

STUDY ON THE INFLUENCE OF *GELUCIRE* SORT ON THE RELEASE OF ACETAMINOPHEN FROM ORALLY DISINTEGRATING TABLETS

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Abstract

The present research continues our previous studies of investigating the application of polyglycolized glycerides (*Gelucire* 44/14 and 50/13) as possible binders in wet granulation, with the final aim to prepare orally disintegrating tablets (ODT). Acetaminophen (APAP) was used as a model drug (300 mg/tablet) and *Gelucire* sorts were associated with povidone (Kollidon K30) in aqueous solutions in order to improve the properties of tablets and to induce the fast release of acetaminophen. Release of APAP was analyzed at intervals of 1 minute, 5 minutes and 10 minutes, which were set as response variables, by means of a factorial mixed experimental design (2-3-2). The independent variables were set as: % *Gelucire*, % Kollidon and % Explotab per tablet mass. Both *Gelucire* types increased the release of APAP, multiple regression equations showing high coefficients for the variable % *Gelucire* on the release of APAP after 1 minute and 5 minutes. The data fitted better the experimental model for *Gelucire* 50/13, with better R^2 values (> 0.8) compared to *Gelucire* 44/14.

Rezumat

Studiul prezentat în această lucrare continuă o direcție de cercetare anterioară privind utilizarea gliceridelor poliglicolizate (*Gelucire* 44/14 și 50/13) ca lianți la granulara umedă, pentru prepararea de comprimate orodispersabile (ODT). Ca substanță model a fost ales paracetamolul (APAP - 300 mg./comprimat), iar tipurile de *Gelucire* s-au asociat cu *Kollidon K30* în soluții apoase pentru a îmbunătăți proprietățile farmacotehnice ale comprimatelor și dizolvarea APAP, care s-a dozat spectrofotometric. S-a analizat cedarea la 1 minut, 5 minute și 10 minute, valori ce au fost setate ca variabile de răspuns prin intermediul unui plan factorial mixt (2-3-2). Variabilele independente au fost: % *Gelucire*, % Kollidon și % Explotab (dezintegrant) raportate la masa comprimatului. Ambele sorturi de *Gelucire* au crescut cedarea paracetamolului încă din primul minut, cu coeficienți de regresie crescuți ai variabilei % *Gelucire* în expresia cedării. Fitarea datelor pe modelul experimental a fost mai bună pentru sortul *Gelucire* 50/13, care a avut valori superioare pentru R^2 ($> 0,8$).

Keywords: Orally disintegrating tablets, Acetaminophen release, *Gelucire*.

Introduction

Orally disintegrating tablets (ODT) represent a dosage form that is often formulated nowadays. The manufacture methods for ODT include: freeze drying, molding, compaction with or without prior granulation, sublimation (1,2). The conventional methods are also taken into account, due to the possibility of large scale application and low cost. The basic requirements for ODT are: good hardness, low friability, very short disintegration times (less than 3 min.), good palatability. Low or medium dose active drugs are preferred, since taste masking can be a serious challenge (1, 2, 3). In our previous studies, we investigated the use of polyglycolized glycerides with high hydrophilic-lipophilic (HLB) values (*Gelucire* sorts) as multiple binders for improving ODT properties, with good results (4). Also, these excipients have been used as pseudo-solubilizers and as matrix formers for sustained release tablets (4). The present research aims at investigating the release of acetaminophen (model drug) from ODT prepared with a combination of binders (*Gelucire* sorts and povidone). Since ODT are a rapid release dosage form, an increase in the dissolution speed of acetaminophen in the presence of *Gelucire* is desired and expected (5, 6, 7).

