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Bioavailability of starch based hot stage extrusion formulations

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Abstract

The aim of the study was to develop a starch based hot stage extrusion formulation for controlled drug delivery and to evaluate its in vivo behavior. The extrusion mixture consisted of 53% corn starch as the matrix forming agent, 15% sorbitol as a plasticizer, 30% theophylline monohydrate as the model drug and 2% glyceryl monostearate as a lubricant. The extrudates were produced by means of a corotating twin screw extruder of APV Baker equipped with a twin screw powder feeder and a 3-mm cylindrical die. During extrusion 20% water (based on the wet mass) was added to the powder mixture. The extrudates were dried in an oven at 60°C during 48 h, cut and filled out in hard gelatine capsules, in a way that the content of two capsules corresponded with a dose of 300 mg anhydrous theophylline. The dissolution profile of the experimental dosage form was retarded with a drug release of around 80% in 8 h. The in vivo behavior of the experimental formulation was evaluated in a randomized crossover design study ($n = 8$) with a commercially available multiple unit sustained release product as the reference formulation. The plasma samples were analyzed by a validated HPLC-UV method with solid phase extraction for the sample preparation. It was clear that the experimental formulation exhibited sustained release behavior, but that it performed less well than the multiple unit dosage form.

Keywords: Hot stage extrusion; Starch; Sustained release matrix; Theophylline; In vivo

1. Introduction

Hot stage extrusion is a technique derived from the polymer and food industry (van Zuilichem, 1992). The pharmaceutical industry also took interest in this technology, and during the last 10–15 years, research has been performed to explore the possibilities and drawbacks of hot stage extrusion as a new production technique for matrix formulations into which a drug is homogeneously embedded (Mank et al., 1989, 1990; Follonier et al., 1994, 1995; Gruenhagen, 1996; Sprockel et al., 1997). Dependent on the operating temperature, either solid dispersions or solid solutions can be produced with this method. The major advantage over the more conventional matrix production

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methods is the continuity of the production process. Furthermore this technique is characterized by a high throughput and low material loss, a good homogeneity of the products, the absence of organic solvents in the production process and the possibility to minimize the use of excipients (Mueller et al., 1992; Breitenbach et al., 1995).

Starch is a widely used pharmaceutic aid due to its low cost, high availability and non-toxicity and its excellent feasibility for hot stage extrusion has been established by a variety of applications in the polymer, food and agriculture technology (Launay and Lisch, 1983; Doane, 1992; Fritz and Widmann, 1993; Shogren et al., 1993; Carr et al., 1994; Krishnan et al., 1994; Schreiber et al., 1994). However, no literature is yet available about its possible application as a basic polymer for the production of hot stage extruded drug/matrix formulations.

Therefore it was the objective of this work to develop a starch based hot stage extrusion formulation for sustained drug release and to compare its in vivo behavior to that of a commercially available drug delivery system with the same drug.

2. Materials and methods

2.1. Materials

Corn starch and sorbitol were received from Eridania Béghin Say Cerestar (Vilvoorde, Belgium). Theophylline monohydrate was purchased from Ludeco (Brussels, Belgium) and glyceryl monostearate was obtained from Mosselman (Brussels, Belgium).

The powder mixture for extrusion consisted of 53% corn starch, 15% sorbitol as a plasticizer, 2% glyceryl monostearate as a lubricant, and 30% theophylline monohydrate as the model drug. This composition was mainly based on patent literature (De Bock et al., 1993, 1994) and on prior experience.

Xanthium® 300 was obtained from SMB (Brussels, Belgium). Each capsule contains 300 mg anhydrous theophylline and consists of coated microgranules.

2.2. Production process

Prior to hot stage extrusion, the different components of the formulation were premixed in a Hobart A 200 planetary mixer (Kampenhout, Belgium).

The extrusion was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder of APV Baker (Newcastle-under-Lyme, UK). The machine was equipped with a control panel (for the installation and/or control of the barrel and melt temperatures, the screw speed, the powder feed rate, the die pressure and the torque), a standard screw profile with two mixing sections, a 3-mm cylindrical die, a twin screw powder feeder and a peristaltic pump connected to the first barrel zone of the extruder. The pump was used for the addition of water, acting as a plasticizer, during the extrusion.

