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Fast and Controlled Release of Triamcinolone Acetonide from Extrusion-Spheronization Pellets Based on Mixtures of Native Starch with Dextrin or Waxy Maize Starch

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Pellets composed chiefly of inexpensive starches allow modulation of the rate of release of the poorly soluble drug triamcinolone acetonide in media of pH 1.2–6.8. Wheat- or maize-starch-based pellets with 20% of white dextrin release the drug in vitro almost completely within 20 min, while maize-starch-based pellets with 5–35% of waxy maize starch sustain gradual release over periods of 9–12 hr or longer when prepared using appropriate amounts of granulation fluid.

Keywords extrusion-spheronization; pelletization; starch; Controlled release; dextrin

INTRODUCTION

Since the early works of Conine and Hadley (1970) and Reynolds (1970), the use of pellets as multiparticulate dosage forms has become widespread. Their advantages over traditional monolithic forms include the possibility of being released in targeted regions of the digestive tract, where their dispersal enhances absorption and reduces side effects (Follonier & Doelker, 1992) and technologically desirable properties such as spherical shape, free flow and low friability (Erkoboni, 1997), which fit them for packing into hard gelatin capsules, for compression as tablets, or for individual coating. Amenability to individual coating, in particular, is of interest for achieving sustained release of the active principle and for targeting the colon (Milojevic et al., 1996; Villar-López et al., 1999). However, since coating increases manufacturing costs, an even more attractive possibility is the development of pellets that implement sustained release without any coating.

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Pellets obtained by extrusion-spheronization have an intrinsic tendency towards slow release of active principles (Zhang et al., 1990; Robinson & Hollenbeck, 1991; Zhang et al., 1991). Factors influencing this tendency include their shape (Chopra et al., 2002), the quantity and nature of the granulation liquid (Baert & Remon, 1993), and the kind and quantity of microcrystalline cellulose (MCC), which is usually the major excipient (O'Connor et al., 1984; O'Connor & Schwartz, 1985; Ghali et al., 1989a; Pinto et al., 1992). Ingredients added with the aim of further delaying drug release include polymer dispersions such as Aquacoat and Eudragit (Goskonda et al., 1994), polyacrylic acid (Vila Jato et al., 1995; Neau et al., 1996; Rodríguez Gómez et al., 1996; Neau et al., 2000; Awad et al., 2002), sodium alginate (Chatchawalasasin et al., 2004), chitosan (Tapia et al., 1993; Chatchawalasasin et al., 2004) polyvinyl acetate (Schmidt et al., 1996), polyvinyl pyrrolidone, mixtures of starch and gelatin (Varshosaz et al., 1997), particle core pH modifiers (Bianchini et al., 1992; Krogars et al., 2000; Costa et al., 2004), and wax (Ghali et al., 1989b). Finally, Zhou and coworkers´ obtained starch based pellets by melt pelletization technique (Zhou et al., 1996, 1997, 1998a,b).

MCC, which as noted above is usually the major excipient of pellets obtained by extrusion-spheronization, is relatively expensive. Also, the reluctance of MCC-based pellets to disintegrate even when mixed with disintegrating agents, though convenient for the preparation of sustained-release formulations, hinders exploitation of the advantages of pellets when fast release of drugs with poor solubility in aqueous media is desired (Schröeder & Kleinebudde 1995; Villar-López et al., 1999; Pérez-Feás et al., 2003; Rodríguez et al., 2003). We recently investigated the technical properties of drug-free extrusion-spheronization pellets based on starch and a second excipient that was either a material that would favour sustained release (waxy maize starch, which increases the proportion of gel-forming—and hence release retarding-amylopectin) or a

highly soluble material that would favour fast release (dextrin) (Almeida-Prieto et al., 2005). Here we report the drug release behaviour of pellets of this kind when loaded with the poorly hydrosoluble drug triamcinolone acetonide.

MATERIALS

Triamcinolone acetonide (TAc) was supplied by Roig Farma SA (Barcelona, Spain), and native wheat starch (Meritena 200), native maize starch (Meritena 100), pregelatinized waxy maize starch (WMS; Merigel 341), and white dextrin by Inigarbe SL (Padrón, A Coruña, Spain). Talc was purchased from J. Escuder (Barcelona, Spain). The granulation liquid was distilled water.