Materials and methods

Materials: Acetaminophen powder (APAP, Chemicals, UK); Excipients: *Gelucire* 44/14, *Gelucire* 53/13 (kindly offered by Gatefossé, France), coded respectively G1 and G2; *Kollidon K30* (K) (BASF); microcrystalline cellulose (MC *Vivapur 101*, JRS Pharma); Aerosil 200 (Degussa, Germany); sodium starch glycolate (*Explotab - E*), magnesium stearate (Union Derivan, Spain);

Methods: APAP (300 mg/tablet) was granulated with aqueous solutions of G1 and respectively G2, both combined with K in order to enhance the hardness of tablets. The wet mass was sieved through an 800 μ m screen (TGL 7354/TGLO 4188 set) and then dried in the oven for 10 min at 40°C. A proportion of extra filler (MC) was added to the dried granules, along with 1% magnesium stearate and 1% aerosil per tablet; granules were compressed on a *Korsch EK0* tablet press (12mm flat punches, 8kN compression force). All tableting mixtures contained an APAP/MC ratio of 3/2 per tablet. A *mixed experimental design* (2-3-2) was built in order to ascertain the influence of *Gelucire* sort on the release of APAP. The independent variables were set as: x_1 - proportion of K binder (on 2 levels: 2% and 2.5%), x_2 - proportion of G1, respectively G2 (on 3 levels: 2%, 4.5% and 7% of total granule mass) and x_3 - proportion of superdisintegrant *Explotab - E* (on 2 levels: 2% and 5%).

Consequently, a number of 12 experiments were run for each type of *Gelucire* (Table I).

Table I
Matrix of factorial analysis

Run	x_1	x_2	x_3
1	2	2	2
2	2.5	2	2
3	2	4.5	2
4	2.5	4.5	2
5	2	7	2
6	2.5	7	2
7	2	2	5
8	2.5	2	5
9	2	4.5	5
10	2.5	4.5	5
11	2	7	5
12	2.5	7	5

In vitro dissolution test was performed according to the USP protocol for *Acetaminophen tablets* on a SR8 Plus dissolution station (AB&L Jasco), equipped with a V530 spectrophotometer (dissolution medium: 5.8 pH buffer, Q= not less than 80% release after 30 min.) (8). In this study, the collecting intervals for the prepared tablets were set according to our goal of quick release: 1 min., 5 min. and 10 min., expecting an enhanced dissolution in the presence of *Gelucire*.

The amounts of APAP released at the collecting intervals were set as dependent variables: y_1 (% APAP released after 1 min. from the G1/G2 formulations); y_2 (% APAP released after 5 min. from the G1/G2 formulations) and y_3 (% APAP released after 10 min. from the G1/G2 formulations). The results were statistically interpreted using the *Matlab 7.9* Software.

Results and discussion

The release of APAP was found to be very much influenced by the tablet binders, having values above 70% after 1 minute; after 10 minutes, APAP was almost completely dissolved from all tablets, regardless of *Gelucire* sort (Table II.). For the response variable y_1 , the regression coefficients showed significant differences concerning the influence of the G sort. For G1 (x_2 variable), we can notice an increase in the release of APAP (a coefficient of 20.271 on the regression equation – Table III). For the experiments with G2, there was also a high influence of this binder on the release of APAP after 1 min., but we can notice as well a high coefficient for variable x_1 (K). The interaction between the two variables (x_1

and x_2) had a negative coefficient for both types of *Gelucire*. The interactions of variable x_2 with x_3 (representing the proportion of E) were less significant.

Table II

Procentual acetaminophen release on the dissolution test

Run	1 min y_1		5 min y_2		10 min y_3	
	(G1)	(G2)	(G1)	(G2)	(G1)	(G2)
1.	90.87	92.39	98.2	98.94	99.82	100
2.	83.9	99.26	86.18	99.92	97.5	100
3.	85.59	97.49	100	99.48	100	100
4.	79.05	84.72	100	91.56	100	94.23
5.	97.87	88.56	100	92.66	100	95.47
6.	79.56	74.47	95.18	90.02	100	96.06
7.	91.08	86.57	100	96.85	100	99.86
8.	97.83	93.69	100	100	100	100
9.	75.7	93.33	88.3	98.7	91.18	100
10.	75.49	89.6	93.26	93.99	96.96	100
11.	86.78	84.04	93.48	92.91	97.6	99.06
12.	66.14	73.88	86.86	90.62	89.21	98.34

After 5 minutes (response variable y_2), the influence of G1 maintained the same trend, but with a much lower coefficient (Table III); the interactions between variables x_1 and x_2 had a low coefficient. We could notice though a high negative coefficient for variable x_1 (percent of K), which limits the release at this moment. For the experiments with G2, the influence was similar, increasing the percent of APAP dissolved.

