

OPTIMIZATION BY EXPERIMENTAL DESIGN OF AN IMMEDIATE RELEASE TABLET FORMULATION COMPRISING METFORMIN AND GLIBENCLAMIDE

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Abstract

The association of metformin and glibenclamide presents notable advantages with respect to the administration of the two active ingredients separately, because it significantly improves the compliance in older patients and in patients subjected to polytherapy with other drugs.

The aim of this study consisted in developing a formulation of an immediate release tablet that contained 500 mg metformin and 2.5 mg glibenclamide and optimizing it in order to attain a similar dissolution profile to the innovator product (Glucovance[®]).

The statistical method employed was Partial Least Squares multilinear regression, using Modde 9.0 Umetrics software. The tablets obtained according to the experimental plan were evaluated regarding the release of metformin hydrochloride and glibenclamide using validated HPLC methods.

The results demonstrated that the optimal formulation corresponded to the specifications of the European Pharmacopoeia 6th edition for immediate release coated tablets with a very similar dissolution profile to the innovator product (Glucovance[®]), f_2 (similarity factor) showing values of 92.89 for the release of glibenclamide and of 90.98 for the release of metformin.

Rezumat

Asocierea în terapie a metforminului cu glibenclamida prezintă avantaje notabile administrării separate a acestor doi agenți antidiabetici, deoarece asigură îmbunătățirea semnificativă a complianței la pacienții în vârstă și la cei aflați sub tratament cu multiple medicamente.

Scopul acestei cercetări constă în optimizarea formulării unor comprimate cu eliberare imediată ce conțin 500 mg metformin și 2,5 mg glibenclamidă, în așa fel încât să se obțină profile de eliberare ale substanțelor active similare cu cele corespunzătoare medicamentului inovator.

Metoda statistică de prelucrare a datelor a constat în regresia multilinară multiplă (*Partial Least Squares*), iar implementarea acesteia s-a realizat cu ajutorul softului Modde 9.0 Umetrics Suedia.

Rezultatele studiului s-au concretizat într-o formulă optimă ce corespunde criteriilor impuse de Farmacopeea Europeană editia a 6-a și care prezintă o similaritate foarte bună cu medicamentul inovator (Glucovance®), în ceea ce privește profilele de eliberare *in vitro* pentru cei doi agenți terapeutici.

Keywords: metformin, glibenclamide, experimental design, tablets, dissolution profile

Introduction

The combined sulphonylureas and biguanides treatment assumes an important role in the therapy of type II diabetes, in that it allows an improved metabolic control in those patients in which biguanides or sulphonylureas alone have proved to be ineffective in time. Amongst the two categories of mentioned drugs, the most used for the treatment of type II diabetes are metformin and glibenclamide [5].

The association of metformin and glibenclamide presents notable advantages with respect to the administration of the two active ingredients separately, since it significantly improves the compliance and, in addition, it reduces the risk of error in administration especially in older patients and in patients subjected to polytherapy with other drugs [4, 6]. The aim of this study consists in developing a formulation of an immediate release tablet that contains 500 mg metformin and 2.5 mg glibenclamide and optimizing it in order to attain a similar dissolution profile to the innovator product (Glucovance® that contains 500mg metformin and 2.5mg glibenclamide).

Whether it is to understand or to interpret a phenomenon as in a factor study, or to predict results under different conditions by response surface modelling, a mathematical model that is close enough in its behaviour to that of the real system is required. The models to use are polynomials of coded (normalised) variables, representing factors that are all transformed to the same scale and with constant coefficients. It is the unknown value of each coefficient that must be estimated with the best possible precision by experiments whose position in the experimental factor space is chosen according to the form of the mathematical model postulated. For this to be possible, the number of distinct experiments must be at least equal to the number of coefficients in the model. Calculating estimations of the coefficients cannot be performed manually. The method of Partial Least Squares multilinear regression employed during our study involves the use of a computer program [3].

