Influence of different types of low substituted hydroxypropyl cellulose on tableting, disintegration, and floating behaviour of floating drug delivery systems

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Abstract The object of the present study is to evaluate the effect of application of low-substituted hydroxypropyl cellulose (L-HPC) 11 and B1 as excipients promoting floating in gastroretentive tablets. Directly compressed tablets were formed based on experimental design. Face-centred central composite design was applied with two factors and 3 levels, where amount of sodium alginate ($X_1$) and L-HPC ($X_2$) were the numerical factors. Applied types of L-HPCs and their 1:1 mixture were included in a categorical factor ($X_3$). Studied parameters were floating lag time, floating time, floating force, swelling behaviour of tablets and dissolution of paracetamol, which was used as a model active substance. Due to their physical character, L-HPCs had different water uptake and flowability. Lower flowability and lower water uptake was observed after 60 min at L-HPC 11 compared to L-HPC B1. Shorter floating times were detected at L-HPC 11 and L-HPC mixtures with 0.5% content of sodium alginate, whereas alginate was the only significant factor. Evaluating results of drug release and swelling studies on floating tablets revealed correlation, which can serve to help to understand the mechanism of action of L-HPCs in the field development of gastroretentive dosage forms.

1. Introduction

Floating drug delivery systems belong to the group of gastroretentive dosage forms firstly described by Davis in 1968 (Davis, 1968). These dosage forms are able to achieve prolonged gastric residence time with increased period for active pharmaceutical ingredients (API) to be released. Action can be local for treatment of the stomach or may be systemic. In the development of floating dosage forms, two different technologies are applied based on...
their mechanism of buoyancy. Various types of effervescent and non-effervescent approaches have been discussed by Singh et al. (Singh and Kim, 2000). In our experiments, effervescent floating tablets (EFT) were prepared based on sodium alginate as a swelling agent and sodium hydrogen carbonate generating carbon dioxide in the acidic media. During the swelling of sodium alginate, carbon dioxide is entrapped in a hydrating gel frame leading to drop of internal density, which leads to the buoyancy of the preparation. One of the most important aims of application of floating drug delivery systems is the fact that several drugs have only narrow absorption window in the gastrointestinal tract, which raises difficulties during the enhancement of the bioavailability. Prolonged gastric residence is also reasonable for drugs which are unstable in the lower section of the gastrointestinal tract or having poor absorption from intestines (Srivastava et al., 2005). In our experiments, sodium alginate floating matrix tablets were produced by simple direct compression.

Mechanisms of different types of disintegrants applied in floating tablets have various effects including swelling, particle repulsion as well as gas generation (Rudnic et al., 1982). Low-substituted hydroxypropyl cellulose (L-HPC) is a widely used disintegrant in direct compression of tablets and granulation as well. Applied concentration is generally between 2.5% and 5.0% (Kawashima et al., 1993a,b). Its disintegrating effect is due to its rapid and intense water uptake and swelling, in which the dominant parameter is the particle size described by Kawashima et al. (1993a,b) as well as shape of particles controlling the process of disintegration.

Another commonly applied excipient in gastroretentive tablets is sodium alginate, which is a non-toxic, biodegradable co-polymer composed of l-guluronic and D-mannuronic acid blocks (Whitehead et al., 1998) derived from brown seaweed species and extracted by the ion-changing technique (Miller, 1996). Sodium alginate also hydrates and swells in aqueous media, however in acidic medium insoluble alginic acid is formed which contributes to the buoyancy.

In the present study the nonsteroidal anti-inflammatory drug (NSAID), paracetamol was used as a model API, which is a widely applied analgesic and antipyretic agent, acting by the inhibition of COX 3 enzyme (Botting and Ayoub, 2005). Paracetamol is highly metabolized, its mean plasma half-life is 2 h in healthy adults (Thomas, 1993), therefore preparation of a floating drug delivery system containing paracetamol is also reasonable. Its solubility is high, 20.2 mg/ml in 0.1 M HCl, therefore its dissolution from matrix tablets is considered to be independent from solubility properties (Obeidat et al., 2010).

In the present study EFTs were prepared according to an experimental design including categorical face-centred central composite set-up with two numeric factors (concentration of sodium alginate and L-HPC) having three levels with one centre point. To accomplish the difference between L-HPC types, categorical factor was introduced, including the two types of L-HPC applied and their 1:1 mixture. Linear, quadratic and cubic fitting models were assessed on the responses in order to find the best model to evaluate the results.