Table III

Coefficients of multiple regression equations for prediction of response variables

Tablets with G1								
V.	k	x_1	x_2 <i>G1</i>	x_3	$x_1x_2^*$	$x_1x_3^*$	$x_2x_3^*$	R^2
y_1	63.016	5.768	20.271	-4.385	-7.746	3.937	-1.288	0.765
y_2	126.172	-18.495	2.849	-4.002	-0.116	3.373	-1.015	0.605
y_3	86.97	4.045	4.057	1.2827	-1.214	0.064	-0.529	0.618
Tablets with G2								
V.	k	x_1	x_2 <i>G2</i>	x_3	$x_1x_2^*$	$x_1x_3^*$	$x_2x_3^*$	R^2
y_1	71.767	15.213	13.927	-8.428	-7.648	2.937	0.209	0.854
y_2	105.268	-0.779	2.268	-3.266	-1.812	1.273	0.095	0.830
y_3	113.786	-5.254	-1.126	-2.562	-0.05	1.022	0.200	0.715

*interactions between variables respectively.

The release of APAP after 10 minutes was almost complete (variable y_3), the influence of the independent variables being low; however, regression equations still showed for G1 experiments a positive influence of x_2 on the percent of APAP released. The superdisintegrant E (x_3) had little influence together with the two binders; however, almost in all cases, this variable displayed negative coefficients.

Conclusions

The release of acetaminophen from the prepared tablets with a combination of two sorts of binders: *Gelucire 44/14* and *50/13* with Kollidon K30 was fast, showing high percents of active drug dissolved after the first minute. The proportion of *Gelucire*, both sorts, and the percent of release of APAP were found to be directly correlated, this excipients highly influencing the dissolution of APAP after 1 minute and after 5 minutes. The independent variables had less influence on the release of APAP after 10 minutes, when the dissolution was almost complete. The experimental model fitted better for *Gelucire 50/13* experiments, which had higher values for R^2 .

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References

1. Hirani J.J., Rathod D.A., Vadalia K.R., Orally Disintegrating Tablets: A Review, *Trop. J Pharm. Res.*, 2009, 8 (2), 161.
2. xxx European Pharmacopoeia VI, Strassbourg, 2008, Supplm. 2010.
3. Abdelbarry G., Prinderre P., Eouani C., Joachim J., Reynier J.P., Piccerelle Ph., The preparation of orally disintegrating tablets using a hydrophilic waxy binder, *Int. Journal of Pharmaceutics*, 2004, 278(2), 423-433.
4. Gratiela Popa, Lacramioara Ochiuz, Iulian Stoleriu, Iuliana Popovici, Binder and superdisintegrant influence on the properties of orally disintegrating tablets high doses acetaminophen tablets, *Farmacia*, 2010, 58(3), 303-307.
5. Madgulkar AR, Bhalekar MR, Padalkar RR, Formulation design and optimization of novel taste masked mouth-dissolving tablets of tramadol having adequate mechanical strength, *AAPS Pharm. Sci. Tech.*, 2009; 10 (2); 574-81.
6. Johannsson F., Formulation of finasteride, *U.S. Patent no. 0099251*, 2006, www.freshpatents.com.
7. Millan J.R., Solid oral forms of ebastine, *U.S. Patent no. 0304791*, 2009, www.freshpatents.com.
8. *** Acetaminophen Tablets monograph, *USP 30-NF 25*, 2007, 1269.
9. Andreea Stanescu, Lacramioara Ochiuz, Ileana Cojocaru, Iuliana Popovici, Dumitru Lupuleasa, The influence of different polymers on the pharmacotechnological characteristics of propiconazole nitrate bioadhesive oromucosal tablets, *Farmacia*, 2010, 58(4), 279-289.

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