

## FORMULATION AND PREPARATION OF ORALLY DISINTEGRATING TABLETS USING INNOVATIVE BINDER

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### Abstract

The present study investigates the use of glyceryl palmitostearate (Precirol ATO 5 – coded PATO) as binder in orally disintegrating tablets (ODT), prepared by melt granulation. PATO has been mentioned in literature for its lipophilic nature and fine powder properties, providing excellent coating and slow release of active drugs, but it can also be used for taste masking purposes, with possible applications in ODT. In order to use it as an ODT excipient, some challenges must be overcome, given its lipophilicity. Our first goal was to study its potential to improve tablet properties (hardness, friability, disintegration time) and provide fast release of the model drug, by setting the optimal proportion to be used in ODT. We investigated a complete  $3^3$  experimental design with 9 formulations containing 300 mg acetaminophen; the independent variables were: proportion of PATO binder (2.5-7.5 %) and proportion of sodium starch glycolate (Explotab) as superdisintegrant (5-10 %). The regression equations and response surface plots showed the validity of the model, and a significant influence of PATO on the response variables: tablet hardness, disintegration time, and active drug release in a short time. We can conclude that Precirol ATO 5 can be used as binder in ODT (not more than 5 %), higher proportions having a slow-release effect. Also, together with 8 % disintegrant, it provides good tablet properties, fast disintegration and a release of 80 % acetaminophen after 10 min.

### Rezumat

Studiul investighează utilizarea excipientului glicerol palmitostearat (Precirol ATO 5- PATO) ca liant în comprimatele orodispersabile (ODT) preparate prin metoda *melt granulation*. PATO are proprietăți lipofile accentuate și o finețe avansată a pulberii, fiind recomandat în literatură ca agent de acoperire, dar și de retardare în comprimate; el poate fi utilizat și ca agent de mascare a gustului, aplicație utilă în formularea ODT. Utilizarea lui în ODT trebuie să depășească inconvenientele legate de lipofilia sa, păstrând calitățile care pot fi utile în acest tip de formulare: îmbunătățirea proprietăților comprimatelor (duritate, friabilitate, timp de dezagregare) și o cedare accelerată a substanțelor active, prin stabilirea unei proporții optime de PATO care să asigure calitățile menționate. Ca substanță-model s-a ales paracetamolul (300 mg/comprimat) și s-a construit un plan experimental complet  $3^3$  cu 9 experimente, în care variabilele independente au fost proporțiile de PATO (2,5-7,5 %) și amidon glicolat de sodiu ca dezagregant (5-10 %). Ecuațiile de regresie și suprafețele de răspuns au confirmat validitatea modelului ales, liantul PATO influențând proprietățile

comprimatelor, dar și cedarea paracetamolului. Putem concluziona că liantul Precirol ATO 5 este util în ODT în proporția maximă de 5 %, peste această limită manifestând un efect de încetinire a cedării. Asociat cu 8 % dezagregant asigură proprietăți corespunzătoare pentru ODT și o cedare a paracetamolului de 80 % după 10 minute.

**Keywords:** Precirol ATO 5, orally disintegrating tablets, acetaminophen

## Introduction

For orally disintegrating tablets (ODT), considering their administration without the need of water, rapid disintegration, good palatability and release of active drug are required [4,7]. The present study investigates the use of a lipophilic binder – glyceryl palmitostearate (Precirol ATO 5; HLB = 2) in orally disintegrating tablets prepared by melt granulation. Precirol ATO 5 has been used as a tablet lubricant, coating agent and in high proportions as matrix former in modified release tablets [1,2,5,10]. The use of Precirol ATO 5 as binder in ODT formulations is innovative, with the final goal of improving tablet properties (hardness, friability, disintegration time) and also as further purpose, taste masking of tablets [3,8]. Considering the lipophilic nature of Precirol ATO 5, a first step of our study was to set a limit amount of the binder in the ODT formulations for fast release of drug through the dissolution test. For that matter, a class 1 model drug was chosen (acetaminophen), and a superdisintegrant was associated, in order to study the interaction between the two excipients in various proportions, *via* factorial analysis.

## Materials and Methods

Materials: acetaminophen (PARA, Chemicals, UK); Precirol ATO 5 - PATO (kindly offered by Gatefossé), sodium starch glycolate (Explotab, JRS Pharma), microcrystalline cellulose (Vivapur 101-JRS Pharma) magnesium stearate (Union Derivan), Aerosil 200 (Degussa). Formulation of tablets was done according to a complete 3<sup>3</sup> experimental design (Table I).