METHODS

The study comprised two phases. In the first, the solid components affording the best-performing mixtures were identified. In the second, the optimal proportions of the solid components affording the best controlled release and pellet shape in the first phase, and the optimal amount of granulation liquid, were determined using a rotational central composite second-order experimental design.

Preparation of Pellets

Table 1 lists the proportions of the major excipients of the formulations prepared in the first phase of the study. In each case, the TAc content was 2% (w/w), the talc content was 5% (w/w), and the amount of granulation water was chosen on the basis of our previous results (Almeida-Prieto et al., 2005). The solid components (100 g) were mixed for 15 min in a Turbula T2C mixer and wetted by mixing for a further 15 min in a Kenwood Chef Classic orbital mixer with a volume of distilled water chosen on the basis of previous work (Almeida-Prieto et al., 2005), after which the moist mass was left in an hermetically sealed plastic bag for 24 hr to achieve as uniform a moisture distribution as possible, extruded through a 1 mm mesh screen in a Caleva Model 10 apparatus operating at 6 r.p.m., spheronized for 15 min in a Caleva Model 120 spheronizer operating at 2000 rpm, and dried to constant weight in an Haraeus oven. Three batches of each formulation were prepared.

Table 3 lists the proportions of distilled water and binder in the formulations prepared in the second phase of the study, in which the major excipient was maize starch and the binder waxy maize starch. The pellet preparation technique was the same as in the first phase.

Morphological Characterization by Image Analysis

Grey-scale digital images of pellets illuminated vertically under an Olympus SZ-CTV stereomicroscope by an Olympus Highlight 2000 cold light source were obtained with a JVC TK-S350 video camera with a pixel size corresponding to

TABLE 1
Main Constituents and Morphological Characteristics (Means ± Standard Deviations) of the First-phase Formulations

	Composition				Morphological Characteristics					
		Second Excipient			R_m (μm) (%[b])		V_r (%[b])		Vp^a (%[b])	
Formulation	Native Starch	Identity[a]	%	Water (mL/g)	*Pop.1*	*Pop.1*	*Pop.2*	*Pop.1*	*Pop.2*	*Pop.1*	*Pop.2*
1	Maize	WD[a]	20	0.40	497 ± 102 (65)	476 ± 43 (35)	2.77 ± 0.73 (83)	6.19 ± 3.28 (17)	6.00 ± 0.51 (100)	–	
2			5	0.45	396 ± 45 (68)	495 ± 55 (32)	3.77 ± 0.40 (92)	9.06 ± 0.96 (8)	6.03 ± 0.22 (93)	8.74 ± 0.17 (7)	
3		WMS[a]	10	0.45	459 ± 23 (70)	576 ± 62 (30)	4.53 ± 0.09 (89)	12.56 ± 0.75 (11)	6.35 ± 0.11 (72)	9.45 ± 1.61 (28)	
4			20	0.34	451 ± 21 (49)	552 ± 62 (51)	5.52 ± 1.32 (87)	18.20 ± 6.81 (13)	7.32 ± 1.26 (52)	9.90 ± 0.92 (48)	
5	Wheat	WD[a]	20	0.40	413 ± 62 (80)	520 ± 102 (20)	4.48 ± 0.46 (84)	10.25 ± 1.42 (16)	6.30 ± 0.20 (81)	9.51 ± 1.80 (19)	
6			5	0.40	427 ± 37 (77)	482[c] (23)	3.62 ± 0.84 (58)	5.28 ± 2.78 (42)	6.06 ± 0.22 (77)	8.02 ± 0.20 (23)	
7		WMS[a]	10	0.34	447 ± 7 (83)	570[c] (17)	4.70 ± 0.17 (92)	14.17 ± 1.33 (8)	6.70 ± 0.51 (62)	9.32 ± 0.60 (38)	
8			20	0.34	468 ± 53 (53)	588 ± 113 (47)	6.23 ± 0.41 (84)	16.37 ± 5.61 (16)	7.59 ± 0.75 (49)	10.73 ± 1.81 (51)	

[a]WD = white dextrin; WMS = waxy maize starch.
[b]Size of each population as a percentage of the total population.
[c]This population was only observed in one of the three replicate lots.

