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A study on the influence of the formulation factors on in vitro release of ketoprofen from sustained release tablets

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Abstract

Objectives. *The aim of this study was to investigate the influence of formulation factors on in vitro release of ketoprofen from sustained release inert matrix tablets.*

Materials and methods. *Laboratory scale, Ketoprofen sustained release inert matrix tablets were manufactured using Kollidon® SR as matrix formator, by direct tableting of powder blends. The influence of the formulation factors (X1 – matrix formator excipient and X2 – diluent type) on in vitro release of ketoprofen from sustained release tablets was studied by using a full factorial 23 experimental plan.*

Outcomes. *Pharmacotechnical characterization of manufactured laboratory scale batches was performed and all 12 batches fulfilled European Pharmacopeia requests. In vitro release showed a sustained release profile in all cases. Variance analysis (ANOVA) showed a good correlation between experimental conditions and answers. In vitro release testing was performed in phosphate buffer pH = 7.4. Percentage release was determined spectrophotometrically at 258 nm. A decrease in the rate of in vitro release was registered, up to 4 h and 6 h when lactose DC and mannitol DC were used as diluents, respectively. Isomalt DC has increased the rate of in vitro release up to 6 h.*

Conclusions. *In vitro release data, corresponding to formulation N1 shoed a good fitting with Weitbull, Korshmeyer-Peppas and Higuchi models while in vitro release data corresponding to formulation N8 presented a good fitting with Weitbull and Korsmeyer-Peppas. In case of formulations N1 and N8 a non-Fickian diffusion mechanism seems to be involved in drug release from the matrix tablets.*

Keywords: *in vitro* release, formulation factors, drug-release models, ketoprofen, inert matrix

INTRODUCTION

Preparation of solid pharmaceutical dosage forms with poor water soluble active pharmaceutical ingredients is still a challenge for any galenic development scientist [1].

The bioavailability of ketoprofen (low solubility and high permeability) is limited by dissolution rate [2]. Excretion rate is quite high (about 50% of the drug is eliminated in the first 6 h). The excretion process is not modified when sustained release dosage forms are employed [3].

Ketoprofen is a good candidate for a sustained release formulation due to it`s properties/characteristics: it is quickly, fast and uniformly absorbed throughout the

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gastrointestinal tract, it has a short half-life, it is highly bound to plasma proteins. More, the bitter taste of ketoprofen must be masked and also the gastric mucosa must be protected from the irritation it may cause [4].

Modified-release dosage forms have gained much attention in the last half a century. Modified-release dosage forms, despite immediate release dosage forms can increase patient compliance and can offer some benefits: reducing the number of administrations, adequate plasmatic concentrations for a long period of time, enhanced bioavailability and compliance, low incidence of side effects [5].

Due to its excellent pharmaceutical properties (flowablity, compressibility etc), Kollidon® SR is often used in the manufacturing of sustained release inert matrix type tablets [6].

Several papers described different preparations of matrix type tablets with ketoprofen. The role of excipients in modulating drug released was discussed [7-9].

The aim of this paper was to investigate the influence of formulation factors (matrix formator percentage and diluent type) on the release of ketoprofen from sustained release tablets, inert matrix type.

MATERIALS AND METHODS

Materials

Ketoprofen was supplied by S&D Chemical, UK. As diluents, directly compressible lactose (lactose DC) (Supertab 14 SD) from DMV-Fonterra Excipients GmbH&Co, Germany; directly compressible mannitol (mannitol DC) (Parteck M200) from Merck, Germany; directly compressible isomalt (isomalt DC) (GalenIQ 721) from BENEO-Palatinit GmbH, Germany were used. As matrix-forming excipient Kollidon® SR, from BASF-Germany, was used. Hydrophilic fumed silica (Aerosil® 200), manufactured by Degussa AG – Germany was used as flow improver of powder blends and also as anticaking agent. Lubricant (magnesium stearate) was supplied by Merck, Germany.

Reagents

Monopotassium phosphate and sodium hydroxide were supplied by Cristal R Chim, Romania and POCH Basic, Poland, respectively. All reagents were analytical grade. All experiments were performed using distilled water.