**Table I**  
Matrix of the experimental design

| Formulation | % PATO binder $x_1$ | % Explotab $x_2$ |
|-------------|---------------------|------------------|
| 1.          | 2.5                 | 5                |
| 2.          | 2.5                 | 7                |
| 3.          | 2.5                 | 10               |
| 4.          | 5                   | 5                |
| 5.          | 5                   | 7                |
| 6.          | 5                   | 10               |
| 7.          | 7.5                 | 5                |
| 8.          | 7.5                 | 7                |
| 9.          | 7.5                 | 10               |

**Methods:** Acetaminophen (PARA) was granulated with Precirol ATO 5 through melt granulation, which consisted in continuous mixing of fine powders and heating the mixture at a temperature of 75 °C, above Precirol ATO 5 melting point. The mixture was then cooled at room temperature and passed through an 800 µm aperture sieve. The obtained granules were further mixed with extragranular excipients up to a total tablet mass of 500 mg and then compressed on a Korsch EK0 tableting press (12 mm flat punches, 5 kN tableting pressure). The final tablets contained 300 mg acetaminophen, filler up to 500 mg, 1 % lubricant and glidant respectively. For tablet properties, the following response variables were studied: *tablet hardness* ( $y_1$  - on a Dr. Schleuniger hardness tester), *disintegration time* ( $y_2$ , counted in seconds), *friability* ( $y_3$  - on a EFII friabilator). All methods complied with the Romanian Pharmacopoeia X<sup>th</sup> edition [11]. The release of the model drug was investigated setting as response variables: % PARA after 1 min. ( $y_4$ ), % PARA after 5 min. ( $y_5$ ) and % PARA after 10 min. ( $y_6$ ). The dissolution test was performed on a SR8 Plus Dissolution Test Station (AB&L Jasco), equipped with a V530 spectrophotometer, following the USP protocol for acetaminophen tablets: Apparatus 2, 900 mL of 5.8 pH phosphate buffer solution, 50 rpm [6,9]. All results were statistically interpreted using the *Matlab 7.9* software.

## Results and Discussion

The regression equations and surface plots for the response variables were obtained and showed high influence of the innovative excipient PATO on the tablet properties, as well as on the amount of drug released in a short period of time. The hardness of tablets appeared to be highly influenced by PATO, as the regression equation shows (eq.1.); also, an increase in tablet hardness with higher proportions of PATO can be noticed on the response surface plot (Figure 1.). The disintegration time of tablets was much more influenced by the superdisintegrant (with a coefficient for  $x_2 = 12,562$  – eq.2.), the response surface plot showing minimum disintegration times (< 20 s.) at a value of 8 % Explotab (Figure 2). As for the tablet friability ( $y_3$  variable), the excipient PATO had a minimum influence (eq.3).

$$y_1 = 63.437 + 9.715 x_1 - 6.928 x_2 - 0.227 x_1 x_2 - 0.347 x_1^2 + 0.325 x_2^2 \quad (\text{eq. 1})$$

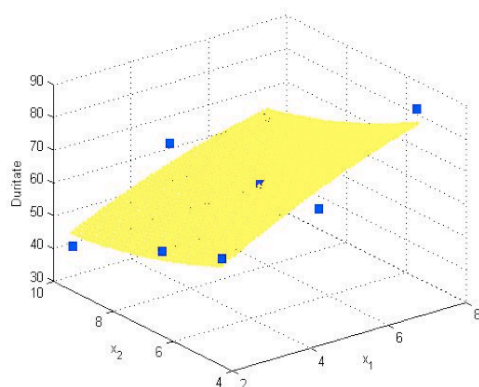
$$\mathbf{R^2 = 0.90}$$

$$y_2 = 58.184 + 2.154 x_1 - 12.562 x_2 - 0.069 x_1 x_2 + 0.296 x_1^2 + 0.783 x_2^2 \quad (\text{eq.2})$$