12.25×12.25 μm squares. The images were imported into the program SigmaScan Pro Image Analysis 5.0.0, the coordinates of the pixels on the boundary of the particle image were extracted from the image, and these data were processed by means of Microsoft® Excel 2000 macros to obtain the mean radius R_m (defined as the mean distance between the boundary pixels and the centre of gravity of the two-dimensional image), and the form factors V_r and V_p (Almeida-Prieto et al., 2004).

In Vitro Dissolution Studies

Dissolution profiles were obtained in an automatic system comprising a Hewlett Packard 8452A diode-array spectrophotometer connected to a Prolabo USP XXIII type II dissolution apparatus operated at 100 r.p.m. In each test, 400 mg of pellets in the size range 750–1250 μm, containing 8 mg of TAc, were dissolved at a temperature of 37.0 ± 0.5°C in each of six replicate tanks, and the release of TAc was monitored spectrophotometrically at 242 nm.

The first phase of the study investigated drug release both under gastric acidity conditions, monitoring dissolution in 1 L of hydrochloric acid buffer (pH 1.20 ± 0.05) over 2 hr, and under enteric acidity conditions, monitoring dissolution in 1 L of phosphate buffer (pH 6.80 ± 0.05) over 12 hr. The two experimental release profiles obtained for each formulation tested were each fitted by a nonlinear curve fitting to Higuchi equation (Origin 7.0, OriginLab Co.)

$$Q = k \cdot t^{1/2}$$

where $Q(t)$ is percentage accumulated release at time t, and the similarity between the two profiles up to $t = 120$ min was characterized in terms of the difference factor f_1 and the similarity factor f_2 recommended by the US Food and Drug Administration, which in this context are given by

$$f_1 = \left\{ \left[\sum_{t=1}^{n} | R_t - T_t | / \sum_{t=1}^{n} R_t \right] \right\} \cdot 100$$

$$f_2 = 50 \cdot \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-1/2} \cdot 100 \right\}$$

where R_t and T_t are the percentages of drug released by time t employed as reference and test in the enteric and gastric media, respectively. The sums are taken over n time points (in this study, $n = 24$).

In the second phase of the study, the dissolution solution was initially 450 mL of USP simulated gastric fluid (pH 1.2), but after 2 hr was brought to pH 6.8 and a volume of 678 mL by addition of 210 mL of phosphate buffer (pH 8) and 18 mL of 2 M sodium hydroxide; drug release was monitored over a total of 12 hr. Release profiles were compared in terms of the Higuchi parameter k and the areas under the profile up to 120 min and 720 min (AUC_{120} and AUC_{720}, respectively).

Scanning Electron Microscopy

Freshly prepared and lyophilized post-dissolution-test pellets were shadowed and photomicrographed by scanning electron microscopy (SEM) using a Carl Zeiss Leo 435 UP apparatus.

Statistical Analyses

First-phase formulations were compared as regards in vitro dissolution test results, AUC_{120} for results obtained at pH 1.2; AUC_{720} for results obtained at pH 6.8 by one- and two-way analyses of variance followed by Student-Newman-Keuls multiple comparison tests (in all cases, the normality and homoscedasticity of the distributions was verified). These calculations were performed using the program Sigmastat 1.0.

The R_m, V_r, V_p, mean radius, AUC_{120}, AUC_{720} and Higuchi k data of the second-phase formulations were fitted with response surfaces using StatGraphics Plus 5.1.

RESULTS AND DISCUSSION

With the exception of the V_p values of formulation 1, the V_p, V_r, and R_m values of all the formulations prepared in the first phase of the study exhibited bimodal distributions. Table 1 lists the means and standard deviations of the pellet populations corresponding to the two peaks, as estimated by fitting Gaussian distributions to each. In the case of V_r only formulations 1, 2 and 6 present values that correspond with almost circular shapes. Only in formulation 6, a second important population was identified, showing the presence of a 42% of rounded squares. For formulations containing WMS there was a clear association between increasing WMS content and (*a*) an increase in the mean V_r values of both V_r populations (i.e., decreasing roundness); (*b*) an increase in the mean V_p values of both V_p populations (i.e., increasing roughness and decreasing roundness. Pellet mean radius was virtually always between 400 and 500 μm, showing that the quantities of water used, though not optimized for the influence of water on roundness and roughness, were sufficient to ensure the cohesion and rheological adequacy of the extrusion mass.

