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A new generation starch product as excipient in pharmaceutical tablets
III. Parameters affecting controlled drug release from tablets based on high surface area retrograded pregelatinized potato starch

G.H.P. Te Wierik [a], A.C. Eissens [a], J. Bergsma [b], A.W. Arends-Scholte [b], G.K. Bolhuis [a,*]

[a] *Groningen Institute for Drug Studies (GIDS), Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV, Groningen, The Netherlands*
[b] *Avebe, Foxhol, The Netherlands*

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Abstract

This paper describes the general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems. It was prepared by enzymatic degradation of potato starch followed by precipitation (retrogradation), filtration and washing with ethanol. The advantages of the material include ease of tablet preparation, the potential of a constant release rate (zero-order) for an extended period of time and the possibility to incorporate high percentages of drugs with different physicochemical properties. Constant release profiles are the result of solvent penetration into the tablet. For theophylline as test drug, constant release profiles could be realized up to a drug content of 75%. This illustrates the possibility to control the release of highly dosed drugs. Release rates from retrograded pregelatinized starch tablets can be enhanced or decreased to the desired profile by different parameters, like geometries of the tablet, compaction force and the incorporation of additional excipients. For procaine HCl it is demonstrated that larger tablets show slower release rates. The incorporation of soluble excipients like lactose and mannitol results for paracetamol in enhanced release rates. The delivery of bases and their salts can be modified by the incorporation of organic acid or alkaline excipients, as is demonstrated for lidocaine and procaine HCl. © 1997 Elsevier Science B.V.

Keywords: Direct compression; Modification of release profile; Retrogradation; Starch; Zero-order release

* Corresponding author.

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1. Introduction

Oral controlled drug release systems are increasingly used for short half-life drugs to reduce peak blood-levels and side-effects, to maintain optimum drug concentration and to stimulate patient compliance (Robinson and Lee, 1987; De Haan and Lerk, 1984). For the aim of a constant drug blood-level during an extended period a constant in vitro drug release rate is desired. The most popular controlled-release system is the matrix tablet (Desai et al., 1965; Lehmann, 1984), because its ease of fabrication involves only blending and compaction. However, release from most matrix tablets is governed by (porous) diffusion resulting in a decreasing drug release rate with time (Higuchi, 1963).

In a previous paper a new starch product for controlled drug release was introduced (Te Wierik et al., 1997). It consists of linear glucose polymers with a mean degree of polymerization (DP) of 30 and was prepared by enzymatic degradation of gelatinized potato starch followed by precipitation (retrogradation), filtration and washing with ethanol (Te Wierik et al., 1996; Arends-Scholte et al., 1996). The latter process proved to create powders with a specific surface area > 1.5 m^2/g. Tablets compressed from a physical mixture of this material with theopylline released the drug with a decreasing rate due to porous diffusion when the tablet porosity was $> 7\%$, but a nearly constant drug release was observed for lower porosities (Fig. 1). Release from tablets with porosity $< 7\%$ was explained by the rate of penetration of a solvent front into the tablet (Te Wierik et al., 1997), which is the result of glass–rubber transition of the amorphous oligosaccharide upon contact with the dissolution medium (Peppas, 1984; Alfrey et al., 1966). These tablets did not disintegrate during the dissolution test, whereas addition of α-amylase to the solvent did not change the release profile. This makes the new starch product a suitable candidate as excipient in controlled-release matrix tablets.

The present paper describes the general applicability of retrograded pregelatinized starch as a directly compressible filler–binder for matrix tablets. Increase or decrease of the drug release to the desired profile by changing of tablet geometries or drug load was investigated. Moreover, the effect of incorporation of extra excipients on the release profile was tested.