The following extrusion conditions, based on preliminary research work, were used: a screw speed of 200 rpm, a powder feed rate of 2.4 kg/h and a water addition rate of 0.6 kg/h. The following temperature profile was installed: 60–90–100–100–80°C from the powder feeder to the die. The effective temperatures equaled the installed temperatures except for the die zone where the effective temperature was higher (95°C) than installed since the experiments were performed without cooling system.

The extrudates were cut into pieces of approximately 10 cm and prior to further analysis they were oven dried at 60°C during 48 h. Afterwards the extrudates were cut in smaller pieces and six parts were filled out in hard gelatine capsules No. 0, in a way that the content of two capsules corresponded with a dose of 300 mg anhydrous theophylline.

2.3. In vitro characterization

A dissolution was performed for both the experimental formulation and Xanthium® in a VK 7000 dissolution system with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). The paddle method (Eur. Ph.) at 37 ± 0.5°C and 100 rpm in water was selected as the dissolution method. The dissolution was per-

formed on three dosage forms. Samples were taken after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. After appropriate dilution they were measured at 272 nm by means of a Perkin Elmer Lambda 12 UV-VIS double beam spectrophotometer (Zaventem, Belgium). The theophylline monohydrate concentrations were calculated from a calibration curve between 0 and 0.025 g/l.

2.4. In vivo evaluation of the reference extrudates

2.4.1. Subjects and study design

A group of eight male, Caucasian volunteers, aged between 20 and 27 years, gave written informed consent to participate in the study, which was approved by the Medical Ethics Committee of the University Hospital. The subjects were non-smokers and their weight was within 15% of their ideal weight. They were judged healthy on the basis of medical history, physical examination, electrocardiogram and investigation of biochemical and haematological parameters in blood and urine. The subjects abstained from intake of medication from 2 weeks prior to and during the whole study.

The preparations consisted of 300 mg anhydrous theophylline, either as the commercial multiparticulate sustained release drug delivery system Xanthium® (SMB) or as a hot stage extrusion formulation. The preparations were taken in a crossover randomized sequence with a time interval from 6 to 7 days between the administrations. The formulations were administered with 200 ml of water between 07:45 and 09:00 h, after an overnight fast. During the first 2 h after intake the subjects remained in a sitting position. Water was available from 2 h after drug intake; standard lunch and dinner were provided at 4 and 10 h after drug intake. From 12 h post-administration the volunteers could resume their usual diet except for ethanol containing beverages, which were not allowed until 24 h after ingestion of theophylline.

The blood samples were collected in dry heparinized tubes before and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14 and 24 h after theophylline intake. The blood was centrifuged for 5 min at 3000 rpm within 1 h after collection and the plasma was stored at -20°C until assay of theophylline.

2.4.2. Theophylline assay procedure

Plasma theophylline concentrations were determined by a HPLC-UV method. All chemicals were of analytical or HPLC grade.

One hundred microliters of an internal standard solution (70 μg ml^{-1} of β-hydroxyethyltheophylline in water) and 100 μl of water were added to and mixed with 1 ml plasma. The drug was extracted using a solid phase extraction (SPE) method. The SPE columns were conditioned with 1 ml methanol and 1 ml water. The samples were transferred quantitatively on the columns afterwards. The rinsing step was performed with 1 ml water and the elution with 1 ml methanol. The obtained eluates were evaporated to dryness under a nitrogen stream, the residue was redissolved in 1 ml eluens and 25 μl was injected into the chromatograph. The plasma concentrations were determined via a calibration curve. The standards for the calibration curve were treated as the samples: 1 ml blank plasma was spiked with 100 μl of internal standard solution and 100 μl of a standard solution with known concentration of theophylline in water and next SPE was performed.