The experiments were carried out to determine the relationship (in the form of a mathematical model) among the formulation factors acting in

the system and the response or properties of the same system (the system being the pharmaceutical product) [2].

Materials and methods

Materials

Table I
API's (active pharmaceutical ingredients) and excipients used in formulation development

Active ingredients and excipients	Manufacturer
Metformin hydrochloride	Microsin Romania
Glibenclamide micronized	USV India
Glibenclamide non-micronized	Cadila India
Microcrystalline cellulose (Vivapur [®] Type 101)	JRS Pharma Germany
Granulated lactitol monohydrate	Purac Biochem Holland
Croscarmellose sodium (Vivasol [®])	JRS Pharma Germany
Povidone (Plasdone [®] S-630)	ISP, Switzerland
Magnesium stearate (Kemilub [®] EM-F-V)	UNDESA, Spain

Methods

The starting formulation (Table II) has two general quantitative compositions depending on the average weight of the tablet : 600 mg or 620 mg.

Table II
The general qualitative and quantitative composition for the starting formulation

Starting formulation		Metformin hydrochloride	Glibenclamide micronized/ non-micronized	Povidone (intragranular)	Microcrystalline cellulose / Lactitol monohydrate	Povidone (extragranular)	Croscarmellose sodium	Magnesium stearate	Sum
Var. I	%	83.333	0.4166	3	5.45-10.45	0-3	2-4	0.8	100
Var. II		80.645	0.4032	3	8.15-13.15	0-3	2-4	0.8	100
Var. I	mg/	500	2.5	18	32.7-62.7	0-18	12-54	4.8	600
Var. II	tablet	500	2.5	18.6	50.536-81.536	0-18.6	4.8	4.96	620

Micronized/non-micronized glibenclamide was geometrically dispersed into the granules of metformin comprising drug substance and Plasdone[®] S-630. The granulation was performed using a two sigma arms homogenizer-granulator.

The filler (Vivapur 101[®]/LactyTab[®]), the desintegrant (Vivasol[®]) and the rest of the binder (Plasdone[®] S-630) were added to the resulted mix. The homogenization of the active ingredients with the excipients took place into a V-type mixer at 15 rpm, for 10 minutes. The formulations were lubricated with 0.8% magnesium stearate. The final compositions were

compressed on an instrumented rotary press with a medium tableting force. Biconvex round shape tablet tooling with 12.0 ± 0.5 mm diameter was used. Tablet (manufactured according to the experimental plan) physical properties were measured on 20 tablets for friability (Electrolab EF-2 fraibilator), 10 tablets for hardness (Logan HDT 300 Hard.tester) and on 6 tablets for disintegration (Erweka ZT 42). The tablets were evaluated for the release of metformin hydrochloride and glibenclamide using validated HPLC methods. Tablets dissolution was tested on: USP apparatus II paddles Electrolab TDT-08L (100 rpm). The dissolution medium consisted of 900 mL of pH 7.4 phosphate buffer solution and polysorbate 80 0.03%, at a temperature of $37 \pm 0.5^\circ\text{C}$. The similarity factor (f_2) was calculated for the dissolution profiles in order to assure comparative evaluation with the innovator product Glucovance[®]. After the identification of the optimal formulation for the tablets, we proceeded with the coating of the cores using a hydroxypropyl methyl cellulose (HPMC) film. The coating process was performed on O'Hara LabCoat drum and it resulted in a tablet weight gain of 4 %.

The experimental plan was generated by using Modde 9.0 Umetrics software through the variation of five formulation factors (independent variables) on two levels. The independent variables (formulation factors) (Table III) were the following: filler (Microcrystalline cellulose / Lactitol monohydrate) – qualitative variable, desintegrant (2% / 4%) – quantitative multilevel variable, tablet average weight (600 mg / 620 mg) – quantitative multilevel variable, extragranularly added binder (0% / 3%) – quantitative multilevel variable, glibenclamide particle size (micronized / non-micronized powder) –qualitative variable.