2. Materials and methods

2.1. Materials

Paracetamol (Molar Chemicals, Hungary) was used as a model drug substance. High viscosity sodium alginate (Hungaropharma, Hungary) was used as the swelling excipient promoting flotation. Viscosity of the applied 1% sodium alginate solution was 213.80 ± 0.83 mPas measured at 100 s⁻¹ shear rate with Anton Paar Rheolab QC viscometer at 30 °C. Low substituted hydroxypropyl cellulose B1 (Egis Pharmaceuticals PLC, Hungary) and 11 (Egis Pharmaceuticals PLC, Hungary) were used as disintegrants. Sodium bicarbonate (Molar Chemicals, Hungary) was used as effervescent agent. Tale, magnesium stearate, microcrystalline cellulose and silica colloidal anhydrous were used as excipients for tablet compression (Hungaropharma, Hungary).

2.2. Comparative physical examination of L-HPC 11 and L-HPC B1 disintegrants

2.2.1. Microscopic examination

Microscopic examination at 160× and 640× magnification (Zeiss, Axio Imager A1 Microscope, Germany) was performed to measure particle size and shape parameter of the two different types of L-HPCs by using a 5 megapixel microscopic camera (Zeiss AxioCam MRc 5, Germany). For particle size examination 50 largest separated particles were measured.

Sphericity (Ψ) was calculated by the following formula:

\[
Ψ = \frac{4\pi A_\text{r}}{P_\text{cr}}
\]

Sphericity of particles describes the form of region on the bases of their circularity. Numerically range is from 0 to 1. The value of the sphericity for a perfect round shape particle is 1. Filled area (A_

Crofton perimeter (P_\text{cr}) determines circular region with correction, which is optimized for circular objects. For digital photo analysis Zeiss Axio Vision Rel. 4.7 software (Carl Zeiss, Germany) was used.

2.2.2. Flowability

Differences in flow properties of the types of L-HPCs were examined to highlight further physical dissimilarities. Determination of angle of repose was carried out according to 2.9.16. test of Ph. Eur. 5.0. During the examinations ASTM standard funnel was used having 111 mm height and 10 mm size of orifice. The funnel was fixed 4 cm above a glass plate. Measurement was carried out in triplicate. Angle of repose was calculated by the following formula (USP, 2007):

\[
tg(x) = \frac{H}{R}
\]

where, \(x\) is the angle of repose, \(H\) is the height above the glass plate, and the \(R\) is the radius of the conical pile. Result was considered to be valid, when symmetric cone shape was formed.

Apparent density examination was carried out by a volumetric device (Erweka SVM 121, Germany) according to 2.9.15. Ph. Eur. 5.0. During the experiments tapped and bulk densities were calculated. 100.0 g L-HPC types were filled into a dry graduated cylinder, after which the cylinder was locked on a tapping platform performing 10, 500, and 1250 taps. Bulk densities (\(\rho_{\text{bulk}}\)) were recorded after filling into graduated cylinder; tapped densities (\(\rho_{\text{tapped}}\)) were recored after 1250 taps referred to 100.0 g sample. Using these measurements Carr index (Ci) (Carr, 1965) was calculated according to the following formula:
were studied at C0 and (%) 0.50 17.82 35.15

\[ C_i = \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \times 100 \]  \hspace{1cm} (3)

Hausner ratio (Hr) was also determined by using ratio between tapped and bulk density of powders applying the following formula:

\[ H_r = \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \]  \hspace{1cm} (4)

2.2.3. Wettability

Force tensiometer (KSV, Sigma 701) was used to evaluate water uptake of the applied HPCs. Glass sample holder vessel was applied with 1.15 mm width and with 1.00 mm diameter glass filter at the bottom holding 50.0 mg of samples, immersed into distilled water and 0.1 M hydrochloric acid with 0.5 mm immersion depth for 60 min. Sampling was done every 5 s. Accuracy of force tensiometer instrument was 0.01 mg. Wettabily tests were performed in triplicate.

2.3. Preparation of floating tablets

2.3.1. Experimental design

Central composite design was implemented to view the difference of two types of L-HPCs in dissolution and floating properties of tablets. The design contained two numeric factors (X1, X2) with three-levels (−1, 0, +1) in a face-centred central composite set-up (α = 1) with one centre point. One categorical factor was also applied including the types of two L-HPCs and their 1:1 mixture (X3). Each experimental composition had two independent variable ingredients: the concentration of sodium alginate (X1) and the particular L-HPCs (X2). Sodium alginate and L-HPC content is shown in Table 1. Table 2 represents the 9 possible combinations for the third, categorical factor (X3). Each tablet contained 150 mg paracetamol and fixed amounts of excipients contributing the floatation and tablet compressing ability. Examined variables were the following: floating time, floating lag time, floating force, swelling capability and drug dissolution.