Figures 1 and 2 show the drug release profiles of the first-phase formulations at pH 1.2 and pH 6.8, respectively. As hoped, the formulations containing dextrin released their drug content rapidly (over 95% within 20 min), while release from all the WMS formulations was much more gradual, though faster in the acidic medium. Two-way analyses of variance with native starch type and proportion of WMS as factors showed that in both media final AUC was smaller with maize starch than with wheat starch, at least on average ($\alpha < 0.01$), but depended less regularly on the proportion of WMS, although slowest release was in both media achieved with maize starch and a 10% WMS content (formulation 3). Figure 3 (photo H) shows that this formulation afforded

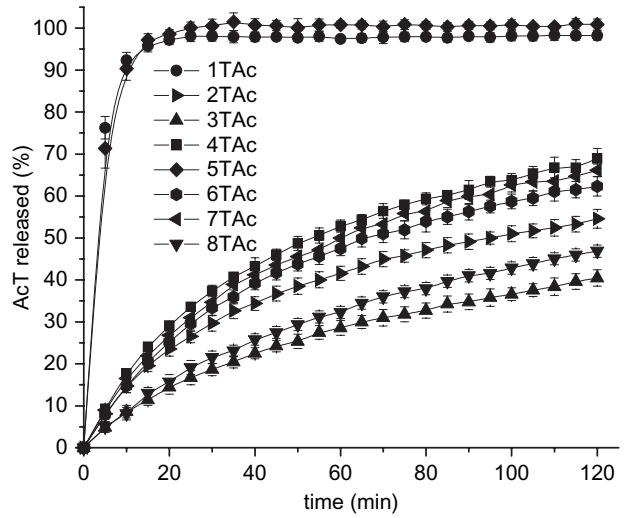


FIGURE 1. TAc release profiles of the first phase formulations described in Table 1 at pH 1.2.

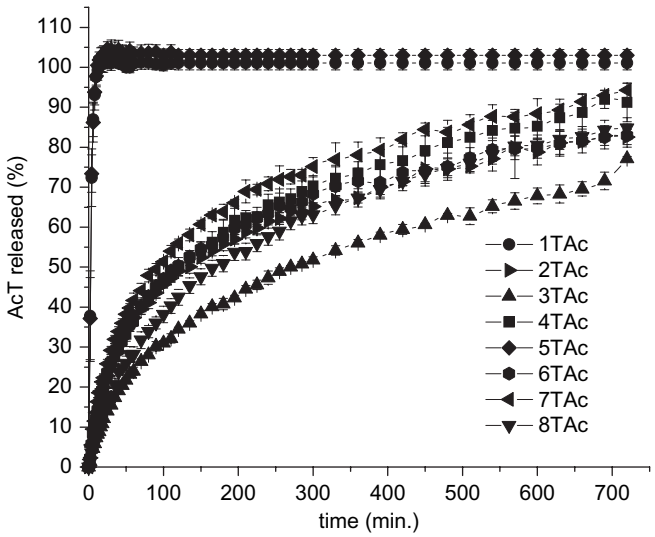


FIGURE 2. TAc release profiles of the first-phase formulations described in Table 1 at pH 6.8.

pellets that were smoother and more compact than those formulated with wheat starch or with a larger proportion of waxy maize starch, which in the latter case seems likely to have been due to the amount of granulation water used in formulation 4 having been insufficient for optimal extrusionate plasticity and pellet density (Baert & Remon 1993; Sousa et al., 1996).

Comparing the results between the profiles of gastric and enteric medium, factor f1 (Table 2) shows that formulation 2TAc and 8TAc only present similar profiles in both mediums (f1 < 15) during the first 120 min, being 3AcT in the limit. In fact these are the formulations that present better control release in gastric juice. Some values of these parameters are not indicated, because the release was so quick that there were not enough points for its calculation. On the other hand if we use the f2 values all formulations show different profiles in both mediums (f2 < 50). In general we can state that a faster release is observed with gastric medium.