Table III
Independent variables and their levels of variation

Independent variables	Abbreviation	Units	Type	Levels of variation
Filler	Fill	-	Qualitative	Microcrystalline cellulose / Lactitol monohydrate
Desintegrant	Dis	%	Multilevel	2/4
Tablet average weight	Mass	mg	Multilevel	600/620
Extragranularly added binder	BindE	%	Multilevel	0/3
Glibenclamide particle size	GlibPS		Qualitative	Micronized / non-micronized powder

The non-independent variables (quality attributes) (Table IV) were the following: friability (variation limits: 0-1 %), hardness (variation limits: 50-120 N), disintegration time (variation limits: 0-240 sec), dissolution profile similarity factor f_2 for the two API's (variation limis: 30-100%, target value: 60 %) (F2G, F2M).

Table IV
Non-Independent variables and their admissibility limits

Non-Independent variables	Abbreviation	Units	Type	Values		
				Min.	Target	Max.
Friability	Fria	%	Regular	0	-	0.1
Hardness	Hard	N	Regular	50	-	120
Desintegration time	Dis	sec	Regular	0	-	240
Dissolution profile similarity factor f_2 (glibenclamide) (F2G)	F2G	%	Regular	30	60	100
Dissolution profile similarity factor f_2 (metformin) (F2M)	F2M	%	Regular	30	60	100

The generated experimental plan contained 36 trials - core formulations, that were tested for their essential quality attributes: friability, hardness, desintegration time and similarity of dissolution profile when compared with the innovator product (Table V).

Results and discussion

The reproductibility of the model was of at least 81.05 % for all the non-independent variables investigated.

Table V
Factorial Design for the Quality Profile of the Uncoated Tablets

Exp. No.	Exp. Name	Run Order	Fill	Dis	Mass	BindE	GlibPS	Fria	Hard	Dis	F2G	F2M
1	N1	18	MCC 101	2	600	0	Micronized	0.42	107	116	42.7	52.2
2	N2	25	Lactitol	2	600	0	Micronized	0.72	75	100	46.3	54.3
3	N3	5	MCC 101	4	600	0	Micronized	0.48	98	56	47.13	57.2
4	N4	22	Lactitol	4	600	0	Micronized	0.89	65	43	56.2	63.5
5	N5	15	MCC 101	2	620	0	Micronized	0.72	99	176	40.5	50.2
6	N6	12	Lactitol	2	620	0	Micronized	0.92	72	156	44.5	52.3
7	N7	32	MCC 101	4	620	0	Micronized	0.8	97	122	43	55.7
8	N8	6	Lactitol	4	620	0	Micronized	0.98	69	102	52.2	61.7
9	N9	3	MCC 101	2	600	3	Micronized	0.38	110	113	57.2	63.1
10	N10	35	Lactitol	2	600	3	Micronized	0.67	82	97	58.1	62.2
11	N11	4	MCC 101	4	600	3	Micronized	0.41	102	54	60.11	60.21
12	N12	29	Lactitol	4	600	3	Micronized	0.75	70	40	71.2	62.3
13	N13	13	MCC 101	2	620	3	Micronized	0.62	101	172	52.5	58.2
14	N14	19	Lactitol	2	620	3	Micronized	0.86	80	150	57.5	61.3
15	N15	10	MCC 101	4	620	3	Micronized	0.71	100	116	55	63.2
16	N16	17	Lactitol	4	620	3	Micronized	0.91	73	96	65.3	65.3
17	N17	23	MCC 101	2	600	0	Non-Micronized	0.4	103	117	38.6	50.2

Table V (continued)

