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Simultaneous controlled vitamin release from multiparticulates: Theory and experiment

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ABSTRACT

The aim of this study was to simultaneously control the release of multiple vitamins exhibiting very different water-solubility and molecular weights from multiparticulates. Several types of sucrose esters and triglycerides were studied as matrix formers in granules prepared by wet granulation, melt granulation or compression and grinding. The vitamin release kinetics were measured in 0.1 N HCl, phosphate buffer pH 6.8 and water in a USP paddle apparatus. An appropriate analytical solution of Fick's second law of diffusion was used to better understand the underlying mass transport phenomena. Importantly, the release rates of nicotinamide, pyridoxine hydrochloride, riboflavin 5′-phosphate, riboflavin, thiamine chloride hydrochloride and thiamine nitrate can simultaneously be controlled from the investigated multiparticulates. Varying the total vitamin content, granule size, type of preparation technique and type of matrix former (Sucrose Stearate S370, Sucrose Stearate S1170, glycerol dibehenate, glycerol dipalmitostearate), desired vitamin release rates can be adjusted. Interestingly, diffusion seems to be the dominant mass transport mechanism in most cases. Thus, appropriate solutions of Fick's law can be used to quantitatively predict the effects of the systems' composition and dimensions on the resulting vitamin release patterns. This knowledge can significantly help facilitating device optimization.

1. Introduction

Generally, only one drug is released in a time-controlled manner from an advanced delivery system. So far, little is known on devices, which are able to control the release of several active agents simultaneously (Sivak et al., 2009; Vukomanović et al., 2011). If the substances to be delivered exhibit very different physicochemical properties (e.g., molecular weight, water-solubility), it might be highly challenging to adjust the release kinetics of a specific compound, while avoiding undesired fast/slow release of the other compounds. In this study, nicotinamide, pyridoxine hydrochloride, riboflavin 5′-phosphate, riboflavin, thiamine chloride hydrochloride and thiamine nitrate were investigated. Their molecular weights vary from 122 to 478 Da, their water-solubility from 0.07 to 1000 g/L (Table 1, note that the presence of other compounds might alter the latter values). Multiparticulates (granules) containing these compounds were prepared, providing the advantage of a more uniform spreading throughout the gastro intestinal tract upon oral administration compared to single unit dosage forms, and avoiding the all or nothing effect of the latter.

Sucrose esters and triglycerides have been selected as matrix formers, optionally combined with ethylcellulose or microcrystalline cellulose. Sucrose esters are non-ionic, non-toxic, tasteless, odorless and well-known in the food and cosmetics industry. Depending on the type and number of fatty acids, they exhibit very different HLB values. Sucrose esters are also widely used in the pharmaceutical industry, for example as solubility enhancers, surfactants, lubricants and in controlled release dosage forms (Ntawukulilyayo et al., 1995). Tablets containing sucrose esters can be prepared by direct compression or wet granulation. It has been found that the amount of sucrose ester in the formulation as well as a thermal treatment of sucrose ester-based granules prior to tabletting affects the resulting release kinetics (Ntawukulilyayo et al., 1996). Due to their relatively low melting ranges, sucrose esters can also be used in melt granulation processes and pelletization technologies (Hoffmann et al., 2001). Szűts et al. (2010) investigated physical mixtures of sucrose esters, which were able to control the release of acetaminophen when filled into in hard gelatin capsules.

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Table 1
Molecular weight (MW) and aqueous solubility (c_s) of the investigated vitamins (from "The Merck Index, 1996").

	MW (Da)	c_s (g/L)
Nicotinamide	122.13	~1000
Pyridoxine hydrochloride	205.64	~220
Pyridoxine H^+	170.18	–
Thiamine nitrate	327.36	27
Thiamine chloride HCl	337.28	1000
Thiamine cation	265.35	–
Riboflavin	376.37	0.07
Riboflavin-5′-phosphate	478.33	112

However, to the best of our knowledge, sucrose esters have not yet been described as matrix formers in controlled release multiparticulates, nor have they been used for the *simultaneous* controlled release of multiple compounds. Furthermore, the characteristics of sucrose esters are yet not fully understood and still the focus of ongoing research (Szűts et al., 2007; Ullrich et al., 2008). One of the reasons for this is the fact that commonly used (commercially available) sucrose esters are *blends* of a several different types of esters. Consequently, various key properties of the systems are not sharply defined, e.g. sucrose esters often do not have one single melting peak, but show a more or less broad melting range (Szűts et al., 2007). In addition, sucrose esters can form liquid crystalline mesophases (Queneau et al., 2001; Sadtler et al., 2004; Molinier et al., 2006; Ullrich et al., 2008). Obviously, their lyotropic and thermotropic behavior can affect the performance of the sucrose esters as matrix formers in controlled release dosage forms.