TABLE 2
Values of f_1 and f_2 (See Materials and Methods) for the First-phase Formulations Described in Table 1, Together with the Results of Fitting Higuchi's Equation to Their Release Profiles

			Higuchi's k / $min^{-1/2}$ (R^2)	
Formulation	f_1	f_2	pH 6.8	pH 1.2
1	–	–	31.589 (0.873)	–
2	11.641	38.259	3.594 (0.920)	5.192 (0.985)
3	15.058	39.999	2.892 (0.990)	3.632 (0.985)
4	29.456	12.916	3.845 (0.952)	6.533 (0.983)
5	–	–	31.735 (0.879)	–
6	19.831	23.231	3.675 (0.902)	5.924 (0.984)
7	16.441	26.289	4.084 (0.910)	6.254 (0.987)
8	10.942	43.291	3.470 (0.982)	4.200 (0.976)

Photomicrographs of first-phase WMS-bearing pellets that had undergone 12-hr dissolution tests at pH 6.8 show no tendency to disintegration, and that surface erosion, and the formation of pores and channels, were least for the formulation that released the drug most slowly (and was most compact), formulation 3 (Figure 3, top row). This suggests that the mechanism of drug release was dissolution followed by diffusion through the hydrophilic starch matrix, an hypothesis that is supported by the satisfactory values obtained for the coefficient of determination, r^2, when the Higuchi model was fitted to the experimental dissolution data (Table 2). The fit was especially good, at least at pH 6.8, for the slowest-releasing formulations, 3 and 8.

In view of the first-phase ANOVA results discussed above, the second phase of the study was designed to optimize, for slow release, the WMS content and amount of granulation water of pellets having maize starch as their major excipient. This excipient was selected because it seems to present the better controlled release of triamcinolone than wheat starch. Tables 3 and 4 list the results, Figure 4 shows the release profiles of the second-phase formulations, and Figure 5 shows response surfaces for the form factor V_r, the Higuchi constant k, AUC_{120} and AUC_{720}. Whenever two R_m populations were detected, the results reported refer only to the low-R_m population, which was the larger. Somewhat surprisingly, the form factor V_p was statistically significant influenced by neither WMS content nor the quantity of granulation water, and the mean radius R_m and form factor V_r (which was always indicative of fairly rounded pellets) were only significantly influenced by WMS content, which our earlier study had already shown to affect the plasticity of the extrusion mass

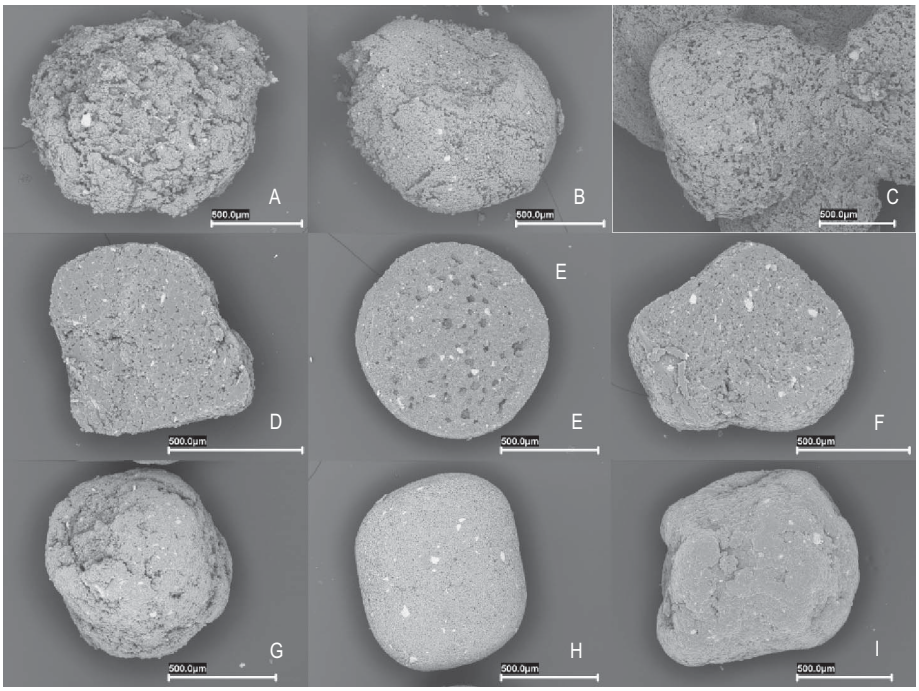


FIGURE 3. SEM photomicrographs of pellets of formulations 4 (left), 3 (middle column) and 7 (right). Top row: after a 12 hr dissolution test at pH 6.8 followed by lyophilization. Middle row: sections through freshly prepared pellets. Bottom row: freshly prepared pellets.

