TECHNICAL INFORMATION

# The Use of Sodium Alginate in Extended Release Tablet Formulations


## Abstract

Extended release tablets are commonly based on partially synthetic cellulose ethers, such as hypromellose (HPMC), hydroxyethyl cellulose (HEC), or hydroxypropyl cellulose (HPC).
Alginates offer an interesting, all-natural alternative to these polymers.
The aim of the present study was to investigate the effect of particle size, concentration, and viscosity of various grades of sodium alginate on the performance of modified release tablets.
Caffeine tablets with extended release over 8-10 hours were successfully prepared by direct compression with VIVAPHARM® sodium alginate.


## Introduction

Therapeutic requirements as well as patient convenience make it desirable to present dosage forms with prolonged release of the active principal. Among the available formulation techniques, the so-called hydrophilic matrix is the easiest and most cost-efficient form. The key components of hydrophilic matrices are the active ingredient(s) and a sufficient quantity (usually 20-30 %) of a hydrophilic polymer. Upon contact with water, the polymer will form a gel layer at the interface of the release medium and the tablet core. Drug release will then occur controlled by diffusion through the gel layer and/or by erosion of the same.
A number of excipient properties are critical to the performance of extended release systems:
The **viscosity** of the polymer affects the strength of the release-controlling gel layer. It has, therefore, a significant impact on the release rate.
The **concentration** of the extended release polymer in a hydrophilic matrix has to exceed a certain level, in order to enable the reproducible formation of a robust gel structure [1].
The **particle size distribution** (**PSD**) of the release-controlling polymer will have an influence on the velocity of the gel formation. I.e. in the case of coarse particles, gel-formation will take longer than for a material of finer PSD. The more time elapses before a consistent gel is formed, the more API can diffuse out of the tablet in an uncontrolled manner. This phenomenon is often referred to as the “burst effect”.

## Aim of the Study

As shown in the introduction, viscosity, concentration, and particle size have an impact on the drug release kinetics. The goal of this study was to understand the interactions of these parameters in order to develop criteria for the selection of sodium alginate grades for extended release tablets made by direct compression. In addition, suitable formulations were compared against corresponding formulations based on HPMC, which is the most widely used release-controlling polymer in hydrophilic matrix tablets.

## Materials and Methods

Modified release caffeine tablets were produced by direct compression using caffeine as a model API, different levels of VIVAPHARM® sodium alginate or HPMC as release-controlling polymer, silicified microcrystalline cellulose (SMCC) as a filler-binder and magnesium stearate as the lubricant.
For comparison, immediate release tablets were produced by direct compression of caffeine with the all-in-one excipient PROSOLV® EASYtab Nutra CM comprising filler-binder, flow aid, disintegrant, and lubricant.

| | Extended Release [%] | | | | | Immediate Release [%] |
|---|---|---|---|---|---|---|
| Caffeine | 40 | 40 | 40 | 40 | 40 | 40 |
| VIVAPHARM® Sodium Alginate* | 20 | 30 | 40 | 50 | – | – |
| HPMC K4M | – | – | – | – | 30 | – |
| PROSOLV® SMCC 90 | 39.5 | 29.5 | 19.5 | 9.5 | 29.5 | – |
| Mg Stearate | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | – |
| PROSOLV® EASYtab Nutra CM | – | – | – | – | | 60 |

Table 1 Formulations Tested. *See Table 2 for Grades of Sodium Alginates used.

| Viscosity [mPa*s] 1 %, 20 °C | Average Particle Size 50 µm | 100 µm | 310 µm |
|---|---|---|---|
| 100-150 | PH 172 | PHU 152 | |
| 250-350 | | | PH 124 |
| 350-550 | PH 175 | FD 155 | PH 125 |
| 550-750 | PH 176 | | |

Table 2 Viscosities and Particle Sizes of the Tested Sodium Alginate Grades.

Dissolution profiles were recorded with either a pH change from 1.0 to 6.8 after two hours (Method 1) or at a constant pH of 6.8 (Method 2).

## Results and Discussion

### The Effect of Viscosity

The viscosity of release-controlling polymers correlates with their polymer chain length and consequently with the robustness of the gels they form at higher concentrations. The effect of viscosity is shown in Figure 1 for three grades of sodium alginate having the same particle size but spanning a range of 100 – 750 mPa*s in terms of viscosity. All formulations contained 20 % alginate.