Experimental design

Twelve formulations (laboratory batches) were manufactured according to a full-factorial experimental design with 2 factors and 3 levels. The experimental design, statistic parameters calculation and quality of fitting were performed by using Modde 12.0 (Sartorius Stedim Data Analytics AB, Sweden). Partial Least Squares (PLS) was chosen as a multivariate model. All formulation contained 100 mg ketoprofen/tablet and consisted of tablets with a total weight of 430 mg.

The independent factors, or formulation factors (Table 1), were matrix forming agent percent (X1) and the type of diluent (X2).

TABLE 1. Independent factors (formulation factors)

Factors	Symbols	Levels		
		-1	0	1
Kollidon® SR (%)	X_1	25	40	55
	X_2	Lactose DC	Mannitol DC	Isomalt DC

Experimental design matrix is presented in Table 2.

TABLE 2. Experimental design matrix

Sample	Run Order	X_1	X_2
N1	7	25	Lactose DC
N2	11	40	Lactose DC
N3	4	55	Lactose DC
N4	12	25	Mannitol DC
N5	9	40	Mannitol DC
N6	2	55	Mannitol DC
N7	3	25	Isomalt DC
N8	10	40	Isomalt DC
N9	6	55	Isomalt DC
N10	1	40	Lactose DC
N11	8	40	Lactose DC
N12	5	40	Lactose DC

The dependent variables or responses are presented in Table 3.

TABLE 3. Dependent variables (responses)

Number	Responses	Symbols
1	Release percentage after 0.5 h	Y1
2	Release percentage after 1.0 h	Y2
3	Release percentage after 1.5 h	Y3
4	Release percentage after 2.0 h	Y4
5	Release percentage after 3.0 h	Y5
6	Release percentage after 4.0 h	Y6
7	Release percentage after 5.0 h	Y7
8	Release percentage after 6.0 h	Y8
9	Release percentage after 8.0 h	Y9
10	Release percentage after 10.0 h	Y10
11	Release percentage after 12.0 h	Y11

Tablets preparation

All powders were weighed on a three decimal places balance (Sartorius, Germany), passed through a 700 µm sieve and mixed in Mixer Y5, Y-shaped mixing vessel (Erweka, Germany). Tablets were prepared by means of direct compression method using an eccentric tablet press Korsch EK-0 (Korsch, Germany) equipped with an 8 mm die, with flat punch. Qualitative and quantitative composition of tablets (types 1-3) is presented in Table 4.

TABLE 4. Qualitative and quantitative composition of tablets

	Type 1		Type 2		Type 3	
	mg	%	mg	%	mg	%
Ketoprofen	100.0	23.2	100.0	23.2	100.0	23.2
Kollidon SR	107.5	25.0	172.0	40.0	236.5	55.0
Diluent	219.3	51.0	154.8	36.0	90.3	21.0
Aerosil	1.1	0.3	1.1	0.3	1.1	0.3
Magnesium stearate	2.2	0.5	2.2	0.5	2.2	0.5
TOTAL	**430.0**	**100**	**430.0**	**100**	**430.0**	**100**

Pharmacotechnical characterization of tablets

For all tablet batches the determination of the following parameters was performed: uniformity of mass, friability and crushing strength.

Uniformity of mass was determined on 20 tablets, for each batch, according to European Pharmacopoeia – Uniformity of mass single-dose preparations, monograph.

Friability determination was performed on 20 tablets, for each batch, according to European Pharmacopoeia (Friability of uncoated tablets – monograph) using friability tester TA from Erweka GmbH, Germany.

Crushing strength was determined, on 10 tablets, according to European Pharmacopoeia (Resistance to crushing of tablets) with 6D tablet hardness tester (Dr. Schleuniger, Pharmatron, Switzerland).

***In vitro* release of ketoprofen from sustained release tablets**

In vitro release was tested by means of a dissolution tester (PT-DT7 PharmaTest, Germany) equipped with rotative basket (No. 1), according to corresponding monograph in United States Pharmacopoeia. Dissolution media (900 ml) was a phosphate buffer solution with pH = 7.4, thermostated at 37±0.5ºC. In all cases USP/EP Borosilicate glass vessel were used. Stirring speed was 100 rpm.