2.3.2. Production of floating tablets

Table ingredients were accurately weighed on analytical balance (Kern, ABJ 220-4M, Germany). Mixing of the powders was performed every time after adding next substance for 3 min using mortar and pestle, and ultimately all the blends were blended for 10 min. The flow property of final mixtures was qualified to be suitable for direct compression applying eccentric single-punch tablet press (Erweka, EP-1, Germany) using 8, 10, 12 mm round concave punches.

2.3.3. Determination of floating time and floating lag time

Floating time (t_f) is the time, during which the sample tablet floats on the surface of the examined medium, floating lag time (t_lag) is period from the immersion of the tablet until its buoyancy. Before starting experiments, tablets were stored for 24 h in a desiccator. Parameters t_f and t_lag were studied at 37 ± 0.5°C in 450 ml hydrochloric acid (pH = 1.2) in triplicate. Duration of buoyancy and lag time was visually recorded by a camcorder (Sony, DCR-SX85E). Each test was carried out for 4 h.

2.3.4. Determination of swelling capability

Swelling capabilities of floating tablets were examined in triplicate, according to the method described by Dorozynski et al. (2004). Tablet weights were measured (W1) then immersed into a glass beaker filled with 200 ml of 0.1 M hydrochloric acid. Temperature was maintained at 37 ± 0.5°C. At time 30, 60, 120, 180 and 240 min, tablets were removed from the beaker and reweighted (W2) after wiping the excess liquid from its surface. Swelling index (S) was calculated by the following formula:

\[ S = \frac{(W_2 - W_1)}{W_1} \]  \hspace{1cm} (5)

Calculated index was corrected with the actual tablet weight in order to standardize the results. Swelling study was performed only on tablets having no rapid disintegration.

2.3.5. Study of floating forces

Floating force study was carried out based on the theoretical background described by Timmermans and Moes (1989,

### Table 1: Levels and real values of experimental design.

| Levels of factors | Concentration of sodium alginate, X1 (%) | Concentration of L-HPCs, X3 (%) |
|-------------------|------------------------------------------|----------------------------------|
|                   | 0.50                                      | 17.82                            |
|                   | 17.82                                     | 35.15                            |

### Table 2: Experimental layout of categorical face-centred central composite design(X_i).

| Exp. No. | Sodium alginate | L-HPC 11 |
|----------|-----------------|----------|
| PFS01    | −1              | −1       |
| PFS02    | 1               | −1       |
| PFS03    | −1              | 1        |
| PFS04    | 1               | 1        |
| PFS05    | −1              | 0        |
| PFS06    | 1               | 0        |
| PFS07    | 0               | −1       |
| PFS08    | 0               | 1        |
| PFS09    | 0               | 0        |

| Exp. No. | Sodium alginate | L-HPC B1 |
|----------|-----------------|----------|
| PFS10    | −1              | −1       |
| PFS11    | 1               | −1       |
| PFS12    | −1              | 1        |
| PFS13    | 1               | 1        |
| PFS14    | −1              | 0        |
| PFS15    | 1               | 0        |
| PFS16    | 0               | −1       |
| PFS17    | 0               | 1        |
| PFS18    | 0               | 0        |

| Exp. No. | Sodium alginate | L-HPC 11/Bl (1:1) |
|----------|-----------------|-------------------|
| PFS19    | −1              | −1                |
| PFS20    | 1               | −1                |
| PFS21    | −1              | 1                 |
| PFS22    | 1               | 1                 |
| PFS23    | −1              | 0                 |
| PFS24    | 1               | 0                 |
| PFS25    | 0               | −1                |
| PFS26    | 0               | 1                 |
| PFS27    | 0               | 0                 |
Fig. 1 Structure of standard vessel and filtering plate for floating force test.

In order to carry out the measurements KSV Sigma force tensiometer (KSV Instruments Ltd., Helsinki, Finland) was applied, which is a precision scale with 0.1 mg accuracy. Tablets floated in a standard vessel containing 450 ml 0.1 M hydrochloric acid, in which a special filtering plate with 2 mm aperture size was immersed (Fig. 1). Majority of developing carbon dioxide bubbles passed through the filter resulting in less noise during the measurement. Media were treated with ultrasound to avoid gas formation on filtering plate.

During the test, the weight of the filtering plate was continuously measured. EFTs pushed the filtering plate upward, thus change of the weight could be detected in function of time. Evaluation contained the determination of the maximal floating force \((F_{\text{max}})\), time \((t_{\text{fmax}})\) needed for maximal floating force and \((t_{\text{F1/2}})\), which is required for 50% of maximal floating force.

