2, 1.5:1.5, 2:1, 3:0; the total superdisintegrant content is constant - 15%. The total percentage of sweeteners is 2% and the ratio between Sach and Asp (X_3) was 0:3, 1.5:1.5 or 3:0. The ratio between Man and MCC (X_4) was either 0:3, 1:2, 1.5:1.5, 2:1 or 3:0. The experimental design matrix is shown in Table II and Table III illustrates the dependent variables.

Table I.
Independent Variables (Formulation and Process Variables)

Variables	Symbol	Levels					
		-1		0		+1	
Superdisintegrants ratio (CCS:SSG)	X_1	0	0.5	1	2	3	
Compressing force	X_2	15		25		35	
Sweeteners ratio (Sach:Asp)	X_3	0		1		3	
Diluents ratio (Man:MCC)	X_4	0	0.5	1	2	3	

Table II.
Experimental plan matrix

Exp Name	Run Order	X_1	X_2	X_3	X_4	Exp Name	Run Order	X_1	X_2	X_3	X_4
N1	22	0	15	0	0	N14	23	0,5	15	0	2
N2	14	0	35	0	0	N15	25	3	15	1	2
N3	19	3	25	0	0	N16	4	0	35	3	2
N4	2	1	35	1	0	N17	9	3	25	3	2
N5	1	0	15	3	0	N18	12	0	35	0	3
N6	11	0	35	3	0	N19	10	2	15	0	3
N7	16	2	15	3	0	N20	15	3	35	0	3
N8	20	3	35	3	0	N21	18	0	25	1	3
N9	26	3	15	0	0,5	N22	3	0	15	3	3
N10	24	2	35	0	1	N23	21	2	35	3	3
N11	6	0	15	1	1	N24	13	3	25	3	3
N12	17	0,5	25	3	1	N25	8	3	25	3	3
N13	22	0	15	0	0	N26	5	3	25	3	3

X_1 – Superdisintegrant ratio; X_2 – Compressive force; X_3 – Sweeteners ratio; X_4 – Diluents ratio.

Table III.
Dependent variables

No.	Responses	Symbol
1	Crushing strength	Y ₁
2	Friability	Y ₂
3	<i>In vitro</i> disintegration time	Y ₃
4	Wetting time	Y ₄
5	Water absorption ratio	Y ₅
6	% of meloxicam released at 5 minutes	Y ₆
7	% of meloxicam released at 10 minutes	Y ₇
8	% of meloxicam released at 15 minutes	Y ₈
9	% of meloxicam released at 20 minutes	Y ₉
10	% of meloxicam released at 30 minutes	Y ₁₀
11	<i>In vivo</i> disintegration time	Y ₁₁
12	Taste	Y ₁₂
13	The residual volume	Y ₁₃
14	Palatability	Y ₁₄

Tablets preparation. Meloxicam powder was mixed with compression excipients; tablets were obtained by direct compression, using an eccentric tablet press Korsch EK0, equipped with a 10 mm diameter set punch. The machine was adjusted so that the compressed tablets had an average weight of 200 mg, corresponding to a concentration of 7.5 mg meloxicam/tablet.

Determination of the dependent variables. The tablets were evaluated for *hardness*, *friability*, *disintegration time*, according to methods described in the European Pharmacopoeia [4]. For the *wetting time* measurement, two pieces of tissue paper were placed in a 4.5 cm diameter Petri dish, containing 4.5 mL phosphate buffer pH 7.4. The tablet was placed on the tissue paper and the time until dissolution media reached the upper surface of the tablet was noted. The tablets used in the wetting time test were weight before (w1) and after the test (w2) and the *water absorption ratio* (r) was calculated using the equation: $r=100*(w2-w1)/w1$ [8, 10]. The measurements were performed in triplicate.