2. Materials and methods

2.1. Chemicals

Retrograded pregelatinized starch was prepared from food-grade potato starch (Avebe, Foxhol, The Netherlands) by gelatinization followed by enzymatic degradation, retrogradation, filtration and washing with ethanol as described in a previous paper (Te Wierik et al., 1997). The product was stored at 20°C and 50% RH resulting in a moisture content of 12.5%. Theophylline monohydrate, potassium dichromate (both from ACF-Chemiefarma, Maarssen, The Netherlands), procaine HCl, paracetamol (both from Bufa-chemie, Castricum, The Netherlands) and lidocaine (Holland Pharmaceutical Supply, Alphen a/d Rijn, The Netherlands) were used as (model) test drugs, whose aqueous solubility is listed in Table 1. Alpha-lactose monohydrate 100

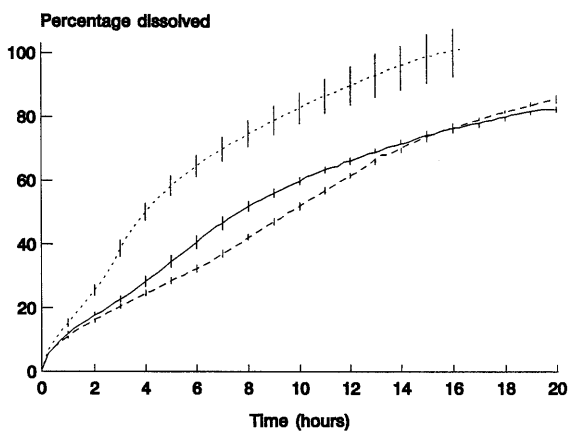

Fig. 1. Release of theophylline from tablets (300 mg, diameter 9 mm) containing 30% drug and 70% retrograded pregelatinized potato starch compressed at (dotted line) 10 kN (porosity 8%); (normal line) 15 kN (porosity 3%) and (dashed line) 25 kN (porosity 1%), respectively, determined in 0.05 M phosphate buffer pH 6.8. Vertical bars indicate standard deviations ($n = 3$).

Table 1
Aqueous solubility of the different active ingredients used as model compound in this study

Compound	Aqueous solubility (g/l)
Procaine HCl	1000
Potassium dichromate	117
Paracetamol	15
Theophylline	8
Lidocaine	4

Mesh was supplied by DMV (Veghel, The Netherlands), whereas mannitol was delivered by Merck (Darmstadt, Germany). Sodium stearate and talc were obtained from Interpharm ('s-Hertogenbosch, The Netherlands) and Centrafarm (Etten-Leur, The Netherlands), respectively, whereas tartaric acid and citric acid were supplied by Brocacef (Maarssen, The Netherlands) and succinic acid was delivered by Janssen Chimica (Geel, Belgium), respectively. HPMC (hydroxypropylmethylcellulose) 4000 mPas was obtained from BUFA (Uitgeest, The Netherlands). Magnesium stearate was delivered by Centrachemie (Etten-Leur, The Netherlands). For all chemicals sieve fractions < 180 μm were used.

2.2. Preparation of tablets

Tablet formulations were prepared by mixing the components in a Turbula mixer (Bachoven, Basel, Switzerland) at 90 rpm during 30 min. If lubricated, mixing was continued after the addition of 0.5% magnesium stearate for 2 min. Tablets were compacted on an instrumented hydraulic press (ESH Testing, Brierley Hill, UK) in a 9 or 11 mm die having flat-faced punches, at a compaction load of 15 kN (9 mm tablets) or 20 kN (11 mm tablets) with a load rate of 2 kN/s. The force was applied during 0.1 s. The porosity of the tablets was calculated from the tablet dimensions, tablet weight and the true density of the powders to be compacted. Latter parameter was determined with a (He)-pycnometer model MVP-1 (Quantachrome, Syosset, USA). Porosity was determined in fivefold.

2.3. Release study

The release profiles of the tablets were measured in a USP XXIII paddle apparatus (Rhône-Poulenc, Paris, France) at 100 rpm in 0.05 M phosphate buffer pH 6.8. The drug concentrations were measured spectrophotometrically using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands) at 248 nm for paracetamol, 261 nm for potassium dichromate, 263 nm for lidocaine, 268 nm for theophylline and 290 nm for procaine HCl. All experiments were carried out in triplicate.