TABLE 3
WMS and Granulation Water Contents, and Morphological and TAc Release Characteristics, of the Second-phase Formulations

	Factors		Morphology			Yield		Release		
Formulation	Water (ml)	WMS (%)	R_m (µm)	V_r	V_p	%[1]	Number of Pellets (%) with R_m between 375 and 675 µm	AUC_{120} (min)	AUC_{720} (min)	k ($min^{-1/2}$) (^{R2})
II.1	34	10	447.77	3.73	6.83	85.59	96.7	5464.1	60507.3	5.803 (0.971)
II.2	34	30	481.22	5.10	8.77	97.44	77.6	4779.2	53670.2	5.171 (0.969)
II.3	40	10	421.41	3.68	7.52	86.34	94.4	4615.3	54043.4	5.012 (0.979)
II.4	40	30	519.92	7.10	10.45	96.64	56.3	3234.7	45154.5	3.804 (0.985)
II.5	37	20	508.34	6.29	10.07	95.69	69.6	3299.7	46636.1	3.912 (0.983)
II.6	37	20	471.51	5.92	8.88	93.96	96.3	3189.4	45234.3	3.787 (0.980)
II.7	37	5.8579	461.78	4.02	8.12	62.40	99.0	5669.0	58362.5	5.810 (0.982)
II.8	37	34.1421	511.06	6.41	6.80	95.79	72.6	4962.6	59365.6	5.501 (0.982)
II.9	32.7	20	459.76	6.84	9.62	94.56	90.4	4080.1	53151.6	4.673 (0.986)
II.10	41.2	20	499.64	6.28	8.16	96.97	79.7	2916.0	43571.3	3.568 (0.967)
II.11	37	20	481.82	5.97	9.71	94.76	79.3	3515.7	48727.8	4.149 (0.984)
II.12	37	20	497.9	7.59	10.35	97.11	70.0	3470.5	48219.1	4.104 (0.985)

1- Fraction of pellets (% w/w) with R_m > 355 µm (25 mesh sieve).

and the susceptibility of the pellets to spheronization (Almeida-Prieto et al., 2005). Drug release, as reflected by AUC_{120} and AUC_{720}, was always slowest for WMS contents around 20%, but it always depends of the quantity of granulation liquid (AUC_{120} or AUC_{720} decreased linearly with increasing amount of granulation water, behaviour that was likewise reflected by the Higuchi constant *k*). The good fit of the Higuchi equation supports the hypothesis that drug release occurred through dissolution followed by diffusion through the starch matrix.

TABLE 4
Statistical Significance of the Terms of Response Surfaces Fitted to the R_m, V_r, V_p, AUC_{120}, and AUC_{720} Data Characterizing the Second-phase Formulations Described in Table 2

Source of Variation	R_m	V_r	V_p	AUC_{120}	AUC_{720}
WMS	$\alpha < 0.01$	$\alpha < 0.01$	ns	$\alpha < 0.01$	ns
Water	ns	ns	ns	$\alpha < 0.01$	$\alpha < 0.05$
WMS^2	ns	$\alpha < 0.05$	ns	$\alpha < 0.01$	$\alpha < 0.01$
$Water^2$	ns	ns	ns	ns	ns
WMS × Water	ns	ns	ns	ns	ns

So, in view of these results it would be helpful establish the same experimental design employed for maize starch with the wheat starch, because probably with appropriate levels of water could be possible obtained similar results. However, the use of maize starch presents an advantage over wheat starch in the fabrication of oral dosage forms related with the absence of gluten in its composition.