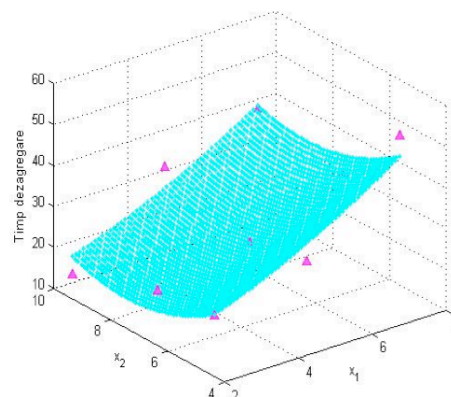
$$\mathbf{R^2 = 0.87}$$

$$y_3 = 1.2591 + 0.045 x_1 + 0.242 x_2 + 0.002 x_1 x_2 - 0.0219 x_1^2 - 0.0132 x_2^2 \quad (\text{eq.3})$$

$$\mathbf{R^2 = 0.85}$$

**Figure 1**

Response surface plot for variable  $y_1$   
(tablet hardness)

**Figure 2**

Response surface plot for variable  $y_2$   
(disintegration time)

The statistic analysis of the variables corresponding to the release of the model drug showed after 1 min. a variation between 56-72 % PARA released, but the regression coefficient of the model ( $R^2 = 0.61$  – eq.4) was less significant compared to the values of the next time intervals. The regression equations showed a higher influence of PATO after 5 min., with an interaction between the variables (eq. 5). The response surface plot (Figure 3) showed a maximum release value after 5 min. (~78 %) for tablets containing 8 % Explotab and 4-5 % PATO. After 10 min, the percent of PARA slightly increased (variable  $y_6$ , Figure 4), with the same values for the independent variables on the surface plot (8 % Explotab and 5 % PATO). The regression equation for variable  $y_6$  (eq. 6) showed a higher coefficient for the independent variable  $x_2$  (indicating the influence of the superdisintegrant).

$$y_4 = 61.749 + 7.331 x_1 - 2.526 x_2 + 0.117 x_1 x_2 - 0.939 x_1^2 + 0.172 x_2^2 \quad (\text{eq.4})$$

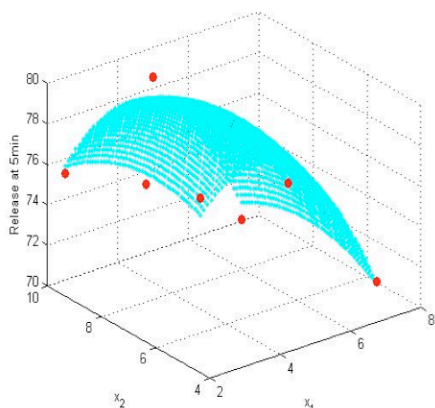
$$\mathbf{R^2 = 0.61}$$

$$y_5 = 60.940 + 5.033 x_1 + 2.277 x_2 + 0.062 x_1 x_2 - 0.660 x_1^2 - 0.181 x_2^2 \quad (\text{eq.5})$$

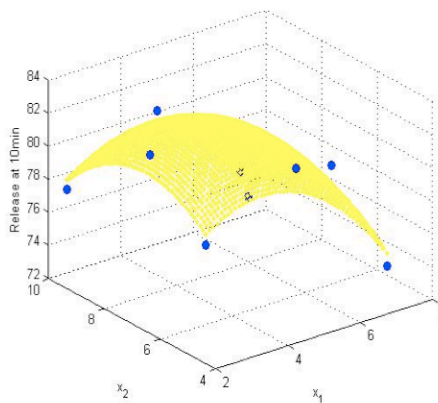
$$\mathbf{R^2 = 0.94}$$

$$y_6 = 54.112 + 4.000 x_1 + 5.440 x_2 + 0.031 x_1 x_2 - 0.508 x_1^2 - 0.385 x_2^2 \quad (\text{eq.6})$$

$$\mathbf{R^2 = 0.80}$$

**Figure 3**

Response surface plot for variable  $y_5$  (%  
*PARA* after 5 min.)

**Figure 4**

Response surface plot for variable  $y_6$  (%  
*PARA* after 10 min.)

### Conclusions

Application of the excipient Precirol ATO 5 in the formulation of orally disintegrating tablets proved to be appropriate associated with sodium starch glycolate. The experimental design was valid, with good regression coefficients for the variables corresponding to tablet properties: hardness, disintegration time and friability. Also, for the release of the model drug (acetaminophen 300 mg/tablet), we concluded that Precirol ATO 5 can speed up the dissolution in an optimum proportion of 4.5 – 5 % per tablet mass, combined with 8 % sodium starch glycolate. Given the results obtained, we can consider a further palatability study of the optimum formulation.

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