The HPLC equipment consisted of a solvent pump (L 6000 pump, Hitachi, Tokyo, Japan) set at a constant flow rate of 1 ml min^{-1}, a variable wavelength detector (L 4000 UV detector, Hitachi, Tokyo, Japan) set at 273 nm, a reversed phase column and precolumn (LiChroCART® 250-4 and 4-4, LiChrospher® 60 RP-select B 5 μm; Merck, Darmstadt, Germany) and an automatic integrating system (D 2000 Chromato-Integrator, Hitachi, Tokyo, Japan). The SPE equipment consisted of OASIS HLB (3 cc 60 mg) cartridges (Waters, Brussels, Belgium) and a 16-port vacuum manifold (Alltech Europe, Laarne, Belgium). The eluens had the following composition: 950 ml of a 50-mM ammonium acetate solution adjusted to a pH of 5.0 with HCl, 50 ml acetonitrile and 5 ml tetrahydrofuran.

2.4.3. Method validation

The mean calibration curve ($y = 0.1812x + 0.001$) between 0.5 and 10 μg ml^{-1} theophylline showed a correlation of 0.999 (r^2). The detection and quantification limits of the method were 0.12 and 0.41 μg ml^{-1}, respectively. The intra assay coefficients of variation for concentrations between 0.5 and 10 μg ml^{-1} of theophylline ($n = 6$) ranged from 10.64 to 0.99%. The interassay coefficients of variation for the same concentrations ($n = 6$) were between 8.85 and 1.04%. The mean analytical recoveries in this concentration range ($n = 10$) were at least 95% and the accuracy of the concentration determination ($n = 6$) varied between 95 and 103%.

2.4.4. Data analysis

The peak plasma concentration (C_{max}), the time to reach C_{max} (t_{max}) and the extent of absorption ($AUC_{0-\infty}$) were calculated using the MW-PHARM program version 3.0 (Mediware 1987–1991, Utrecht, the Netherlands). The $AUC_{0-\infty}$ was calculated using the logarithmic and linear trapezoidal rules. The sustained release characteristics of a formulation with a drug of narrow therapeutic range (like theophylline) are evaluated by the $t_{75\%\ C_{max}}$. This is the time span during which the plasma concentrations are at least 75% of the C_{max} value or the width of the plasma profile at 75% of the C_{max} (Steinijans, 1990). The ratio between the $t_{75\%\ C_{max}}$ of a test formulation and a reference immediate release formulation is indicative for its sustained release effect (a ratio of 1.5, 2 and > 3 meaning a low, an intermediate and a strong sustained release effect, respectively). The $t_{75\%\ C_{max}}$ was determined from the individual plasma concentration-time profiles.

The pharmacokinetic parameters of the formulations were statistically evaluated by a two-way ANOVA (in case of a normal distribution (Shapiro–Wilk test) and homogeneity of variances (Levene test)) and by the non-parametric Wilcoxon-Signed-Ranks test in the other case. They were considered significantly different when $P < 0.05$. A two-way ANOVA method was preferred when possible, to evaluate both the influence of the formulation and of the individuals on the results.

3. Results and discussion

Hot stage extrudates based on starch are to be considered as a novel matrix drug delivery system. In an early stage of the project an in vivo study was performed in comparison with a coated multiple unit pellet system available on the market (Xanthium®) in order to evaluate the value of the in vitro drug release profiles used in the development phase of the starch matrix systems. The hot stage extrusion formulation and Xanthium® showed a slow in vitro drug release profile with a percentage drug released of 80 and 45% in 8 h, respectively (Fig. 1). However, since both systems are composed of different materials and have different geometries and since no in vitro–in vivo correlation is available, it is impossible to draw conclusions concerning their in vivo behavior just based on their in vitro dissolution profiles.

Figs. 2 and 3 show the individual and the mean ($n = 8$) plasma concentration-time profiles after the oral administration of 300 mg theophylline to eight healthy volunteers as Xanthium® and as the experimental hot stage extrusion formulation, respectively. The pharmacokinetic parameters are reported in Table 1.