In order to better understand the underlying mass transport processes controlling compound release in an advanced delivery system, mechanistic realistic mathematical models can be used (Klose et al., 2008; Glaessl et al., 2010). Based on comprehensive experimental results appropriate theories can be identified and used to determine system specific parameters (Guse et al., 2006; Fredenberg et al., 2009). Key properties in the case of controlled release vitamin granules include the size and shape of the systems, degree of homogeneity of the initial drug distribution in the devices, drug content and potential changes of these features upon exposure to different release media. Once the system specific parameters (for instance the apparent diffusion coefficient of a vitamin in a particular granule type) are known, appropriate mathematical theories allow for quantitative predictions of the effects of different formulation and processing parameters on the resulting compound release kinetics. To evaluate the validity of the applied model such theoretical predictions should be compared to *independent* experimental results (Siepmann et al., 2006; Siepmann and Siepmann, 2008).

The aim of this study was to simultaneously control the release of nicotinamide, pyridoxine hydrochloride, riboflavin 5′-phosphate, riboflavin, thiamine chloride hydrochloride and thiamine nitrate from multiparticulates (granules). The type of preparation technique (wet granulation, melt granulation and compression and grinding) was to be varied as well as the systems' composition and dimensions. Fick's second law of diffusion was used to better understand the underlying mass transport mechanisms and to provide the possibility to quantitatively predict the effects of formulation and processing parameters on the resulting vitamin release kinetics.

2. Materials and methods

2.1. Materials

Nicotinamide, pyridoxine hydrochloride, riboflavin 5′-phosphate, thiamine chloride hydrochloride and thiamine nitrate (DSM, Basel, Switzerland), riboflavin (BASF, Ludwigshafen, Germany), sucrose esters: Sucrose Stearate S370–HLB: 3, melting range: 51–69 °C; and Sucrose Stearate S1170–HLB: 11, melting range: 49–55 °C (Ryoto sugar esters, Mitsubishi Kasei Food, Tokyo, Japan), glycerol dibehenate (HLB: 2, melting point: 70 °C) and glycerol dipalmitostearate (HLB: 2, melting point: 56 °C) (Gattefosse, Saint-Priest, France), ethylcellulose (Aqualon T10 Pharm; Hercules, Ashland Division, Hopewell, VA, USA), microcrystalline cellulose (Avicel PH 102; FMC Biopolymer, Cork, Ireland).

2.2. Preparation of granules

Granules containing nicotinamide, pyridoxine hydrochloride, riboflavin or riboflavin 5′-phosphate, thiamine chloride hydrochloride and/or thiamine nitrate were prepared by: (i) melt granulation, (ii) wet granulation, or (iii) compression and grinding. The matrix formers (sucrose esters, glycerol dibehenate or glycerol dipalmitostearate), vitamins and optionally ethylcellulose or microcrystalline cellulose were blended in a Turbula blender (Bachofen, Muttenz, Switzerland) for 30 min.

In the case of melt granulation, the respective blends were heated in a bowl on a water bath to 80 °C and manually mixed using a spatula. The obtained granules were cooled down to room temperature and subsequently passed through a 4.0 mm granulation sieve (Turbo sieve; Bohle, Ennigerloh, Germany).

In the case of wet granulation, the respective blends were mixed with purified water (manually) in a bowl using a spatula and subsequently dried under protection from light at room temperature (over night). The obtained agglomerates were passed through a 2.0 mm sieve (Retsch, Haan, Germany).

In the case of granulation via compression and grinding, the respective blends were first compressed into tablets using an excentric tabletting machine (E1; Fette, Schwarzenbek, Germany) (flat faced punches, diameter = 10 mm), which were subsequently ground and passed through a 4.0 mm granulation sieve (Turbo sieve).

In all cases, differently sized granule fractions were obtained by sieving (0.5, 1.0, 1.6, and 2.0 mm) (Retsch, Haan, Germany).

2.3. Characterization of granules

The morphology of the granules was studied using an optical macroscope (SZX12; Olympus, Hamburg, Germany).

Vitamin release from the granules was measured in 500 mL 0.1 M HCl, purified water or phosphate buffer pH 6.8 (Ph. Eur.) using the USP 32 paddle apparatus (DT 80; Erweka, Heusenstamm, Germany). At pre-determined time points, 3 mL samples were withdrawn (not replaced with fresh medium) and analyzed for their vitamin contents by HPLC analysis (Elite LaChrom; Hitachi, Tokyo, Japan) using a LiChrospher 100 RP 18e, 5 μm column (250 mm × 4 mm I.D.). The mobile phase consisted of a 1:4 blend of methanol and an aqueous buffer solution of the following composition: 1.9 g/L sodium salt of heptansulfonic acid, 1.5 g/L potassium dihydrogen phosphate, 5 mL/L triethylamin, the pH was adjusted with phosphoric acid (85%) to pH 2.4. The flow rate was 1.0 mL/min (0–10 min) and 1.6 mL/min (10–22 min), respectively. The vitamins were detected by UV spectrophotometry at the following wave lengths: nicotinamide λ = 264 nm, pyridoxine λ = 290 nm, riboflavin λ = 270 nm, riboflavin 5′-phosphate λ = 270 nm, thiamine λ = 250 nm.

The specific surface area and pore size of the granules was measured using a "Micromeritics ASAP 2420 Accelerated Surface Area and Porosimetry System" (Micromeritics, Norcross, Georgia, USA; BET method).