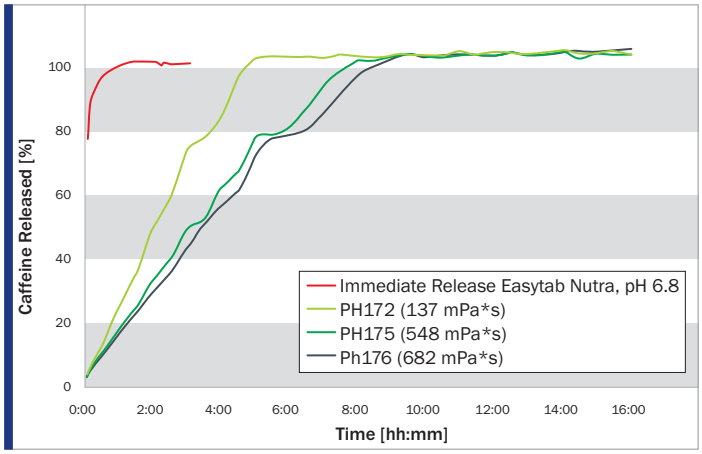


Fig. 1 Dissolution (Method 1) as Function of Polymer Viscosity. (Polymer Concentration and Particle Size kept constant.)

Sodium alginate type PH 175 (548 mPa*s) exhibited a stronger retardation of API release than type PH 172 (137 mPa*s). On the other hand, a further increase from 548 to 682 mPa*s (type 176) did not lead to significant change in the release rate.

### The Effect of Concentration

The strength of the release-controlling gel, and hence the release rate, depends on the polymer concentration in the formulation.

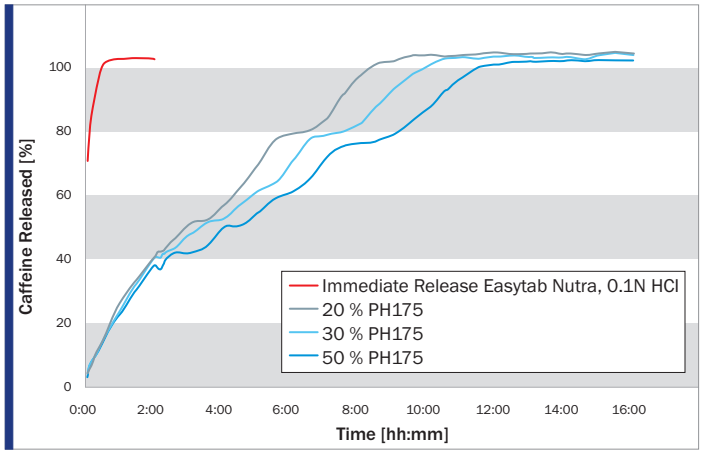


Fig. 2 Dissolution (Method 2) as Function of Polymer Concentration. (Polymer Viscosity and Particle Size kept constant.)

Figure 2 illustrates the effect of polymer concentration on drug release. 80 % API release was reached after approximately six hours in the case of the formulation containing 20 % VIVAPHARM® Sodium Alginate PH 175, whereas the $t_{80}$ for the corresponding formulation with 50 % polymer content was approximately nine hours. While this suggests a wide range of formulation options, certain limitations have to be taken into consideration:

Reduction of the polymer content below 20 % will typically lead to a loss in the consistency of the release rate [1]. It is therefore not a suitable means of achieving faster dissolution. Instead, lower viscosity grades should be considered while maintaining a minimum concentration of 20 %.

In the case of stronger retardation requirements, the poor flowability of sodium alginate powder puts an upper limit on its use level – especially in the case of DC formulations (see Table 3).

### The Effect of PSD

In the interest of directly compressible formulations, the powder flowability of the tableting blend is of vital importance. Both the concentration and the particle size of the sodium alginate used will affect the powder flow. As shown in Table 3, the powder flow can be improved from “poor” (Angle of Repose: 47°) to “passable” (41°) by selecting a coarser grade of the same viscosity type of sodium alginate.

| Viscosity [mPa*s] 1 %, 20 °C | Average Particle Size 50 µm | 100 µm | 310 µm |
|---|---|---|---|
| 100-150 Angle of Repose | PH 172 46° | PHU 152 45° | |
| 250-350 Angle of Repose | | | PH 124 43° |
| 350-550 Angle of Repose | PH 175 47° | FD 155 48° | PH 125 41° |
| 550-750 Angle of Repose | PH 176 47° | | |

Table 3 Effect of Sodium Alginate Particle Size on the Flowability of the Corresponding Tableting Blend.

Figure 3 shows the effect of polymer particle size on the release profiles for tablets containing the same concentration and viscosity of sodium alginate, but differing in particle size. A much faster initial drug release (“burst effect”) is observed for the tablets containing the coarser grade (PH 125). As these tablets contain fewer but larger sodium alginate particles, more time elapses before a consistent formation of a diffusion barrier is reached. During this lag time, API can diffuse out of the tablet in a more or less uncontrolled manner.