The *in vitro* dissolution test was performed according to a Pharmacopoeial method, using type 2 apparatus, equipped with paddles, rotating speed of 50 rpm [4]. As dissolution media, 900 mL phosphate buffer pH 7.4 was used. 5 mL samples were taken at 5, 10, 15, 20 and 30 minutes and their meloxicam concentrations were determined spectrophotometrically, at 360 nm.

The *in vivo* evaluation was performed according to a study protocol that was approved by the Ethical Committee of the "Iuliu Hațieganu" University of Medicine and Pharmacy. 9 healthy volunteers, aged 24 to 32,

were enrolled after signing the written informed consent. The time required for complete *disintegration in the oral cavity* was registered from the volunteers, who were randomly administered each of the 26 formulations. The *taste* was established using a visual analogue scale (VAS), with values from 1 to 5, 1 meaning “the most unpleasant taste” and 5 – “the most pleasant taste”. The same VAS was applied for the *residual volume*, 1 meaning “no residual volume” and 5 meaning “a high volume of residue”. For the *palatability* assessment, the volunteers had to answer (YES/NO) the question “Would you accept a long term treatment with such a tablet?” [1, 16].

Results and Discussion

Table IV contains the results obtained after the pharmacotechnical analysis, the *in vitro* dissolution study and *in vivo* evaluation of tablets prepared according to the experimental design.

Experimental Design Analysis. Goodness of Fit. Modde 9.0 (Umetrics, Sweden) was the optimization software used for experimental design and statistical analysis. The data fitting was done using Partial Least Squares method. The experimental design reliability was confirmed by the values of the following statistical parameters: R^2 , Q^2 and ANOVA test. R^2 indicates the variation fraction of the response explained by the model and Q^2 - the variation fraction of the response that can be predicted by the model; their values vary between 0 and 1, but if they are closer to 1, they show a very good model, with very good predictive power [2, 3, 14]. The results were illustrated in Figure 1, by representing the R^2 , Q^2 , model validity and reproductibility, for every response. They showed excellent fitting for Y_1 and good fitting for the other 13 responses. The ANOVA test results indicated that experimental data were determined by the variation of formulation factors. The „p” parameter for model was lower than 0.05 and „p” for residual exceeded 0.05, for every response.

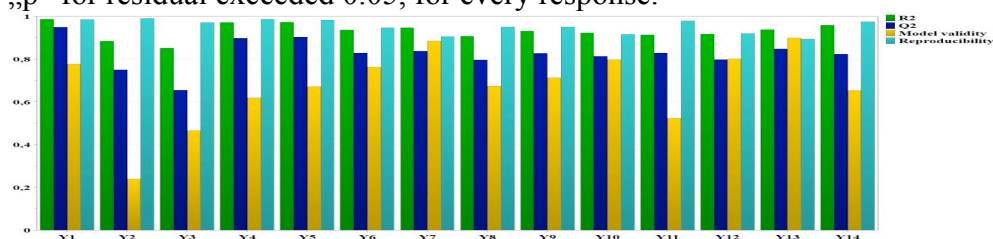


Figure 1.

The fitting of the experimental data to the chosen model

Y_1 - crushing strength, Y_2 - friability, Y_3 - *in vitro* disintegration time, Y_4 - wetting time, Y_5 - water absorption ratio, Y_6 - % of meloxicam released after 5 minutes, Y_7 - % of meloxicam released after 10 minutes, Y_8 - % of meloxicam released after 15 minutes, Y_9 - % of meloxicam released after 20 minutes, Y_{10} - % of meloxicam released after 30 minutes, Y_{11} - *in vivo* disintegration time, Y_{12} - taste, Y_{13} - residual volume, Y_{14} - palatability.