Each time 5 ml o dissolution samples were extracted and replaced with fresh dissolution media in order to keep constant the dissolution media volume (900 ml). Sampling times were: 0.5-1-1.5-2-3-4-5-6-8-10-12 hours. After filtering and appropriate dilutions of samples, the absorbance was measured at 258 nm by means of Specord 200 Plus spectrophotometer (Analytik Jena, Germany). In all tests phosphate buffer (pH = 7.4) was used as blank.

Release kinetics and statistical comparison of in vitro release profiles

Modeling of dissolution profiles was performed by means of DDSolver [10, 11]. Tested kinetic models and corresponding equations are presented in Table 5.

TABLE 5. Kinetic models and equations

Model	Equation
First order	$F= k_0 \times t$
Higuchi	$F= k_H \times t^{1/2}$
Korsmeyer-Peppas	$F= k_{KP} \times t^n$
Baker-Lonsdale	$3/2\times[1-(1-F/100)^{2/3}]-F/100= k_{BL} \times t$
Weitbull_1	$F=100\times(1-e^{-(t-Ti)\beta/\alpha})$

Drug release mechanism, according to Korsmeyer-Peppas equation are presented in Table 6 [12, 13].

Evaluation of the goodness of fit of the kinetic model includes the calculation of several parameters:

TABLE 6. Diffusion mechanisms related to Korsmeyer-Peppas

n value	Mechanism
n<0.5	Quasi-Fickian diffusion
0.5	Fickian diffusion
0.5<n<1.0	Anomalus (non- Fickian) diffusion
1	Non- Fickian case II
n>1.0	Non- Fickian super case II

coefficient of determination (R2) and, meaningful, adjusted coefficient of determination (R2adj) [10,11].

RESULTS AND DISCUSSION

Pharmacotechnical characteristics of tablets

For each tablet batch uniformity of mass, friability and crushing strength fulfilled requests of European Pharmacopoeia (data not shown).

In vitro release of ketoprofen

In vitro release profiles of ketoprofen are presented in Figure 1. In case of all formulations a sustained release is observed.

Experimental data fitting with the model

Variance analysis (ANOVA test) is used to test if results variability is due to formulation factors modification or it represents a natural variation related to phenomenon.

ANOVA test results showed good results for all dependent variables ($p < 0.05$ for the model and also $p > 0.05$ for error). According to data resulted from fitting with the model a good correlation between experimental conditions and experimentally obtained answers.

Results obtained by data fitting using PLS method are presented in figure 2.