Administration of Xanthium® led to an ideal sustained release profile with a $t_{75\%\ C_{max}}$ of 16.4 h and a $t_{75\%\ C_{max}}$ ratio of 5.5 when compared to a

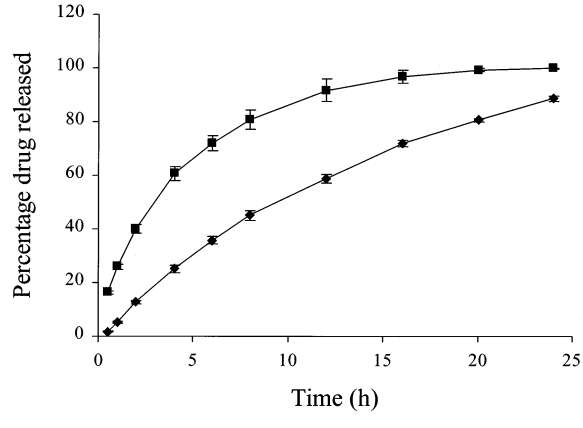

Fig. 1. In vitro dissolution profiles in water of Xanthium® and of a hot stage extrusion formulation consisting of 53% corn starch, 15% sorbitol, 30% theophylline monohydrate and 2% glyceryl monostearate ($n = 3$).

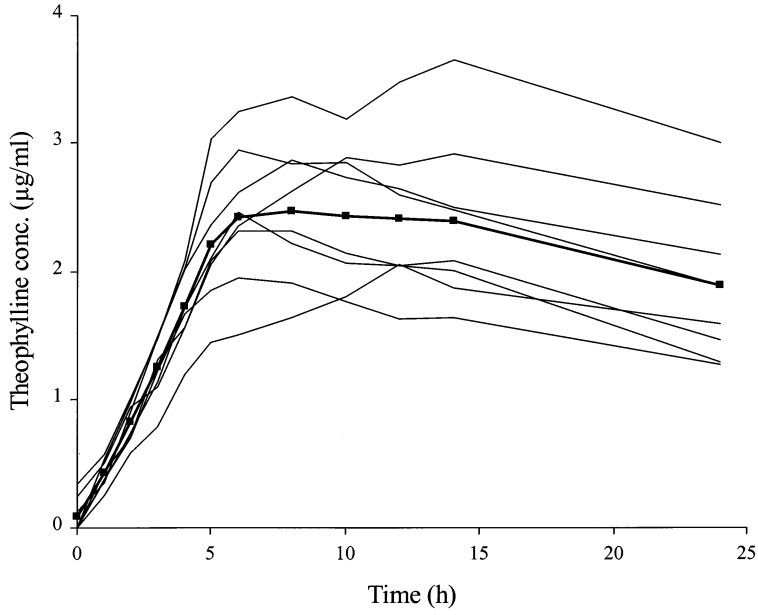

Fig. 2. Individual (–) and mean (–■–) plasma concentration-time profiles after administration of 300 mg theophylline as Xanthium® to eight volunteers.

theophylline syrup with a $t_{75\%\ C_{max}}$ of 3 h (Vandenbossche et al., 1992). The hot stage extrusion formulation only showed a slight sustained release effect with a mean $t_{75\%\ C_{max}}$ of 5.4 h and a $t_{75\%}$ C_{max} ratio of 1.8. The mean t_{max} was significantly higher for Xanthium® than for the hot stage extrusion formulation (9.0 and 4.6 h, respectively) and the mean C_{max} significantly lower (2.6 and 6.3 µg ml^{-1}, respectively). The latter might explain that four volunteers reported headache after intake of the hot stage extrusion formulation, while none did after the intake of Xanthium®. The $AUC_{0-\infty}$ of the hot stage extrusion formulation, was higher than that for Xanthium® (119.4 and 81.8 µg ml^{-1} h^{-1}, respectively).