3. Results and discussion

3.1. Variation of drug load

The effect of drug concentration on the release kinetics is shown in Fig. 2. All tablets (300 mg, 9 mm diameter) compacted at 15 kN from physical blends of theophylline and retrograded pregelatinized starch product showed a porosity of $<$ 5%. Up to a drug concentration of 30% the tablets showed no disintegration whereas the release profile proved to be independent of the

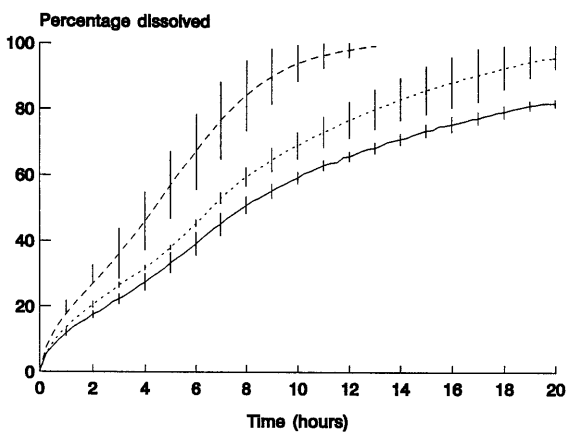

Fig. 2. Release of theophylline from retrograded pregelatinized starch tablets (300 mg, diameter 9 mm) containing (normal line) 30%; (dotted line) 50% or (dashed line) 75% drug, determined in 0.05 M phosphate buffer pH 6.8. Tablets containing 10 or 20% drug showed the same profile as that with 30% theophylline.

theophylline concentration and almost linear during 8–10 h. Moreover, low standard deviations were observed. Increase of the theophylline concentration to 50% resulted in a dissolution curve which is still linear with time but slightly faster than the tablets containing 30% drug. Moreover, some disintegration was observed towards the end of the experiment resulting in an increase in standard deviation. The tablets containing 75% theophylline disintegrated slowly during 12 h and showed a complete drug dissolution during this period with a still surprisingly constant rate. On the other hand, tablets either containing the drug alone or composed of 75% theophylline and 25% HPMC (hydroxypropylmethylcellulose) showed a complete release in about 4 h (not included in the figure). Knowing that the cellulose derivative is one of the most popular excipients for sustained-release matrix tablets, the retrograded starch product appears to be an excellent candidate for the application in directly compressed controlled-release matrices. The curve shown by the tablets with 75% theophylline and 25% starch product is interesting for highly dosed drugs. Moreover, all release profiles shown in Fig. 2 are not affected by lubrication with magnesium stearate and/or by the presence of α-amylase in the dissolution medium. Because of similarity, the profiles of tablets containing magnesium stearate and/or α-amylase are not included in Fig. 2. The latter observation is in agreement with previous results (Te Wierik et al., 1997) and could be confirmed by preliminary in vivo experiments which will be subject of a next study.

The mechanism of solvent penetration-induced glass–rubber transition would imply that the profile is not dependent upon the drug load. Indeed, tablets containing theophylline in a concentration up to 30% showing not any disintegration delivered the drug according to the same profile, as described above. The dependency upon drug load for tablets containing more than 30% theophylline may be attributed to the creation of pores in the tablets by the dissolving drug molecules. Increase of the drug load leads to a larger number and size of pores created, which may facilitate the glass–rubber transition of the remaining unwetted glassy core of the tablet, leading to a faster penetration of the solvent front and an increased release rate. Up to 30% drug the porosity created appears to be too small to influence the release mechanism.

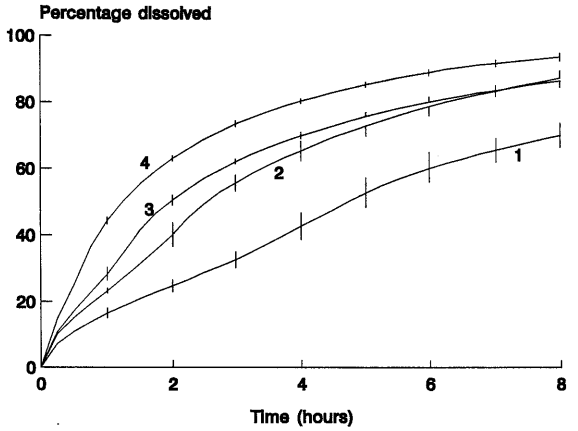

Fig. 3. Release of paracetamol from tablets (300 mg, diameter 9 mm) containing 30% drug and retrograded pregelatinized starch in the presence and absence of lactose, determined in 0.05 M phosphate buffer pH 6.8. Key: (1) without lactose; (2) with 10% lactose; (3) with 20% lactose; (4) with 30% lactose.