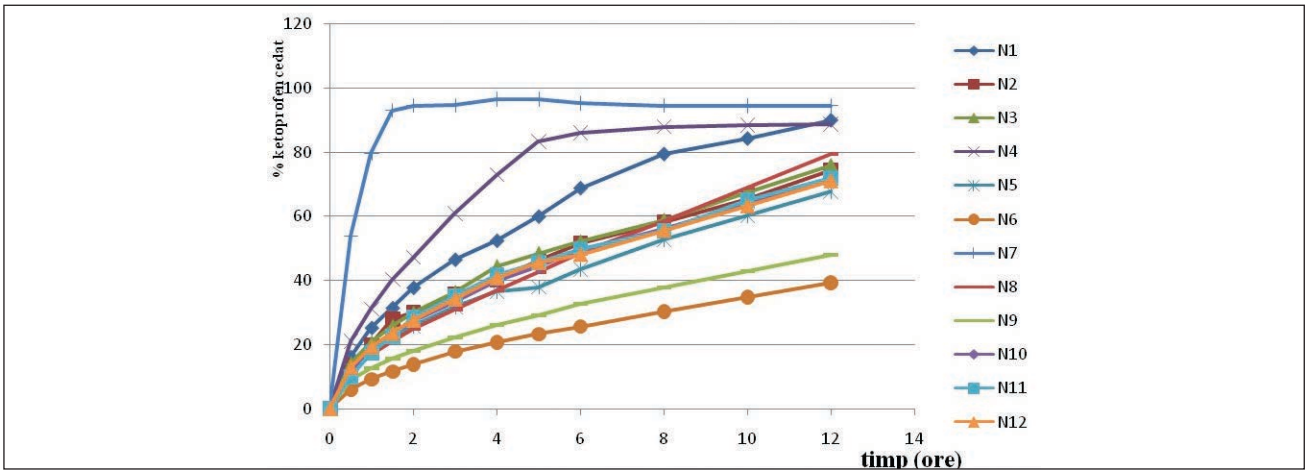

FIGURE 1. Ketoprofen release profiles for rotative basket apparatus (100 rpm)

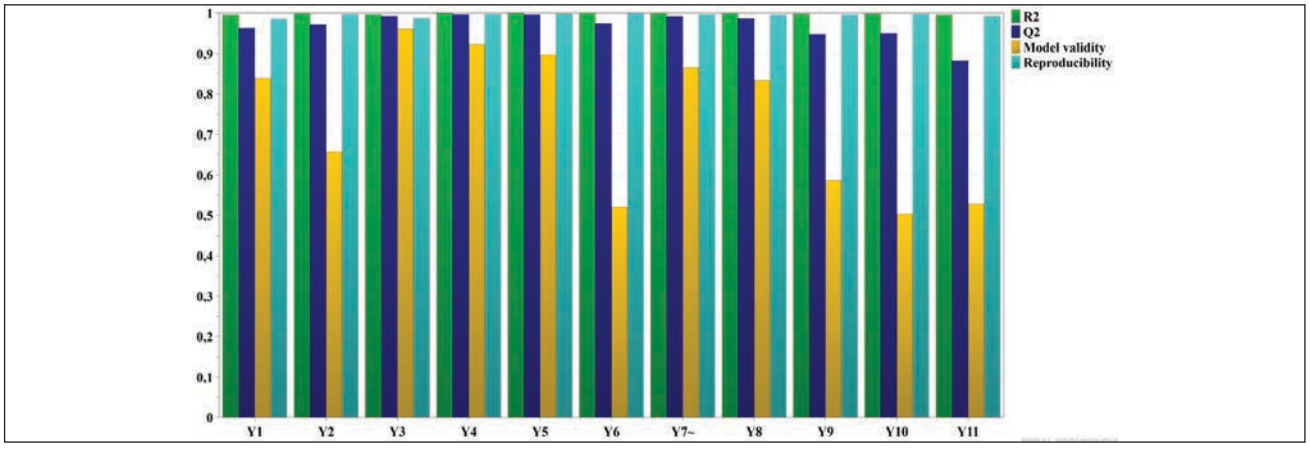

FIGURE 2. Results obtained by data fitting using PLS method. Y1- % release at 0.5 h; Y2- % release at 1 h; Y3- % release at 1.5 h; Y4- % release at 2 h; Y5- % release at 3 h; Y6- % release at 4 h; Y7- % release at 5 h; Y8- % release at 6 h; Y9- % release at 8 h; Y10- % release at 10 h; Y11- % release at 12 h

