

BINDER AND SUPERDISINTEGRANT INFLUENCE ON THE PROPERTIES OF ORALLY DISINTEGRATING HIGH DOSES ACETAMINOPHEN TABLETS

GRAȚIELA POPA^{1*}, LĂCRĂMIOARA OCHIUZ¹, IULIAN
STOLERIU², IULIANA POPOVICI¹

¹University of Medicine and Pharmacy „Gr. T. Popa” Iași, Faculty of
Pharmacy, 16 Universității st., 700115.

² University „Al. I. Cuza” Iași, Faculty of Mathematics

*corresponding author: gratielapopa@yahoo.com

Abstract

The purpose of our study was the formulation and preparation of orally disintegrating tablets (ODT) containing an analgesic combination: a high dose of acetaminophen (500mg) and codeine phosphate (35 mg). The tablets were prepared by wet granulation using a combination of binders (Gelucire 44/14-Kollidon VA64). Formulation variables were: the proportion of binder Kollidon VA64 (0-3%) and the proportion of superdisintegrant Ac-Di-Sol (2-9%). All formulations contained a proportion of 2% Gelucire 44/14. The response variables to be analysed were hardness, friability and disintegration time of the tablets. Factorial analysis of data showed a high influence of Kollidon proportion on hardness and disintegrating time of the tablets and a minimum value of 1% Kollidon was set for satisfactory friability values. The proportion of Ac-Di-Sol alone had small influence on the response variables. The multiple regression equations revealed a very good prediction model for hardness ($R^2 = 0.85$) and disintegration time ($R^2 = 0.94$), and a good prediction for friability ($R^2 = 0.75$).

Rezumat

Cercetarea are în vedere formularea și prepararea de comprimate orodispersabile cu o asociere analgezică de paracetamol/fosfat de codeină (500/35 mg). Metoda de preparare a fost granularea umedă cu o soluție alcoolică de lianți (Gelucire 44/14-Kollidon VA64). Ca variabile independente de formulare s-au ales: proporția de liant Kollidon VA64 (0-3%) și proporția de superdezagregant Ac-Di-Sol (2-9 %), păstrând constantă proporția de Gelucire în toate formulele (2%). Ca variabile de răspuns s-au analizat proprietățile comprimatelor: duritatea, friabilitatea, timpul de dezagregare. Analiza statistică factorială aplicată a pus în evidență o influență semnificativă a proporției de liant Kollidon asupra durității și timpului de dezagregare, iar pentru o friabilitate redusă a comprimatelor s-a stabilit o valoare prag minimă de 1% liant. Proporția de Ac-Di-Sol ca variabilă separată a manifestat o influență redusă asupra variabilelor de răspuns. Ecuațiile de regresie multiplă aplicate sugerează o capacitate de predicție bună a modelului propus pentru variabilele duritate ($R^2 = 0,85$) și timp de dezagregare ($R^2 = 0,94$), și o capacitate de predicție bună pentru variabila friabilitate ($R^2 = 0,75$).

Keywords: Orally disintegrating tablets, Acetaminophen, Gelucire.

Introduction

Orally disintegrating tablets (ODT) represent a modern solid dosage form, which is nowadays formulated with many analgesic drugs, due to its easy administration without the need of water and fast release of substances [8,9,10]. The purpose of our study was the formulation and preparation of ODT with a high dose of acetaminophen in a synergic combination with codeine phosphate [5,6]. Formulating high doses in ODT can be challenging, considering that good palatability is a mandatory condition for this dosage form; also, conditions set by standards require good solubility for active drugs in high doses [9]. The preparation was done with a combination of binders, in order to improve the properties of the tablets. Hardness, disintegration time and friability of the tablets were set as response variables to be analysed by statistical factorial analysis.

Materials and methods

Materials: Acetaminophen powder (APAP, Merck); codeine phosphate (COD, Merck). Excipients: Gelucire 44/14 (Gatefosse); Kollidon VA64 (PVP vinylacetate, BASF); Parteck 300 (direct compression mannitol, Merck); croscarmellose (Ac-Di-Sol, FMC Biopolymer); Aerosil 200 (Degussa); Cocoa flavor (Nutella 82130, Etol); sodium saccharine; magnesium stearate (Union Derivan, Spain);

Methods: tablets were prepared by wet granulation of active substances (APAP 500 mg /COD 35 mg) with an alcoholic solution of binders: Gelucire 44/14 and Kollidon VA64 [1,2,5]; granules were passed through a 800 μ m sieve (system TGL 7354/TGLO 4188), followed by drying in the oven (40°C). Granules were further mixed with the disintegrant, extra-filler (Parteck 300 up to 650 mg. total tablet mass), lubricant and glidant [3,4]. Compression of granules was performed on a Korsch EK0 tableting machine, single station, 36 rpm, 12 mm and 13 mm concave punches, 5-10 kN tableting pressure. All formulations contained 2% Gellucire, 1 % magnesium stearate, 0.5% aerosil, 1% flavour and 1% sweetener. The quality control of the tablets analysed the following parameters: hardness (on a Schleuninger apparatus, European Pharmacopoeia); friability (on an EFII friabilator, United States Pharmacopoeia) and disintegration time of the tablets (Romanian Pharmacopoeia, method B, time counted in seconds) [11].