In conclusion, retrograded pregelatinized starch is a suitable candidate for directly compressed controlled-release matrices, including tablets containing highly dosed drugs. The release profile can be manipulated by varying the drug load. In the remaining sections of this paper, it will be demonstrated that it is possible to obtain profiles without changing the drug dose or the drug load.

3.2. Incorporation of additional water-soluble excipients

One of the methods to increase the release to the desired profile is incorporation of excipients with a high aqueous solubility. This will be demonstrated for controlled-release tablets with paracetamol as a model drug. The water-soluble excipients used were α-lactose monohydrate and mannitol, both generally applied as filler in tablet formulations. Fig. 3 depicts the release of paracetamol from tablets containing 30% drug, retrograded pregelatinized starch and lactose in different concentrations. Again, all tablets showed a porosity $< 5\%$. Incorporation of 10% lactose

resulted up to 60% drug release in an almost constant but increased dissolution rate of paracetamol as compared to the drug delivery from the tablets without lactose. The higher drug release rate may be attributed to dissolution of lactose molecules creating pores and thus facilitating the solvent front penetration, as was discussed in the preceding section. A higher lactose concentration creates an increased porosity upon dissolution, resulting in a further increase in release rate. Indeed higher lactose concentrations lead to an initially faster linear drug release up to 60% dissolved drug. However, at this level the tablet is completely wetted (Alfrey et al., 1966) and subsequently release is determined by drug diffusion resulting in a decreasing release rate with time. Identical release profiles were found if lactose was replaced by mannitol.

The results presented sofar demonstrate that drug release rates from retrograded pregelatinized starch tablets can be increased to a desired profile by increasing drug load or by incorporation of water soluble excipients. For paracetamol 10% lactose is the most suitable concentration, without losing linear kinetics up to 60% drug release. For drugs with lower aqueous solubility a higher quantity of lactose may be required. The effect of incorporation of 10% lactose in paracetamol-retrograded pregelatinized starch tablets could be confirmed by preliminary in vivo experiments.

3.3. Incorporation of acid or alkaline excipients

Comparison of the dissolution of paracetamol and theophylline from the tablets without additional excipient reveals a faster release for paracetamol. The difference can be attributed to the higher aqueous solubility of paracetamol (Table 1). Apparently dissolution of the more soluble drug facilitates wetting and glass–rubber transition of the remaining glassy core, as was discussed above for the effect of increasing the drug load and incorporation of a water soluble excipient.

The dependency of the drug release profile upon drug solubility offers the possibility to incorporate excipients that change the solubility of the active ingredient in order to obtain the desired release profile. About 80% of all drugs are weak bases or their salts. The weak basic drug lidocaine shows a release of only 60% in 8 h from tablets compressed from a physical blend of 10% drug and 90% retrograded pregelatinized starch (Fig. 4). Comparing the Figs. 2 and 4 show that the release rate of lidocaine is higher than that of theophylline. However, from the aqueous solubility (Table 1) of the two drugs a slower release of lidocaine was expected. Moreover, after 4 h the tablets containing lidocaine show some disintegration resulting in an increased standard deviation (Fig. 4). This disintegration and relatively fast dissolution can be explained by the higher porosity (7%) of the lidocaine tablets, as compared to a value of 3% for the theophylline tablets. Incorporation of 20% lactose or mannitol in the lidocain tablets resulted in an improved dissolution profile of 80% released in 8 h (Fig. 4). Incorporation of 10% succinic acid even leaded to a higher release rate of lidocaine being complete in 6 h. Latter tablets showed no disintegration during dissolution and consequently the standard deviation was low. For citric acid and tartaric acid as extra excipient the same profile was obtained as for succinic acid.