Floating forces were calculated based on description by Cromer (1981):

\[
F_{\text{float}} = F_0 - F_t = F_0 - m_t \cdot g = F_0 - (F_0 + m_0 \cdot g)
\]

In the formula above \(F_{\text{float}}\) is the floating force expressed on the filtering plate by a tablet. \(F_0\) equals the multiplication of filtering plate mass in medium with gravitational acceleration \(g\), which was constantly 39.84 mN. \(m_t\) is the weight measured by the devices when a tablet pushed the plate upward. \(m_0\) is the negative weight gradient caused by the tablet directly, which was calculated by subtraction of \(m_t\) from \(m_0\). In absolute value, \(m_t\) is the weight expressed by the buoyancy of EFT tablets. All experiments were done in triplicate.

Paracetamol content was measured by a UV/VIS spectrophotometer (Jasco V-670, Japan) on the absorption maximum of the drug substance at 243 nm. Paracetamol concentrations were calculated according to a linear calibration curve \((R^2 = 0.9997)\) which was measured between 0 and 25 mg/l concentration. All samples were measured in this concentration interval.

2.4. Statistical analysis

Evaluations of our measurements were carried out by Design Expert 7.0.0 software (Stat-Ease, USA). Statistical analysis was carried out by generating polynomial models including interaction and quadratic terms as well. After the analysis of statistical parameters involving coefficient of variation \((\text{CV})\) and regression coefficient \((R^2)\), the best fitting model was chosen. Analysis of variance (ANOVA) was applied to determine significant factors of the experiments. \(F\) test and \(p\)-values were also calculated and evaluated.

The following mathematical model equation shows the effects of various independent variables and their interaction:

\[
Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2,
\]

in which \(Y\) is the response, \(b_0\) is the intercept, and \(b_1\) is the estimated coefficient of factors \((X_1, X_2)\). \(X_1, X_2\) are the main effects. \(X_1\), \(X_2\) is the interaction term, how responses change when factors are changed simultaneously. \(X_1^2, X_2^2\) is the quadratic effect to evaluate non-linearity.

3. Results and discussion

3.1. Comparative physical study of different types of L-HPCs

3.1.1. Microscopic examination

Digital photo analysis revealed different shapes of L-HPCs depicted by Fig. 2. L-HPC 11 particles had a thin, longitudinal shape, while L-HPC B1 formed similar to spheroidal particles. Sphericity of L-HPC 11 was 0.186 ± 0.082, while in the case of L-HPC B1 it was 0.4802 ± 0.183.

Particle sizes varied also in comparison of the two L-HPCs. The 50 largest particle sizes of examined particles were 44.01 ± 10.59 μm in the case of L-HPC B1 compared to L-HPC 11 with 246.35 ± 82.03 μm size.
3.1.2. Wettability
Over the study period (1 h) 50 mg pure disintegrants were tested. Both L-HPCs behaved similarly having intense water uptake in both media (water and hydrochloric acid). Fig. 3 shows the wettability in the function of time in distilled water and 0.1 M HCl. At the end of the first minute, both L-HPCs immersed into distilled water absorbed more than 90% of water compared to the water uptake during 1 h (L-HPC B1: 91.24 ± 1.02%, L-HPC 11: 93.83 ± 1.02%). In hydrochloric acid, liquid absorption was similar to distilled water with a relatively small decrease after 60 s (L-HPC B1: 89.05 ± 2.89%, L-HPC 11: 92.77 ± 1.59%). L-HPC B1 had higher total wettability than L-HPC 11 showed in Table 3. Decrease of wettability could be noticed in 0.1 M HCl compared to distilled water at both L-HPC types. In the case of L-HPC 11, higher rate of water uptake could be achieved with less amount of medium absorbed at the end of examination compared to L-HPC B1.

3.1.3. Flowability
Both Carr index and Hausner ratio showed better flowability properties for L-HPC B1 compared to L-HPC 11. Difference could be detected not only in ratios but also between tapped ($q_t$) and bulk ($q_b$) densities of the L-HPC B1 ($\rho_b = 0.4964 ± 0.0115$, $\rho_t = 0.5908 ± 0.0026$) and L-HPC 11 ($\rho_b = 0.3564 ± 0.0076$, $\rho_t = 0.4428 ± 0.0013$). Measurements of angles of repose indicated the same relation. Results are represented in Table 4.

Responses evinced that flow properties of L-HPCs not markedly differed in comparison in spite of their different shape parameters and particle sizes.

3.2. Floating lag time and floating time
Basic concept for the flotation of the tablets was their 8% sodium hydrogen carbonate content as a gas-forming agent blended with sodium alginate as hydrogel matrix in order to entrap the gas inside the tablet. This process was controlled by the varying L-HPC content, which influenced the floating lag time ($t_{lag}$) and floating time ($t_f$) shown in Table 5.