Table IV.
The response matrix

Exp Name	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10	Y11	Y12	Y13	Y14
N1	39.40	0.23	9.00	3.00	390.46	37.99	57.38	69.01	76.75	85.31	27.44	27	37	7
N2	126.50	0.10	48.16	22.40	345.92	44.82	66.90	77.89	83.23	88.40	94.00	24	31	6
N3	98.70	0.07	47.50	15.20	243.39	45.26	60.68	79.71	86.40	93.32	45.78	22	36	6
N4	139.22	0.10	56.40	21.30	239.30	43.04	69.64	81.47	87.72	93.39	92.67	27	30	7
N5	35.40	0.39	11.16	9.03	403.66	34.63	55.61	67.84	77.56	84.93	25.44	20	38	6
N6	147.10	0.15	76.83	31.90	141.06	40.36	65.84	77.91	85.79	92.11	133.89	22	29	2
N7	35.50	0.30	12.33	3.33	329.44	33.52	52.40	63.94	71.44	80.92	26.44	25	35	7
N8	174.20	0.08	82.33	39.00	189.66	34.18	63.52	78.39	85.70	93.40	123.44	24	30	3
N9	37.70	0.18	21.50	31.00	272.25	30.48	49.06	61.17	70.38	79.30	38.33	25	35	8
N10	125.30	0.05	57.33	64.00	229.38	22.43	47.63	62.20	70.86	81.09	109.44	25	30	2
N11	55.88	0.12	36.33	34.33	338.93	32.88	55.00	67.00	74.61	84.45	41.44	32	25	8
N12	79.40	0.15	53.83	41.33	229.06	24.47	44.75	57.69	66.13	76.92	66.56	30	31	9
N13	49.10	0.30	31.83	35.33	289.00	21.14	41.17	55.33	63.91	75.44	48.44	36	30	9
N14	50.10	0.20	45.00	70.66	191.79	25.66	46.03	58.31	66.73	77.43	49.00	35	32	9
N15	134.90	0.09	67.16	71.33	199.46	24.36	47.10	60.85	69.67	80.93	91.44	31	26	8
N16	84.00	0.02	55.33	143.33	177.40	20.41	40.01	51.27	60.18	69.13	79.22	31	28	9
N17	138.00	0.12	96.67	65.33	163.44	18.82	38.95	50.94	58.93	68.29	110.33	29	22	7
N18	60.40	0.10	56.33	98.33	154.89	16.31	33.24	44.55	52.03	61.48	74.44	35	24	9
N19	144.50	0.12	64.83	239.66	144.84	17.94	38.96	51.93	59.10	67.87	94.00	30	29	8
N20	110.40	0.20	59.33	68.00	186.49	16.81	37.06	49.01	56.86	66.38	102.33	33	23	8
N21	42.00	0.24	48.33	81.33	270.34	21.38	44.60	58.76	68.20	80.20	62.56	38	23	8
N22	143.80	0.12	78.83	163.67	172.49	14.99	35.62	50.25	56.88	67.55	96.22	37	24	9
N23	49.70	0.25	62.67	125.33	170.71	15.95	31.55	40.64	47.11	55.84	68.88	35	22	8
N24	110.00	0.12	48.00	157.00	149.31	16.82	35.22	47.68	54.12	61.36	89.11	34	26	9
N25	106.60	0.54	48.67	171.00	143.39	21.32	41.98	52.06	59.22	67.71	82.56	37	25	9
N26	116.80	0.11	54.67	163.00	141.84	18.88	39.39	52.19	57.25	64.78	90.78	36	28	9

Y₁ - crushing strength, Y₂ - friability, Y₃ - *in vitro* disintegration time, Y₄ - wetting time, Y₅ - water absorption ratio, Y₆ - % of meloxicam released after 5 minutes, Y₇ - % of meloxicam released after 10 minutes, Y₈ - % of meloxicam released after 15 minutes, Y₉ - % of meloxicam released after 20 minutes, Y₁₀ - % of meloxicam released after 30 minutes, Y₁₁ - *in vivo* disintegration time, Y₁₂ - taste, Y₁₃ - residual volume, Y₁₄ - palatability.