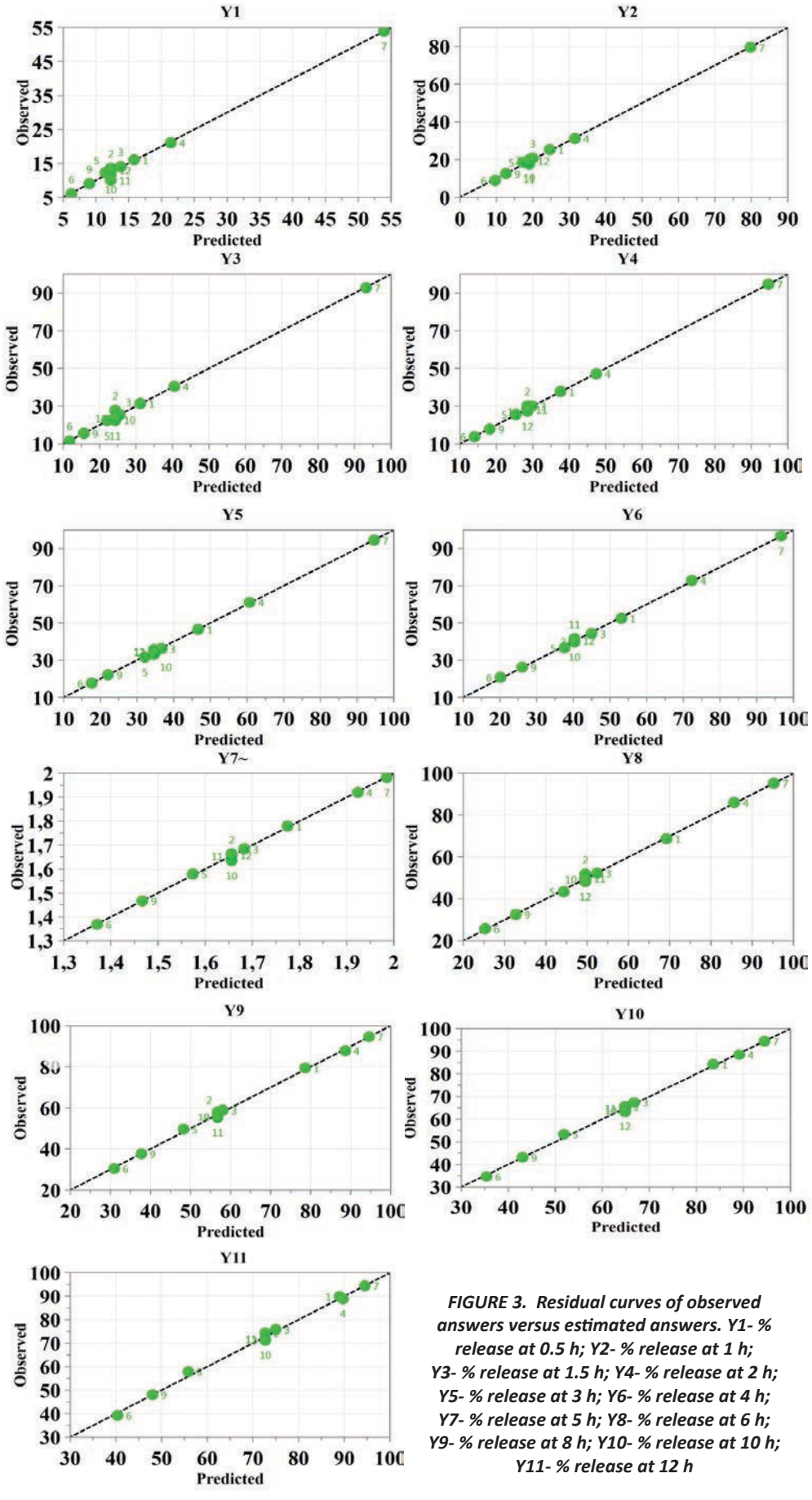

FIGURE 3. Residual curves of observed answers versus estimated answers. Y1- % release at 0.5 h; Y2- % release at 1 h; Y3- % release at 1.5 h; Y4- % release at 2 h; Y5- % release at 3 h; Y6- % release at 4 h; Y7- % release at 5 h; Y8- % release at 6 h; Y9- % release at 8 h; Y10- % release at 10 h; Y11- % release at 12 h