The best fitting model for the floating lag time data was the linear model ($p < 0.01$). Values of $t_{lag}$ indicate that lower level of sodium alginate (0.5%) and various concentrations of L-HPCs resulted in lower floating lag time for tablets. The only significant factor in this experiment was sodium alginate ($p < 0.01$). Result showed that higher sodium alginate content led to the increase of $t_{lag}$. It is supposed that sodium alginate in increased concentration leads to formation of alginic acid layer.

![Figure 2](image.png) Microscopic snapshots of (a) L-HPC 11 and (b) L-HPC B1 particles.

| Table 3 | Total wettability of L-HPC 11 and L-HPC B1. |
|---------|---------------------------------------------|
| Total wettability of 50 mg L-HPCs | In distilled water (mg) | In 0.1 M HCl (mg) |
| L-HPC 11 | 483.7 ± 22.8 | 451.0 ± 17.4 |
| L-HPC B1 | 522.7 ± 36.6 | 480.0 ± 39.6 |

| Table 4 | Flow characteristics of L-HPC 11 and L-HPC B1. |
|---------|-----------------------------------------------|
| Carr index | Hausner ratio | Angle of repose (°) |
| L-HPC 11 | 22.91 ± 0.32 | 1.24 ± 0.04 | 48.77 ± 1.67 |
| L-HPC B1 | 19.05 ± 2.31 | 1.19 ± 0.02 | 39.24 ± 0.86 |

| Table 5 | Data of floating lag time ($t_{lag}$) and floating time ($t_f$). |
|---------|-------------------------------------------------------------|
| Exp. No. | $t_{lag}$ (s) | $t_f$ (min) |
| PFS01 | 6.44 ± 5.19 | 21.70 ± 4.56 |
| PFS02 | 343.00 ± 28.99 | 240.00 ± 0.00 |
| PFS03 | 0.00 ± 0.00 | 7.13 ± 0.47 |
| PFS04 | 507.16 ± 100.35 | 240.00 ± 0.00 |
| PFS05 | 0.00 ± 0.00 | 3.91 ± 0.28 |
| PFS06 | 107.16 ± 75.77 | 240.00 ± 0.00 |
| PFS07 | 109.20 ± 89.32 | 240.00 ± 0.00 |
| PFS08 | 16.69 ± 1.58 | 240.00 ± 0.00 |
| PFS09 | 520.30 ± 20.79 | 240.00 ± 0.00 |
| PFS10 | 16.02 ± 6.58 | 28.63 ± 1.08 |
| PFS11 | 356.55 ± 47.07 | 240.00 ± 0.00 |
| PFS12 | 0.00 ± 0.00 | 15.51 ± 2.96 |
| PFS13 | 230.16 ± 11.87 | 240.00 ± 0.00 |
| PFS14 | 0.00 ± 0.00 | 15.25 ± 1.89 |
| PFS15 | 507.67 ± 161.30 | 240.00 ± 0.00 |
| PFS16 | 273.45 ± 156.64 | 240.00 ± 0.00 |
| PFS17 | 180.00 ± 51.64 | 240.00 ± 0.00 |
| PFS18 | 106.14 ± 24.18 | 240.00 ± 0.00 |
| PFS19 | 25.77 ± 6.53 | 35.74 ± 3.05 |
| PFS20 | 238.16 ± 13.25 | 240.00 ± 0.00 |
| PFS21 | 13.87 ± 3.25 | 17.23 ± 1.25 |
| PFS22 | 417.22 ± 18.12 | 240.00 ± 0.00 |
| PFS23 | 307.71 ± 174.70 | 240.00 ± 0.00 |
| PFS24 | 344.00 ± 29.70 | 240.00 ± 0.00 |
| PFS25 | 238.33 ± 27.79 | 240.00 ± 0.00 |
| PFS26 | 184.00 ± 24.64 | 240.00 ± 0.00 |
on the tablet’s surface, leaving the tablet’s internal space dry. Thus due to the high polymer concentration, tablets with higher weight require longer time to float. In low concentration, sodium alginate swelled more rapidly enhanced by quick water uptake of L-HPCs.

On floating time data, quadratic model was fitted with high significance ($p < 0.0001$, $R^2 = 0.9992$). Both independent variables and their interaction showed acceptable significance. 18 batches showed more than 4 h long buoyancy having 17.82–35.15% sodium alginate. The shortest floating times were recorded in the cases of 12.75% L-HPC 11 and L-HPCs 1:1 mixture. Presence of L-HPC 11 in tablets resulted in short floating due to its faster disintegration.

### 3.3. Determination of swelling capability

In case of floating drug delivery systems, the mechanism of hydration and swelling capability are important parameters, with which more specific physical evaluation can be performed. Swelling capability may determine various parameters of floating drug delivery systems including disintegration, dissolution, as well as adhesion ability.