Analysis of the influence of formulation factors on the pharmacotechnical properties of tablets. All the 26 types of tablets had low disintegration times, less than 3 minutes, as shown in Figure 2.

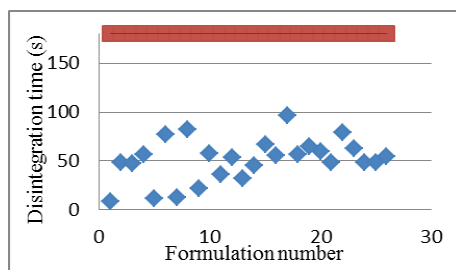


Figure 2.

The disintegration times (s) of the 26 formulations

The effect of factors variations and their interactions are shown in a series of histograms (Figure 3). The crushing strength was strongly influenced by the compression force, and to a lesser extent by higher percentages of CCS and Man. Friability was influenced only by the compression force.

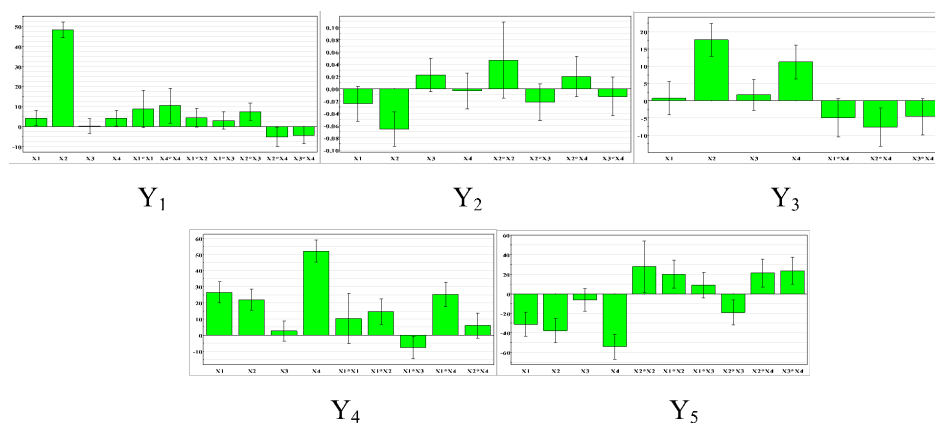


Figure 3.

The influence of formulation factors on the pharmacotechnical properties of tablets
Y₁ – Crushing strength; Y₂ – Friability; Y₃ – *In vitro* disintegration time; Y₄ – Wetting time; Y₅ – Water absorption ratio; X₁ – Superdisintegrant ratio; X₂ – Compressive force; X₃ – Sweeteners ratio; X₄ – Diluents ratio.

The disintegration time depended on the compression force and secondarily, on the diluent ratio. It was shorter for tablets with low crushing strength and that contained a smaller amount of Man, in favour of MCC.

The ratio between the superdisintegrants did not have significant influence. All formulations contained 15% of the chosen superdisintegrants or their mixtures. Although they have different mechanisms of action, CCS works by wicking, while AGNa by swelling, the results show that at this concentration, CCS, AGNa or a mixture of the two - have the same disintegrant capacity. The wetting time was longer for highly compressed tablets, containing large amounts of Man. Unlike the disintegration time, the wetting time was prolonged by high percentages of CCS; that can be explained by the smaller contact surface between the tablet and the medium that in the absence of a swelling agent, determines slower water absorption through capillary forces. The water absorption ratio was mostly influenced by the diluent percentage. High proportions of MCC increased the amount of incorporated water, along with high content of SSG and low compression force. MCC as diluent seems to be the correct choice for a quick disintegration and medium uptake, due to its high water-absorbing capacity, confirmed in previous studies by Gohel et al. [9]. Other researchers obtained similar results regarding the wetting process of superdisintegrants, Fukami et al. prepared orodispersible tablets with 20% of various superdisintegrants, among which CCS was found to delay wetting, fact that determined them to believe that it acts by a double mechanism - wicking and swelling [7]. Fini et al. showed that increasing percentages of SSG decrease the disintegration time, independent of the compression force [6]; that was not confirmed in the present study because of the constant disintegrant mixture percentage – 15%.