The improved release of lidocain from tablets containing 20% lactose or 10% succinic acid (Fig. 4) cannot be explained by the porosity because all

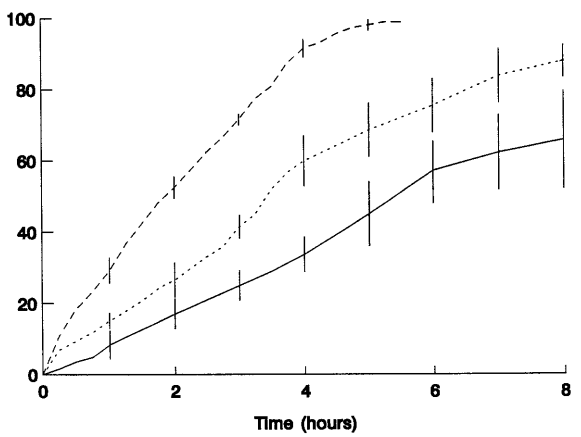

Fig. 4. Release of lidocaine from tablets (600 mg, diameter 11 mm) containing 10% drug and retrograded pregelatinized starch, determined in 0.05 M phosphate buffer pH 6.8. Key: (normal line) without extra excipient; (dotted line) with 20% lactose; (dashed line) with 10% succinic acid.

tablets containing lidocain with or without an extra excipient showed a similar porosity of about 7%. Since the concentration of the acid excipient (10%) was lower than that of lactose (20%) the strongly improved dissolution by succinic acid cannot fully be attributed to facilitated wetting of the glassy core. Moreover, from the lower aqueous solubility of succinic acid (100 g/l, as compared to a value of 250 g/l for lactose) also a slower profile was expected for the tablets with the acid excipient. Incorporation of a weak acid like tartaric, citric or succinic acid leads to a decrease in pH in the tablet. The lidocaine molecule is protonated at lower pH values thereby increasing the drug solubility (Kramer and Flynn, 1972) and thus leading to the strongly increased drug release. This principle offers the possibility to modify the drug release of weak basic drugs from retrograded pregelatinized starch tablets by regulation of the pH in the tablet. This principle has formerly been applied for the release of noscapine (HCl) from diffusion-controlled matrix tablets (Thoma and Zimmer, 1990) and the delivery of ketanserine and mianserine from megaloporous tablets (Van der Veen et al., 1991). The pH regulating effect will depend upon the aqueous solubility and pK_a of the organic acid and upon the solubility–pH profile of the drug.

The reverse effect can be obtained for salts of weak bases, among which procaine HCl is demonstrated as a model. If a slow profile is desired the pH in the tablet can be increased by addition of a base thereby decreasing the aqueous solubility of procaine in the tablet. Because soluble excipients are released from the retrograded pregelatinized starch matrix tablets during a few hours, a poor aqueous solubility is a prerequisite for the alkaline excipient to maintain the increased pH over longer times. Fig. 5 illustrates the dissolution curves of procaine HCl from retrograded pregelatinized starch matrix tablets with and without the weak water-insoluble base sodium stearate. For reason of comparison the figure also shows the curves as obtained for talc as example of a neutral water insoluble excipient and for potassium dichromate as active ingredient, having a pH independent aqueous solubility. The difference between the release of procaine HCl and potassium

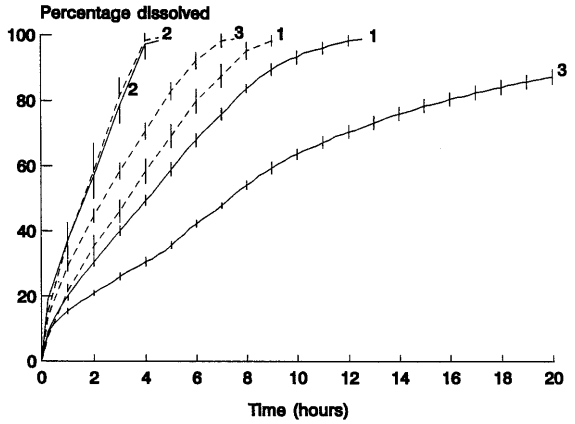

Fig. 5. Release of (normal lines) procaine HCl and (dashed lines) potassium dichromate from tablets (600 mg, diameter 11 mm) containing 10% drug and retrograded pregelatinized starch, determined in 0.05 M phosphate buffer pH 6.8. Key: (1) without extra excipient; (2) with 20% talc; (3) with 20% sodium stearate.