Mechanism of hydration was expounded by Bertram and Bodmeier (2006), according to which water-absorbing ability of hydrogels is influenced by hydrophilic groups in the chemical structure. Hydration of these hydrophilic groups results in the swelling, namely the expansion and ordering of polymer chains. At matrix tablets, swelling process requires certain time to reach deeper layers to be hydrated, which is driven by the passive diffusion. The theory of drug release from matrix tablets was approached by Ju et al. (1995), describing that after immersion of tablets, diffusion creates different hydration layers in tablets. Relatively dry core with low water content is followed by more hydrated middle layer, which is surrounded by a surface layer in contact with water. The surface layer is also considered as an erosion front.

Swelling index ($S_i$) represents the water uptake of tablets standardized to the tablet weight. The result after 4 h shows that tablets with the highest percent of sodium alginate and L-HPCs had the highest swelling property (PFS04, PFS13, PFS22) having $S_i$ more than 2.2. The lowest swelling indices were recorded in the cases of PFS07, PFS16, PFS25 with lower concentration of sodium alginate (17.83%) and 0.5% of L-HPCs. Swelling indices from 1.9 to 2.2 could be detected in the cases of PFS06, PFS15, PFS24 tablets with 35.15% sodium alginate and 12.75% L-HPCs as well as at PFS08, PFS17, PFS26 compositions having less sodium alginate and more L-HPCs (17.83% sodium alginate and 25.0% L-HPCs).

Swelling was evaluated based on the experimental design. Analysis of swelling at particular times revealed sodium alginate as a significant factor ($p < 0.0006$), while L-HPCs were significant from 120 min ($p < 0.0301$). At 30 and 60 min, L-HPCs did not show significant influence, then from 120 min analysis concluded that swelling depends on the quantity of L-HPCs, too.

In this case the categorical factor $X_3$ was not rated to be significant. The most significant fitting on the linear model was shown by the result of swelling at 4 h. Its equation is the following:

$$Swelling(4h) = 1.72 + 0.43X_1 + 0.12X_2 - 3.455e^{-0.003X_3} - 0.017X_3$$

The equation showed that factor $X_2$ (L-HPCs) had less than third influence on swelling after 4 h compared to factor $X_1$ (sodium alginate).

### 3.4. Floating force study

Floating strength measurement was recorded in function of time for 4 h. Two different floating patterns could be observed within the samples: a rapidly disintegrating and an exponentially increasing pattern. Two different types (PFS03/PFS04) are illustrated in Fig. 4.

The two-factor model containing interactions was fitted on $F_{max}$ data with $p < 0.0001$. Significant influence was observed for both factors (sodium alginate and L-HPCs) ($p < 0.0001$) and their interaction was also significant ($p = 0.0004$). Categorical factor had no significance. The final equation relating maximal floating forces as response becomes:

$$F_{max} = 2.05 + 0.53X_1 + 0.51X_2 + 0.18X_3 + 0.083X_4$$

$$+ 0.54X_1X_2 - 0.42X_1X_3 + 0.44X_1X_4$$
$$- 0.013X_2X_3 + 0.055X_2X_4$$

On $t_{F_{max}}$ the data quadratic model was fitted ($p = 0.0009$). ANOVA indicated that the only factor which significantly influences $F_{max}$ was sodium alginate ($p < 0.0001$). The linear model was fitted on $t_{F_{1/2}}$ values with high significance ($p = 0.0045$) resulting sodium alginate to be the only significant factor ($p = 0.0002$). In both cases L-HPCs and categorical factor were not significant model terms.

### 3.5. Paracetamol dissolution study

Release of paracetamol of all EFTs was examined for 4 h. Dissolution of paracetamol of floating tablets containing L-HPCs is shown in Fig. 5. The fastest dissolution was represented by compositions containing 0.5% sodium alginate and 0.5%, 12.75% and 17.82% from particular L-HPCs. Rapid release
was probably caused by the low content of sodium alginate, since the weak alginic layer around the tablet was presumably not strong enough to maintain the coherent structure and L-HPCs could achieve disintegration of tablets.

The quadratic model was fitted onto the curve of 4 h dissolution data. Final equation of dissolution at 4 h was:

\[
\text{Dissolution}(4h) = 16.46 - 57.94X_1 + 2.29X_2 + 6.14X_3
\]

\[
- 3.50X_5 - 1.57X_1X_2 + 3.84X_1X_3
\]

\[
+ 1.32X_2X_3 - 0.81X_2X_5
\]

\[
+ 1.24X_2X_3 + 73.62X_1^2 + 1.34X_2^2 \tag{10}
\]

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**Figure 4** Floating force of (a) PFS03 (25.0% L-HPC 11, 0.5% sodium alginate) and (b) PFS04 (25.0% L-HPC 11, 35.15% sodium alginate).