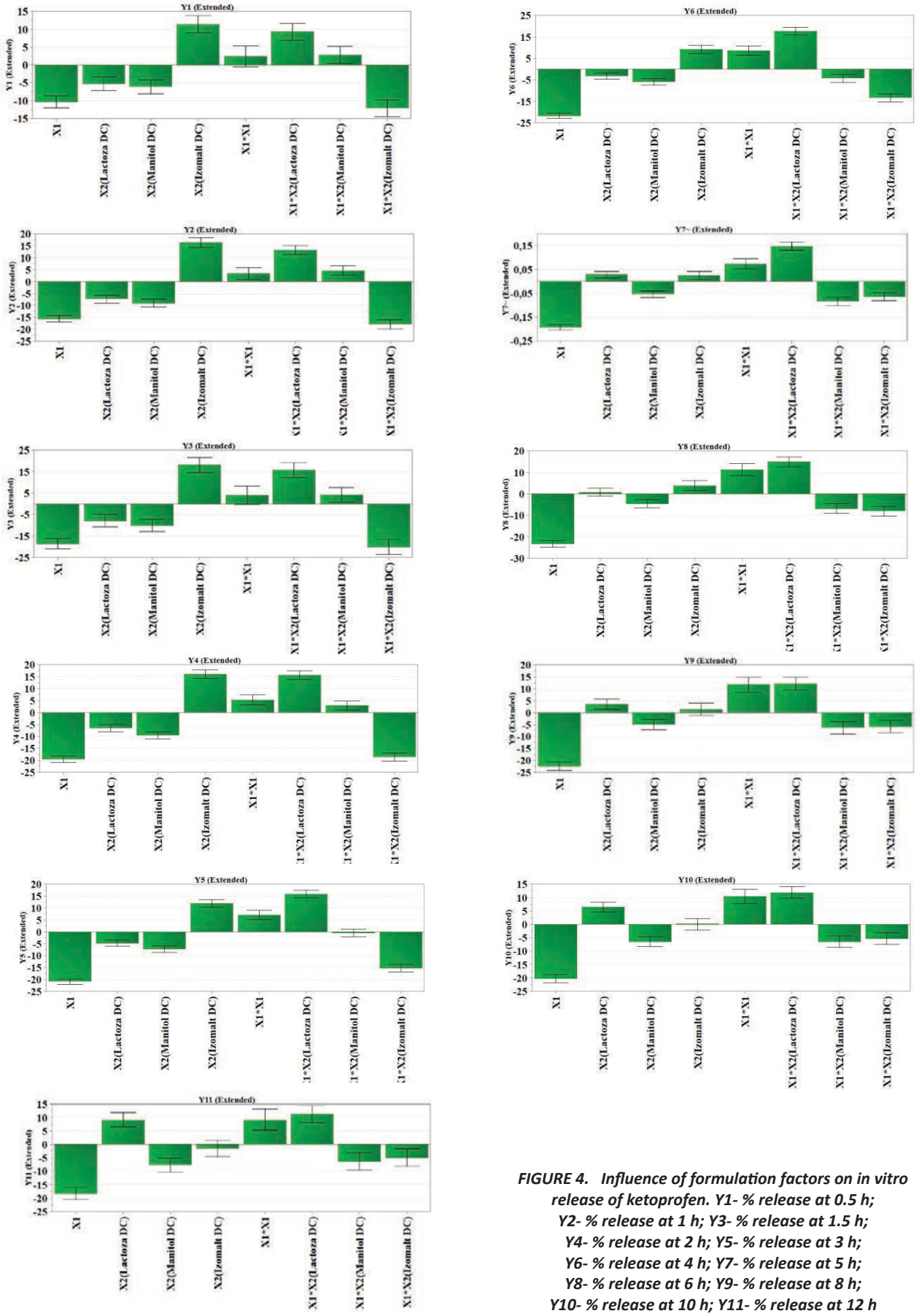

FIGURE 4. Influence of formulation factors on in vitro release of ketoprofen. Y1- % release at 0.5 h; Y2- % release at 1 h; Y3- % release at 1.5 h; Y4- % release at 2 h; Y5- % release at 3 h; Y6- % release at 4 h; Y7- % release at 5 h; Y8- % release at 6 h; Y9- % release at 8 h; Y10- % release at 10 h; Y11- % release at 12 h

Fitting quality evaluation is performed also by means of dependence curves of observed values versus estimated values (residual curves of observed answers versus estimated answers). Curves (Figure 3) indicate a good agreement between obtained results and predicted results (a diagonal at 45° of regression line) and a fair fitting of experimental data with chosen model.

As a conclusion, according to values of R2 and Q2, ANOVA results and residual curves, all answers are fitted satisfactory with chosen model.