When compared to values previously obtained with drum dried corn starch (DDCS) matrix tablets containing 300 mg anhydrous theophylline at a drug loading of 30% and manufactured by direct compression (Vandenbossche et al., 1992), it can be concluded that the sustained release parameter $t_{75\%\ C_{max}}$ and the maximum plasma concentration C_{max} are similar for both formulations (5.4 h and 6.3 µg ml^{-1} for the hot stage extrusion formulation and 5 h and 6.1 µg ml^{-1} for the DDCS formulation, respectively). The t_{max} is higher for the DDCS formulation (8 h versus 4.6 h for the hot stage extrusion formulation), but the $AUC_{0-\infty}$ is lower (74.3 µg ml^{-1} h^{-1} versus 119.4 µg ml^{-1} h^{-1} for the hot stage extrusion formulation). From these data we can conclude that the sustained release behavior of both formulations is very similar, but that the bioavailability of the drug from the hot stage extruded matrix is higher. Therefore the extrusion technique might offer advantages over the direct compression method, although fine-tuning of the release profiles remains necessary.

4. Conclusions

Hot stage extrusion of starch based formulations is a promising new pharmaceutical technique for the continuous production of matrix formulations for controlled drug delivery.

The hot stage extrusion formulation showed a slow drug release profile in vitro. The in vivo comparison, however, between the extrudates and the commercially available sustained release sys-

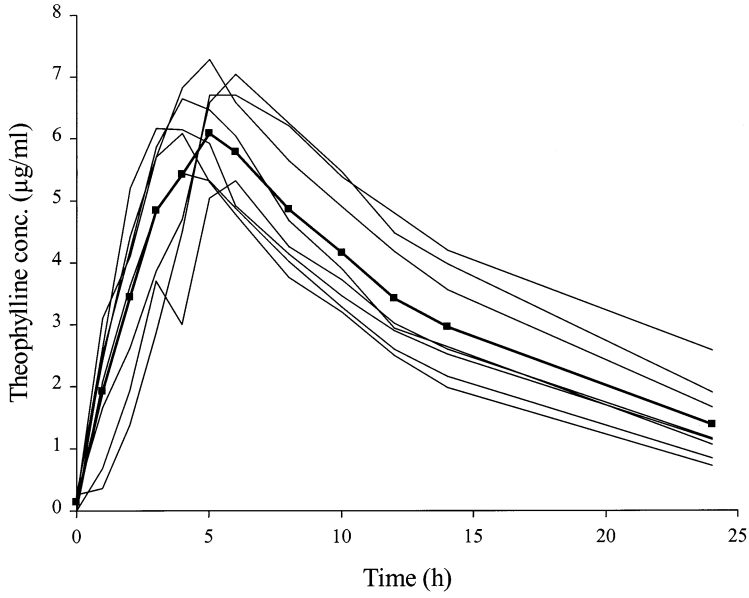

Fig. 3. Individual (–) and mean (–■–) plasma concentration-time profiles after administration of 300 mg theophylline as a hot stage extrusion formulation which consisted of 53% corn starch, 15% sorbitol, 30% theophylline monohydrate and 2% glyceryl monostearate to eight volunteers.

Table 1
Mean pharmacokinetic parameters ($\pm$SD) after oral administration of 300 mg theophylline as Xanthium® and as an experimental hot stage extrusion formulation to eight healthy volunteers

Formulation	t_{max} (h)	C_{max} (µg ml^{-1})	$AUC_{0-\infty}$ (µg ml^{-1} h^{-1})	$t_{75\%\ C_{max}}$ (h)
Xanthium®	9.0 ± 3.70	2.6 ± 0.56	81.8 ± 34.21	16.4 ± 2.62
Experimental formulation	4.6 ± 1.06[a]	6.3 ± 0.71[b]	119.4 ± 41.72[a]	5.4 ± 0.86[a]

[a] Significantly different from Xanthium® according to the Wilcoxon-Signed-Ranks test ($P<0.05$).
[b] Significantly different from Xanthium® according to a two-way ANOVA ($P<0.05$).

tem Xanthium® showed that the hot stage extrusion formulation performed less well, although it did exhibit a low to intermediate in vivo sustained release behavior and although it might offer advantages over a direct compressed drum dried corn starch matrix due to its higher bioavailability. The fine tuning of the in vivo sustained release profile of the hot stage extrusion formulations will be the objective of future research.

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