**Figure 5** Release of paracetamol from EFTs containing L-HPC 11.

**Figure 6** Influence of swelling capability on dissolution comparing PFS22 (25.0% L-HPC 11/B1, 35.15% sodium alginate) and PFS25 (0.5% L-HPC 11/B1, 17.82% sodium alginate).
Significant model terms were $X_1$ ($p < 0.0001$) and $X_2^2$ ($p < 0.0001$) pointing that only the effect of sodium alginate had influence on dissolution at 4 h. Concentration of L-HPC was not significant based on the analysis of variance (ANOVA). Analysis of the quadratic model on dissolution at 60, 90, 120 and 180 min resulted in $X_1$, $X_2^2$ and categorical factors (L-HPC types) as significant model terms ($p \leq 0.05$). These results were similar to the 4 h dissolution.

Statistical analysis of dissolution after 5, 10, 15, 20, 30 and 45 min showed different release behaviour compared to the drug release profile after 1 h. During this time interval L-HPC showed disintegrant activity, which presumably influenced the dissolution of the drug substance. Categorical factor in these six times was not significant. The largest difference between L-HPC types and their 1:1 mixture was observed at 15 min dissolution. More specific difference was between L-HPC 11 and L-HPC B1, because their mixture mostly behaved as L-HPC 11.

In 45 min period of time, not only difference between L-HPC types was permanent, but also significance of particular L-HPCs on the quadratic model could be noticed, hence dissolution was influenced by the amount of L-HPCs in this time interval. As an indicator of significance on model, values of $p < 0.05$ were acceptable. 45 min dissolution meant a special point in the dissolution, since sodium alginate, L-HPCs, and categorical factor all were significant until this point. After this time differences in dissolution between L-HPC types disappeared.

Impact of sodium alginate and L-HPC types on dissolution was evaluated by the analysis of final equations of dissolution at particular times, from which the largest impact of L-HPCs was at 15 min dissolution:

\[
\text{Dissolution (15 min)} = 6.85 - 52.21X_1 + 11.17X_2 + 2.30X_3 - 2.79X_2^2 - 16.56X_1X_2 - 1.79X_1X_3 + 3.24X_1X_3^2 - 1.59X_2X_3 + 0.73X_2^2X_3 + 53.34X_1^2 - 5.64X_2^2
\]

Equation also expresses interaction between L-HPC and sodium alginate, which was only observed between 5 and 45 min.

Release of paracetamol was compared to the swelling behaviour of EFTs in order to achieve a better approach in the mechanism of drug release. Dissolution data were assessed in function of swelling data for each composition at the same sampling time. On evaluating the results, exponential correlation was found, which confirms that increase in swelling enhances the dissolution of paracetamol. Fig. 6 shows the influence of the swelling on the dissolution of PFS22 and PFS25 having the highest and lowest swelling indices.

4. Conclusions

In this study, 27 different EFT tablet samples were successfully prepared by using various amounts of sodium alginate, L-HPC 11 and L-HPC B1 as excipients and paracetamol as the active pharmaceutical ingredient. Relevant, but small differences were observed at the two L-HPC types during the physical examinations of the substances. In these tests, L-HPC 11 had lower water uptake and slightly worse flowability, which may be explicable due to its longitudinal shape and larger particle size. Prepared tablets were further investigated from the viewpoint of floating dosage forms. Analysis of floating lag time values and times for maximal and half maximal floating force coincided so that the only influencing factor was the amount of sodium alginate. L-HPCs were detected to have impact on maximal floating force and showed to behave differently. Higher and lower floating force values could be noticed at L-HPC B1 in compositions, while values of L-HPC 11 produced smaller maximal floating force. Effect of L-HPCs on disintegration could be observed in paracetamol release examinations in the first hours, which coincided with the results of swelling capabilities. Function of release and swelling tests showed exponential increasing relationship. Though L-HPCs did not affect the paracetamol release after 1 h, swelling after 1 h showed to have an inverse influence on swelling with different L-HPCs. In both results, sodium alginate had significant influence. During the experiments and their evaluation a cooperative effect of L-HPCs and sodium alginate was revealed, which resulted in the liquid uptake without disintegrating effect, enhancing the entrapment of the developing carbon dioxide in the floating system. Our results may stand as a basis for further studies in the field of development and optimization of disintegrating floating dosage forms.

References

Bertram, U., Bodmeier, R., 2006. In situ gelling, bioadhesive nasal inserts for extended drug delivery: in vitro characterization of a new nasal dosage form. Eur. J. Pharm. Sci. 27, 62–71.