Exp. No.	Exp. Name	Run Order	Fill	Dis	Mass	BindE	GlibPS	Fria	Hard	Dis	F2G	F2M
18	N18	26	Lactitol	2	600	0	Non-Micronized	0.73	78	97	41.3	52.7
19	N19	14	MCC 101	4	600	0	Non-Micronized	0.52	97	57	42.5	54.3
20	N20	24	Lactitol	4	600	0	Non-Micronized	0.85	67	45	52.3	60.5
21	N21	33	MCC 101	2	620	0	Non-Micronized	0.78	100	188	48.9	51.2
22	N22	20	Lactitol	2	620	0	Non-Micronized	0.9	76	162	51.6	56.7
23	N23	27	MCC 101	4	620	0	Non-Micronized	0.82	96	127	52.7	63.5
24	N24	34	Lactitol	4	620	0	Non-Micronized	0.97	70	107	63.5	67.8
25	N25	9	MCC 101	2	600	3	Non-Micronized	0.37	109	114	54.2	63.2
26	N26	11	Lactitol	2	600	3	Non-Micronized	0.65	86	93	56.1	65.25
27	N27	30	MCC 101	4	600	3	Non-Micronized	0.45	103	58	58.13	60.25
28	N28	8	Lactitol	4	600	3	Non-Micronized	0.76	71	41	62.3	68.5
29	N29	31	MCC 101	2	620	3	Non-Micronized	0.65	104	179	53.2	55.5
30	N30	16	Lactitol	2	620	3	Non-Micronized	0.83	85	159	65.3	67.3
31	N31	1	MCC 101	4	620	3	Non-Micronized	0.78	101	120	69.3	68.2
32	N32	21	Lactitol	4	620	3	Non-Micronized	0.92	83	99	70.1	69.7
33	N33	28	MCC 101	2	600	0	Micronized	0.41	106	112	40.5	50.3
34	N34	2	MCC 101	2	600	0	Micronized	0.42	107	116	52.6	52
35	N35	7	MCC 101	2	600	0	Micronized	0.44	109	122	45.1	58.3

After performing data fitting the optimal formulation was identified using Contour Plot diagrams generated by Modde 9.0 (figure 1). The influence of the formulation factors on the quality profile of the uncoated tablets was tested.

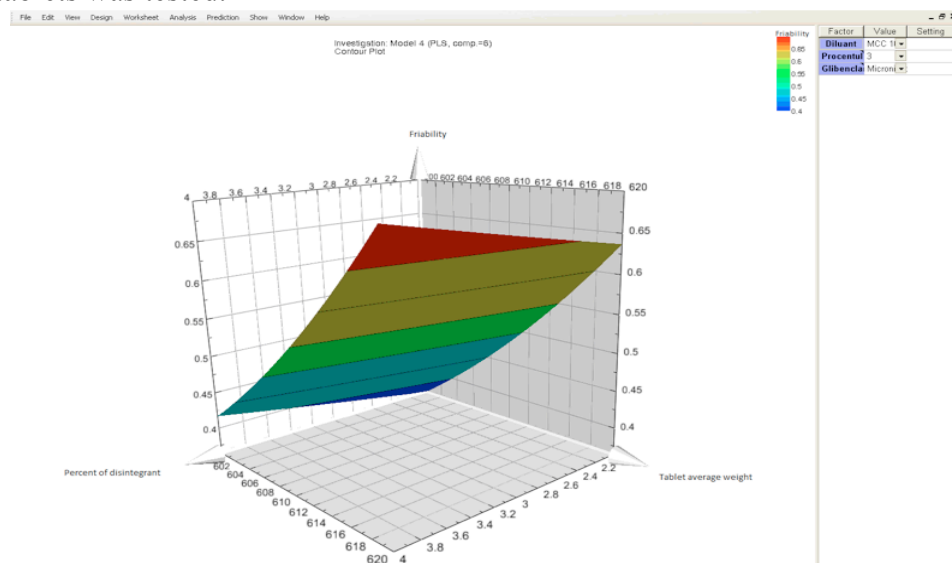


Figure 1
Contour Plot diagram for prototype formulation 1

Table VI
Quality profile for the optimal formulation (uncoated tablets)

Quality attribute	Admisibility limits
Friability, %	max 0.5
Hardness, N	min 100
Desintegration time, sec	max 80
F2 G	60
F2 M	60

Having as starting point the general formulation, by varying the formulation factors on two levels, the statistical program generated 8 prototype formulations (Table VII).