Analysis of the influence of formulation factors on the dissolution profile of meloxicam. The dissolution profiles of the 26 types of tablets are presented in Figure 4 and the effect of factors and their interactions are presented as histograms in Figure 5.

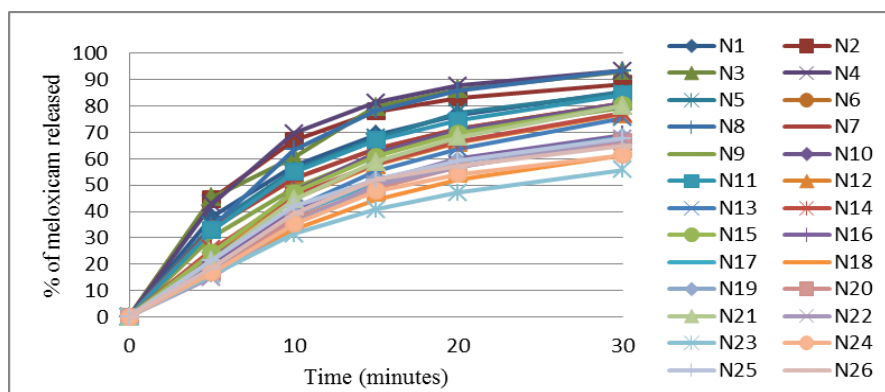


Figure 4.

The dissolution profiles of the 26 formulations

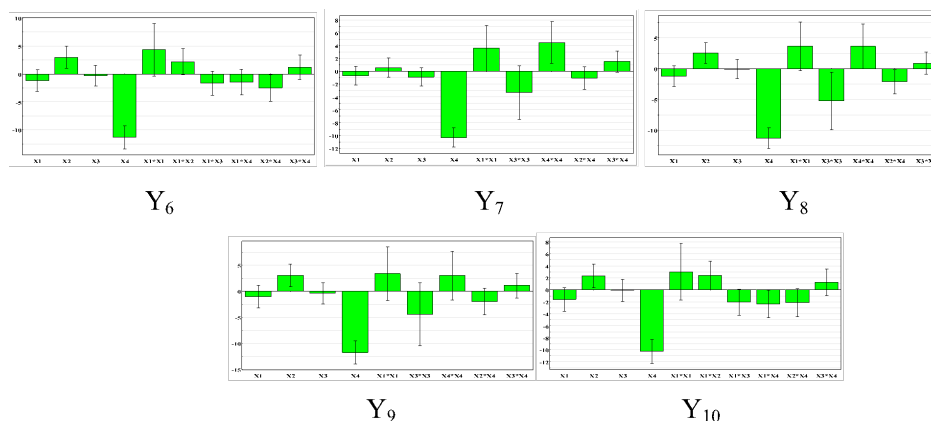


Figure 5.

The influence of the formulation factors on the dissolution profile of meloxicam
 Y_6 – % of meloxicam released at 5 minutes; Y_7 – % of meloxicam released at 10 minutes; Y_8 – % of meloxicam released at 15 minutes; Y_9 – % of meloxicam released at 20 minutes; Y_{10} – % of meloxicam released at 30 minutes; X_1 – Superdisintegrant ratio; X_2 – Compressive force; X_3 – Sweeteners ratio; X_4 – Diluents ratio.