Botting, R., Ayoub, S.S., 2005. COX-3 and the mechanism of action of paracetamol/acetaminophen. Prostaglandins Leukot. Essent. Fatty Acids 72, 85–87.

Carr, R., 1965. Evaluating flow properties of solids. Chem. Eng. 72, 163–169.

Cromer, A.H., 1981. Physics for Life Sciences, 2nd ed. McGraw-Hill Intern. Book Co., Tokyo, Japan, int. student edition, 134–153.

Davis, D.W., 1968. Method of swallowing a pill. US Patent 3,418,999.

Davis, R.K.S.S., 1990. The effect of tablet size on the gastric emptying of non-disintegrating tablets. Int. J. Pharm. 62, R9–R11.

Dorozynski, P., Jachowicz, R., Kulinowski, P., Kwiecinski, S., Szybinski, K., Skorka, T., Jasinski, A., 2004. The macromolecular polymers for the preparation of hydrodynamically balanced systems-methods of evaluation. Drug Dev. Ind. Pharm. 30, 947–957.

Ju, R.T.C., Nixon, P.R., Patel, M.V., 1995. Drug-release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug-release based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1455–1463.

Kawashima, Y., Takeuchi, H., Hino, T., Niwa, T., Lin, T.L., Sekigawa, F., Kawahara, K., 1993a. Low-substituted hydroxypropylcellulose as a sustained-drug release matrix base or disintegrant depending on its particle size and loading in formulation. Pharm. Res. 10, 351–355.

Kawashima, Y., Takeuchi, H., Hino, T., Niwa, T., Lin, T.L., Sekigawa, F., Ohia, M., 1993b. The effects of particle size, degree of hydroxypropyl substitution and moisture content of low-substituted hydroxypropylcellulose on the compactability of acetaminophen and the drug release rate of the resultant tablets. STP Pharma Sci., 170–177.

Klauser, E.A., Levy, E., Friedman, M., Hoffman, A., 2003. Expandable gastroretentive dosage forms. J. Control. Release 90, 143–162.
Miller, I.J., 1996. Alginate composition of some New Zealand brown seaweeds. Phytochemistry 41, 1315–1317.

Obeidat, W.M., Abuznait, A.H., Sallam, A.S., 2010. Sustained release tablets containing soluble polymethacrylates: comparison with tableted polymethacrylate IPEC polymers. AAPS PharmSciTech 11, 54–63.

Oth, M., Franz, M., Timmermans, J., Moes, A., 1992. The bilayer floating capsule: a stomach-directed drug delivery system for misoprostol. Pharm. Res. 9, 298–302.

Rudnic, E.M., Rhodes, C.T., Welch, S., Bernardo, P., 1982. Evaluations of the mechanism of disintegrant action. Drug Dev. Ind. Pharm. 8, 87–109.

Singh, B.N., Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release 63, 235–259.

Srivastava, A.K., Wadhwa, S., Ridhurkar, D., Mishra, B., 2005. Oral sustained delivery of atenolol from floating matrix tablets – formulation and in vitro evaluation. Drug Dev. Ind. Pharm. 31, 367–374.

Stops, F., Fell, J.T., Collett, J.H., Martini, L.G., Sharma, H.L., Smith, A.M., 2006a. Citric acid prolongs the gastro-retention of a floating dosage form and increases bioavailability of riboflavin in the fasted state. Int. J. Pharm. 308, 14–24.

Stops, F., Fell, J.T., Collett, J.H., Martini, L.G., Sharma, H.L., Smith, A.M., 2006b. The use of citric acid to prolong the in vivo gastro-retention of a floating dosage form in the fasted state. Int. J. Pharm. 308, 8–13.

Thomas, S.H., 1993. Paracetamol (acetaminophen) poisoning. Pharmacol. Ther. 60, 91–120.

Timmermans, J., Moes, A.J., 1989. Determining in vitro the resultant-force acting on a pharmaceutical form immersed in a fluid, an apparatus and a method. In: Proceedings of the Fifth APGI International Conference on Pharmaceutical Technology Part 2, pp. 294–303.

Timmermans, J., Moes, A.J., 1990a. How well do floating dosage forms float. Int. J. Pharm. 62, 207–216.

Timmermans, J., Moes, A.J., 1990b. Measuring the resultant-weight of an immersed test material. 1. Validation of an apparatus and a method dedicated to pharmaceutical applications. Acta Pharm. Technol. 36, 171–175.

USP, 2007. Powder flow <1174> USP30 NF 25.

Whitehead, L., Fell, J.T., Collett, J.H., Sharma, H.L., Smith, A.M., 1998. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. J. Control. Release 55, 3–12.