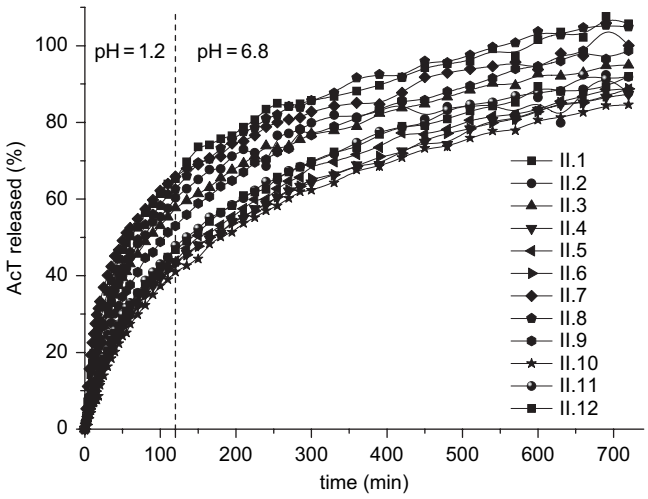
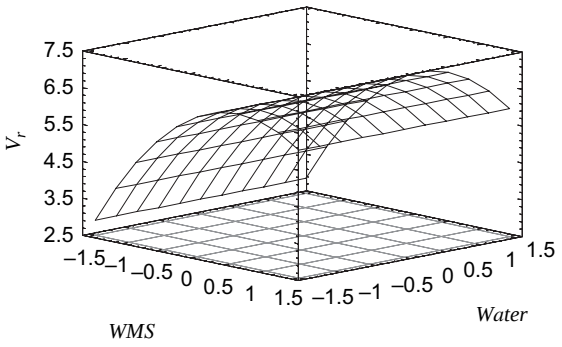
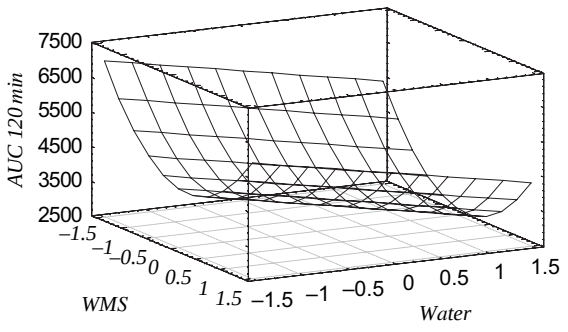


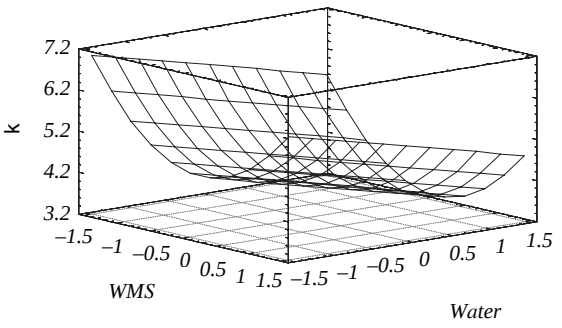
FIGURE 4. TAc release profiles of the second-phase formulations described in table 2.



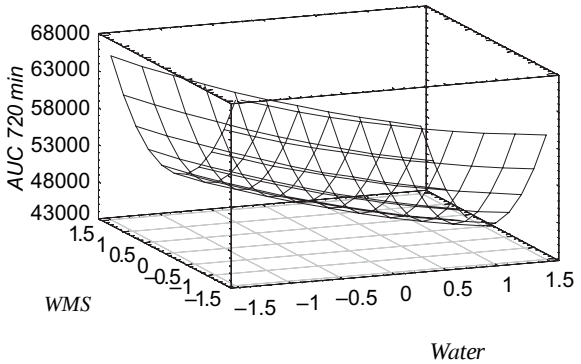
$$Vr = 6.2925 + 1.0213 \times WMS - 0.8225 \times WMS^2$$
$$R^2 = 66.7\%$$



$$AUC_0^{120} = 3443.8 - 383.1 \times WMS - 504.9 \times Water + 983.8 \times WMS^2$$
$$R^2 = 95.22\%$$



$$k = 4.05 - 0.285 \times WMS - 0.465 \times Water + 0.832 \times WMS^2$$
$$R^2 = 93.24\%$$



$$AUC_0^{720} = 47613.4 - 3566 \times Water + 5660.4 \times WMS^2$$
$$R^2 = 81.2\%$$

FIGURE 5. Response surfaces for V_r, AUC_{120}, AUC_{720}, and Higuchi's k fitted to the experimental data of the second-phase formulations described in Table 2.

CONCLUSION

Pellets composed chiefly of inexpensive starches allow modulation of the rate of release of triamcinolone acetonide in both gastric and enteric media. In vitro, wheat- or maize-starch-based pellets with 20% of white dextrin release the drug almost completely within 20 min, while maize-starch-based pellets with 5–35% of waxy maize starch sustain gradual release over periods of 9–12 hr or longer when prepared using appropriate amounts of granulation fluid.

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