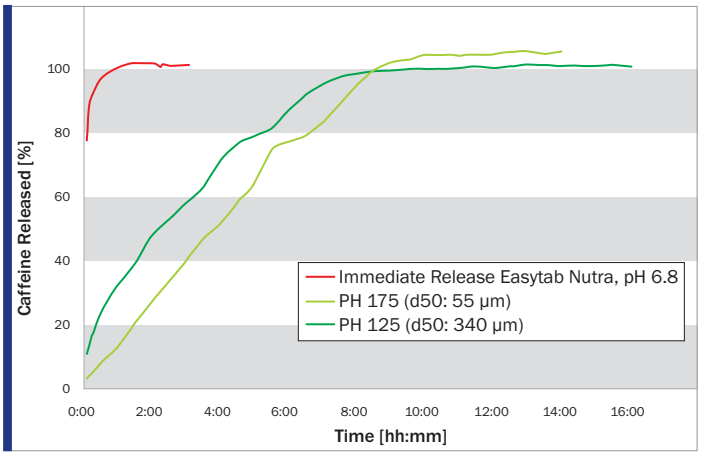


Fig. 3 Dissolution (Method 2) as Function of Polymer Particle Size. (Polymer Viscosity and Concentration kept constant.)

While PH 125 appeared favorable in terms of improved powder flowability (see Table 3), its coarse particle size led to a delayed formation of the release matrix and hence to a considerable burst effect.

### Comparison with HPMC

The most widely used release-controlling polymer in hydrophilic matrix formulations today is HPMC (hypromellose, substitution type 2208). The ability of sodium alginate to extend the release of caffeine was, therefore, compared against a formulation containing an equal percentage of HPMC K4M.
Both formulations showed a significant retardation of drug release compared to the immediate release formulation used as control. The effect was more pronounced in case of HPMC, which yielded an incomplete dissolution during the timeframe observed. Sodium Alginate showed a significant retarding effect, which supports its suitability as a natural alternative to semi-synthetic polymers in the formulation of extended release tablets.

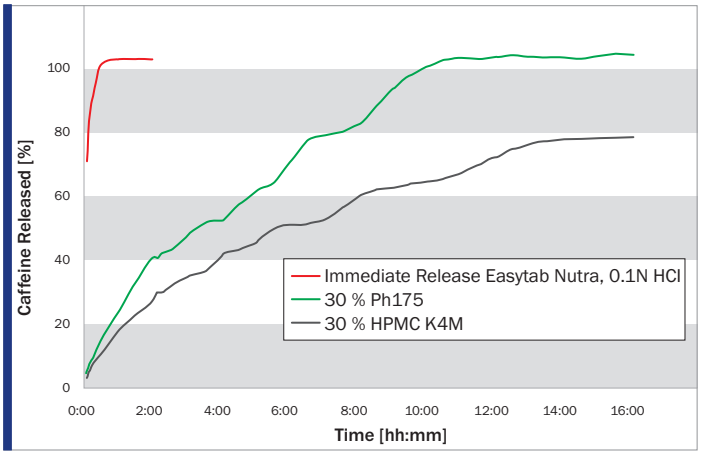


Fig. 4 Dissolution (Method 1) as Function of Polymer Type. (Polymer Concentration kept constant.)

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## Conclusion

Sodium alginate was found to be a suitable release-controlling polymer for directly compressed, extended release tablets.

Its behavior followed the same rules as are commonly accepted for partially synthetic polymers, such as HPMC. I.e., the same formulation boundaries were identified: Particle size has to be balanced between sufficient flowability (large particles) and fast hydration (small particles). Concentration has to be adjusted to a level which avoids inconsistent release behavior (too low concentration) and poor powder flow (too high concentration). The only variable to be freely selected is viscosity, which enables the design of release profiles within the otherwise rigid framework of formulation parameters.

In summary, a general recommendation for the formulation of an alginate-based extended release tablet sums up to a use level of 20-30 % of alginate, with an average particle size of about 50 µm.

Directly compressed caffeine tablets formulated according to this guideline, using VIVAPHARM® Alginate PH 175 at 30 % concentration with PROSOLV® 90 SMCC as filler/binder and magnesium stearate as a lubricant, consistently achieved 8-hour extended release profiles.

Outlook:
Unlike HPMC, alginates are anionic polymers, which are susceptible to pH variation. Different dissolution methods, with and without pH changes, were used in this study. Some interesting effects of the pH of the release medium on the early-phase dissolution behavior were observed and further analyzed. These rather complex findings will be reported in a separate paper.

**Reference:**

[1] Leuenberger et al., Int. J. Pharm., 38 (1987) 109-115

For details regarding the processing conditions and the equipment used, please contact technical-support@jrspharma.de.

Find out more about **VIVAPHARM® Alginates in Extended Release Tablet Formulations** on *www.jrspharma.com*



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