Table VII
Prototype formulations (uncoated tablets) generated in the statistical investigation

Prototype formulation	1	2	3	4	5	6	7	8
Microcrystalline cellulose	+	+	+	+	-	-	-	-
Lactitol monohydrate	-	-	-	-	+	+	+	+
Povidone (extragranular)	+	-	+	-	+	-	+	-
Glibenclamide micronized	+	+	-	-	+	+	-	-
Glibenclamide non-micronized	-	-	+	+	-	-	+	+

From these 8 prototype formulations, only 1 and 3 met all the requirements specified by the quality profile.

Table VIII
Quality attributes for the optimal formulations (uncoated tablets)

Prototype formulation		Friability (%)	Hardness (N)	Disintegration time (sec)	F2G (%)	F2M(%)	Optimal formulation
1	Admisibility limits	max 0.5	min 100	max 80	60	60	Meets the requirements
	Tablet average weight	600-606	600-620	600-604	600-602	600-614	600-604
	Desintegrant	2-4	2-4	3.6-4	3.8-4	2.6-4	3.8-4
3	Admisibility limits	max 0.5	min 100	max 80	60	60	Meets the requirements
	Tablet average weight	600-606	600-620	600-603	600-603	600-608	600-603
	Desintegrant	2-4	2-4	3-3.7	3.6-4	3.4-4	3.6-3.7

The interpretation of the Contour plot diagrams generated for each prototype formulation resulted in two optimal formulations (Table IX).

Table IX

Quantitative and qualitative composition for the two optimal formulations that corresponded to the quality profile

	Optimal formulation 1		Optimal formulation 2	
	(%)	(mg)	(%)	(mg)
Metformin hydrochloride	83.333	500.0	83.333	500.0
Glibenclamide micronized	0.417	2.5	-	-
Glibenclamide non-micronized	-	-	0.417	2.5
Povidone (intragranular)	3.000	18.0	3.000	18.0
Microcrystalline cellulose	5.450	32.7	5.660	34.5
Povidone (extragranular)	3.000	18.0	3.000	18.0
Croscarmellose sodium	4.000	24.0	3.700	22.2
Magnesium stearate	0.800	4.8	0.800	4.8
Purified water*				
Sum	100.000	600.0	100.000	600.0

*used for the granulation of metformin hydrochloride

The results for the *in vitro* release of metformin hydrochloride and glibenclamide from the coated tablets are presented in Tables X and XI.

Table X

Percentages of metformin dissolved at four sampling times
(coated tablets)

Optimal formulation	Sampling time (minutes)			
	15	30	45	60
1	96.79	97.04	97.56	96.41
<i>Std. Dev.</i>	0.657	0.560	0.563	0.361
2	90.41	94.44	94.55	91.49
<i>Std. Dev.</i>	0.653	0.595	0.566	0.485
Glucovance®	97.93	97.63	97.22	95.02
<i>Std. Dev.</i>	0.545	0.528	0.471	0.565

Table XI

Percentages of glibenclamide dissolved at four sampling times
(coated tablets)

Optimal formulation	Sampling time (minutes)			
	15	30	45	60
1	80.10	85.30	89.91	88.30
<i>Std. Dev.</i>	0.417	0.675	0.360	0.598
2	68.92	75.40	80.70	80.20
<i>Std. Dev.</i>	0.545	0.652	0.407	0.493
Glucovance®	78.85	86.55	88.50	88.05
<i>Std. Dev.</i>	0.444	0.528	0.577	0.594

The dissolution profiles corresponding to the two active principles for Optimal formulation 1 and 2 and for Glucovance® are depicted in figure 2 and figure 3.