The highest percentage of released meloxicam, after 5 minutes, was 45.26%; after 30 minutes, the highest dissolution rate was 93.39% - registered for tablets containing large amounts of MCC and CCS. *In vitro* dissolution of meloxicam was strongly influenced by X_4 formulation factor, meaning that the increase in Man content, while decreasing the MCC, determined a lower dissolution rate for meloxicam. The results can be explained by the fast disintegration induced by MCC that leads to a higher percent of dissolved meloxicam at a certain time. Dissolution after 10 minutes was only influenced by X_4 , but the data shows that at 5, 15, 20 and 30 minutes, the compression force (X_2) increase determined a faster meloxicam release. After 10 and 20 minutes of dissolution, strong interactions between $X_2 * X_4$ were obtained, indicating that simultaneous increases in compression force and mannitol percentage determine slow meloxicam release. Therefore, the fast dissolution noted at high hardness values occurs only at high MCC contents.

Analysis of the influence of formulation factors on the in vivo evaluation of tablets. The disintegration times reported by the volunteers were short, ranging between 25 and 133s. Equation coefficients used for fitting the experimental data obtained at *in vivo* evaluation are represented graphically as histograms in Figure 6. The oral disintegration time (Y_{11}) was influenced by the same factors as the *in vitro* disintegration time – the compression force and the diluent ratio. The most influential factor was the compression force, whose rise determined a delayed disintegration. Second was the diluent mixture that improved oral disintegration times at high

percentages of MCC. A strong interaction was observed between X_2 and X_4 , meaning that high compression forces applied on a mixture containing high percentages of Man, determined low oral disintegration times. X_3 and X_4 also interacted – high contents of Sach and Man rushed the disintegration. The taste (Y_{12}) was first influenced by the diluent ratio and secondly, by the sweeteners. High percentages of Man gave a pleasant taste to the tablets and so did the interaction between increased Man content (X_4) and Sach (X_3). The residual volume (Y_{13}) decreased with the increase in Man and SSG contents, due to their high water solubility. Larger volumes of residue were reported for the formulations containing insoluble and/or highly swellable excipients, like CCS and MCC.

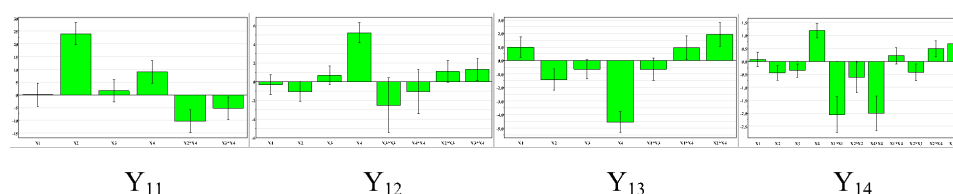


Figure 6.

The influence of the formulation factors on the *in vivo* evaluation

Y_{11} – *In vivo* disintegration time; Y_{12} – Taste; Y_{13} – Residual volume; Y_{14} – Palatability; X_1 – Superdisintegrant ratio; X_2 – Compressive force; X_3 – Sweeteners ratio; X_4 – Diluents ratio.

The palatability is a global parameter that brings together all the other subjective characteristics: disintegration speed, taste, texture, residual volume, mouth feel. A good palatability was reported for tablets with low crushing strength and that contained high percentages of Man and Asp.

Optimal formula determination. The optimal formulation was determined using the Modde 6 software. The conditions for the obtaining of the highest crushing strength, shortest disintegration time and best palatability were generated. The optimal formulation contained 4.14% CCS, 10.86% SSG, 63.10% MCC, 15.14% Man, 0.16% Sach, and 1.84% Asp and was compressed using a low compression force.

Conclusions

From this experimental design we can conclude that the most influential factors on tablets' characteristics are the diluents' ratios and the compression forces. Low compression forces and high a MCC content yield fast disintegration, yet maintaining the official requirements on the physical properties of the orodispersable tablets. At 15% total disintegrant content, the percentages of SSG and CCS had no influence on the disintegration

time, but more CCS determined slower water absorption by wicking, while SSG favoured the incorporation of high amounts of water. The *in vivo* disintegration time was influenced by the same factors as the *in vitro* disintegration, and the palatability evaluation favoured the pleasant taste and mouth feel to a short disintegration time and high resistance.

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