dichromate from the tablets without extra excipient can be explained by the different porosities (Table 2). The two formulations containing talc as additional excipient showed an increased porosity and hence faster release. Thus, an excipient with poor aqueous solubility and without acidic or basic properties has no extra retarding effect on the drug release. Just like the tablets with talc as excipient, the tablets containing potassium dichromate and sodium stearate showed an increased drug release as compared to the tablets without extra excipient, which is again explained by the increased porosity. Although the procaine HCl tablets with sodium stearate also showed an increased porosity, this formulation demonstrated a

Table 2
Porosity (%) of tablets (600 mg, diameter 11 mm) containing 10% procaine HCl or 10% potassium dichromate

	Procaine HCl	Potassium dichromate
Without extra excipient	5.8	7.1
With 20% talc	10.3	10.8
With 20% sodium stearate	8.1	8.7

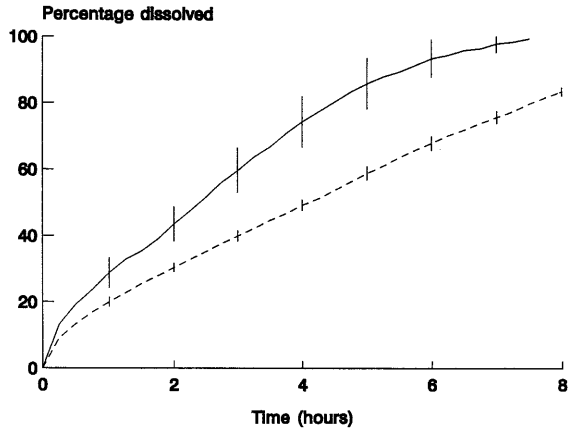

Fig. 6. Release of procaine HCl from (dashed line) one 600 mg tablet with diameter 11 mm or (normal line) two 300 mg tablets with diameter 9 mm, both tablets containing 10% drug and 90% retrograded pregelatinized starch, determined in 0.05 M phosphate buffer pH 6.8.

strongly decreased release profile. This result confirms the pH increasing effect of sodium stearate during the prolonged time, resulting in a decrease in solubility and dissolution rate for procaine HCl and not for potassium dichromate. Incorporation of an organic base with a poor aqueous solubility is a method for further retardation of salts of organic bases from retrograded pregelatinized starch tablets.

Modification of the tablet geometries can also influence the drug release from retrograded pregelatinized starch matrix tablets as demonstrated for procaine HCl from different tablets with a porosity of 5.8% (Fig. 6). Release from two 300 mg tablets with a diameter of 9 mm (outer surface 4.4 cm^2 for two tablets) is faster than that from one 600 mg tablet with a diameter of 11 mm (outer surface 3.4 cm^2). For the latter the total surface area available for penetration of a solvent front is smaller than for two 300 mg tablets. Moreover, the solvent front has to penetrate over a longer distance into the larger tablets. Both factors lead to a slower drug release rate from the tablets of 600 mg.

In conclusion, retrograded modified starch is a suitable candidate as excipient in controlled-release matrix tablets. Next to the advantage of the ease of tablet manufacturing it is able to sustain the release of many active ingredients with different physico-chemical properties. Acceleration or retardation to a desired profile can be achieved easily by changing tablet geometries, drug load, incorporation of water-soluble excipients or weak acid or basic compounds or by a combination of two or more of these factors. In the next paper of this series, flow properties as well as the effect of both granulation and compression at high speed of retrograded modified starch will be presented.

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