A factorial analysis was performed using SPSS 10 for Windows and Mathematica (Wolfram Research) softwares, in order to find out the influence of some formulation variables on the properties of the tablets [6,7]. The independent variables were: the proportion of binder (Kollidon VA64) from 0 to 3%, noted x_1 and proportion of disintegrant (Ac-Di-Sol)

from 2 to 9%, noted x_2 . The response variables were: hardness (noted y_1); disintegration time (noted y_2); friability (noted y_3).

Results and discussion

Results for response variables (as the properties of compressed tablets) for each formulation containing various proportions of binder (x_1) and disintegrant (x_2) are shown in table I.

Table I
Matrix of factorial analysis

Formula	x_1 % Kollidon	x_2 % Ac-Di-Sol	y_1 hardness (N.)	y_2 disintegration time (s.)	y_3 friability %
I	0	2	24.48	22.20	1.74
II	0.5	5	5.37	19.52	1.58
III	1	7	26.27	27.32	0.12
IV	1.5	9	26.65	30.33	0.50
V	2	5	50.05	60.22	0.27
VI	2	7	30.45	49.13	0.32
VII	2	9	27.40	37.25	0.55
VIII	3	5	65.53	65.98	0.30

The hardness of the tablets was low for formulations I and II (containing zero to very low proportion of Kollidon), and satisfactory for the rest of the formulations (26-65 N). Friability values were all below 1%, except formulations I and II, for the same reasons. The disintegration time of all tablets met the conditions in Pharmacopoeias requirements for ODT (orally disintegrating tablets), which is less than 3 minutes.

A statistical factorial analysis was performed considering the values of independent and response variables: the normalized coefficients (Table II) revealed a high influence of variable x_1 (binder proportion) on variables y_1 (hardness) and y_2 (disintegrating time). The independent variable x_2 (superdisintegrant proportion) had little influence on the response variables (Table II).

Table II
Coefficients and multiple regression equations for prediction of response variables

	x_1 (% Kollidon)	x_2 (% Ac-Di-Sol)	x_1x_2 (% Kollidon, % Ac-Di-Sol)
y_1 (hardness)	1.00	-0.52	0.00
y_2 (disint. time)	1.03	-0.42	0.04
y_3 (friability)	-0.38	-0.24	0.36

Analysing the influence of independent variables together x_1x_2 on response variables, a coefficient value of 0.36 was found for y_3 (friability), which is significant especially considering that each independent variable alone has a small impact. For the other two response variables (y_1 , y_2), addition of independent variables x_1x_2 showed coefficients close to zero. Furthermore, in order to predict the values of disintegration time, hardness and friability of the tablets at any random value of independent variables, multiple regression equations were generated by quadratic approximation. Regression coefficients revealed a very good prediction model for the variables hardness ($R^2 = 0.85$) and disintegration time ($R^2 = 0.94$), and good prediction for the variable friability ($R^2 = 0.75$). The multiple regression equations are:

$$y_1 = 66.7388 + 71.2524 x_1 - 5.0458 x_1^2 - 26.7288 x_2 - 6.4169 x_1x_2 + 2.4010 x_2^2$$

$$(R^2 = 0.85)$$

$$y_2 = 41.2862 + 50.5052 x_1 - 8.6901 x_1^2 - 10.5678 x_2 - 0.4060 x_1x_2 + 0.4094 x_2^2$$

$$(R^2 = 0.94)$$

$$y_3 = 1.6044 - 2.2340 x_1 - 0.3306 x_1^2 + 0.1848 x_2 + 0.1494 x_1x_2 - 0.0287 x_2^2$$

$$(R^2 = 0.75)$$

Conclusions

The granulation of a high dose of acetaminophen with a combination of binders Gelucire 44/14-Kollidon VA64 leads to tablets meeting the basic condition for ODT: disintegration time less than 3 min. Also, satisfactory hardness and low friability are required. For the formulations involved, a limit value of 1% Kollidon VA64, was set for the appropriate friability values of the tablets. A high influence of the variable binder proportion on the response variables hardness and disintegrating time was found. The independent variable superdisintegrant proportion alone had a small influence on the response variables. The two independent variables: proportion of binder, proportion of superdisintegrant were found to interact in the friability expression. For the other two response variables (hardness, disintegration time), the interaction between independent variables was very weak. Applying multiple regression equations, optimal formulations can be selected following the required criteria: short disintegration time, high hardness values and low friability of the tablets. The regression coefficients revealed a very good prediction model for the response variables hardness and disintegration time and a good prediction for the variable friability.

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