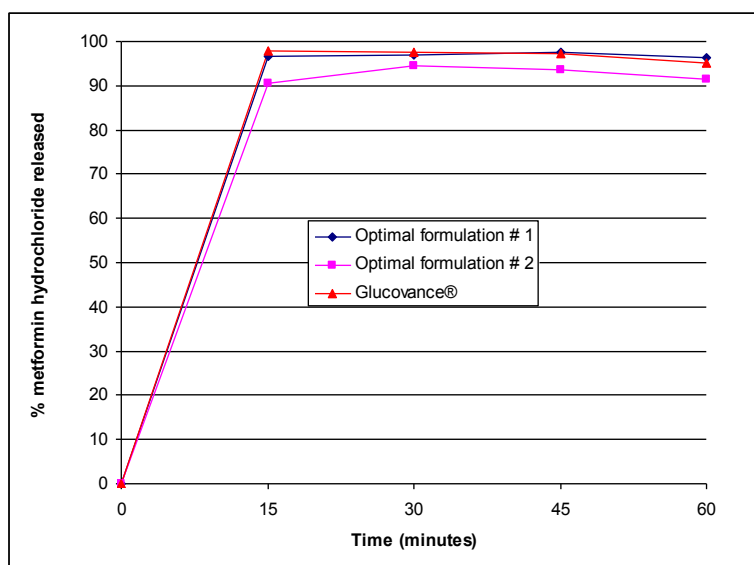


Figure 2

Metformin hydrochloride dissolution profile for Optimal formulation 1, 2 and Glucovance®

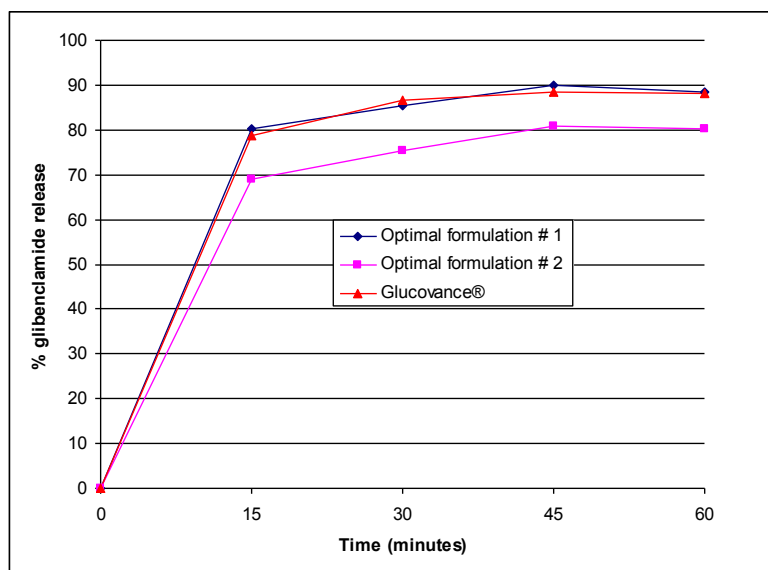


Figure 3

Glibenclamide dissolution profile for Optimal formulation 1, 2 and Glucovance®

Conclusions

The results from the dissolution tests demonstrated that the two optimal formulations corresponded to the specifications of the European Pharmacopoeia 6th edition for immediate release coated tablets [1]. The dissolution profile of the optimal formulation 1 is very similar to the innovator product (Glucovance[®]), f_2 showing values of $F2G = 92.89$ and $F2M = 90.98$.

The optimal formulation 2 presented lower values for the similarity factor corresponding to the two active principles: $F2G = 65.42$ and $F2M = 51.46$.

The pharmacotechnical attributes of the two optimal formulations (friability, hardness, dissolution time and dissolution profile similarity) corresponded to the target quality profile instituted for the final dosage form – uncoated tablets.

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