Influence of formulation factors on *in vitro* release of ketoprofen

According to obtained data and analyzing coefficients of equation used for experimental data fitting (Figure 4) the following conclusions can be presented:

The matrix formator percentage (X1 - Kollidon® SR), as expected, has the role to slow the release of ketoprofen from tablets. By increasing percentage of matrix formator from 25 to 55%, the release rate is decreased at all release times (Y1-Y11). In case of tablets with increased matrix formator percentage, dissolution media can penetrates with difficulty, observed by a decreased release rate.

The diluent lactose DC (X2) has the role to decrease the release rate, between 0.5 h (Y1) and 4 h (Y6) due to its low solubility in dissolution media resulting in a prolonged release.

The diluent mannitol DC (X2) has the role to decrease the release rate, between 0.5 h (Y1) and 6 h (Y8) due to its low solubility in dissolution media resulting in a prolonged release. The solubility of mannitol DC in dissolution media is higher in comparison with the one of lactose DC.

The diluent isomalt DC (X2) increases the release rate due to its high solubility in dissolution media. Dissolution media can penetrate much easier into the matrix facilitating ketoprofen release. This observation is valid for dissolution times between 0.5 h (Y1) and 6 h (Y8).

FIGURE 5. Matrix tablets before (left) and after (right) in vitro release test

The influence of the dissolution on matrix tablets is observed in figure 5.

By analyzing Figure 5 it can be observed that tablets are inert matrix type due to the fact that the matrix has was not eroded during in vitro release test. The matrix remained intact, just a light swelling process can be observed (mostly in diameter).

***In vitro* release profiles modeling**

Two dissolution profiles were fitted by First order, Weitbull, Korsmeyer-Peppas and Higuchi models (Table 7).

In case of N1 formulation, good fitting was achieved by using Weitbull, Korsmeyer-Peppas and Higuchi models while a fair fitting was achieved by using First order model. Release kinetics of formulation N8 was good fitted by Weitbull and Korsmeyer-Peppas models while using First order and Higuchi models a fair goodness of fit was obtained. A non-Fickian diffusion mechanism seems to be involved in drug release, considering formulations N1 and N8.

TABLE 7. Goodness of fit for kinetic release models for ketoprofens

Kinetic model	First order		Weitbull		Korsmeyer-Peppas			Higuchi	
Formulation	R^2	R^2_{adj}	R^2	R^2_{adj}	n	R^2	R^2_{adj}	R^2	R^2_{adj}
N1	0.9725	0.9725	0.9966	0.9958	0.544	0.9930	0.9922	0.9927	0.9927
N8	0.9728	0.9728	0.9963	0.9953	0.610	0.9969	0.9965	0.9589	0.9589

CONCLUSIONS

Based on a full factorial experimental plan, with 2 factors and 3 levels, a total of 12 formulations (inert matrix type) with ketoprofen were manufactured by means of direct tableting of powder blends. Independent variables were matrix forming agent percentage (Kollidon® SR) and diluent type (lactose DC, mannitol DC and isomalt DC).

Pharmacotechnical characterization of tablets showed a fulfill of pharmacopeial requests (uniformity of mass, friability and crushing strength).

The majority of the formulations presented a sustained release profile (for almost 12 h) while performing *in vitro* release test. Results (answers) were well fitted with chosen model meaning a good agreement between obtained results and predicted results was found.

By analyzing coefficients of equation used for experimental data fitting it can be concluded that matrix formator percentage has the most significant influence on ketoprofen release. Increasing this percentage of Kollidon® SR from 25% to 55% a decrease in release rate was observed resulting in a sustained release profile. While some diluents (lactose DC and mannitol DC) are able to decrease release rate (for the first 6 or 7 hours), isomalt DC increased release rate for the first 7 hours, due to its high solubility in dissolution media.

The release kinetics of two formulations (N1 and N8) presented a good fitting with Weitbull and Korsmeyer-Peppas models while a fair goodness of fit was observed by fitting data with First order and Higuchi models.

Inert matrix type sustained released tablets containing ketoprofen (a substance insoluble in water and with a short half-life) were manufactured using Kollidon® SR as matrix formator by means direct tableting. Formulations presented a sustained release profile for 12 h.

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