The hardness of the granules was determined using a texture analyzer (TA.XT plus; Stable Micro Systems, Godalming, UK),

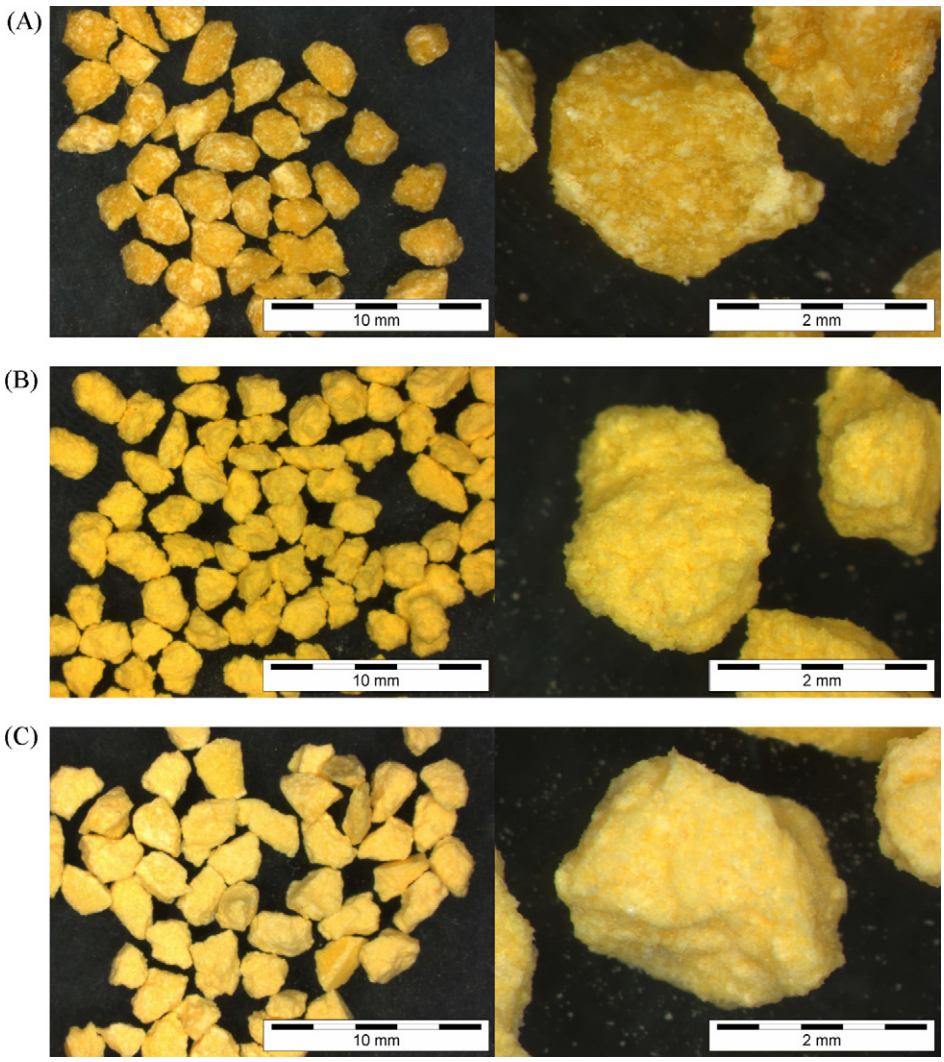

Fig. 1. Optical pictures of granules prepared by: (A) melt granulation, (B) wet granulation, or (C) compression and grinding (Sucrose Stearate S370; sucrose ester content: 80%, total vitamin content: 5%, microcrystalline cellulose content: 15%). Left hand side: lower magnification, right hand side: higher magnification.

equipped with a flat-tipped cylindrical stainless steel probe (diameter: 6 mm); pre-test velocity: 1 mm/s, test velocity: 0.2 mm/s, post-test velocity: 0.2 mm/s, maximum force: 50.0 N, trigger force: 0.005 N, load cell: 5 kg.

3. Results and discussion

3.1. Granule morphology, specific surface area, pore size and hardness

Fig. 1 shows optical photographs of vitamin-loaded, Sucrose Stearate S370-based granules prepared by: (A) melt granulation, (B) wet granulation, or (C) compression and grinding. The left column shows ensembles of granules (lower magnification), the right column single granules at higher magnification. The systems consist of 3.6% nicotinamide, 0.5% pyridoxine hydrochloride, 0.4% thiamine nitrate, 0.3% riboflavin, 80% sucrose ester and 15% microcrystalline cellulose. In all cases similarly shaped particles were obtained, with a relatively narrow size distribution. The geometry of the granules might best be approximated by that of a sphere or ellipsoid. The yellow color is due to the presence of riboflavin (the other compounds are colorless). Importantly, the uniformity of the color indicates that riboflavin is rather homogeneously distributed throughout the systems. The differences in the brightness of the yellow can probably be explained as follows: During *melt granulation* riboflavin can be expected to (at least partially) dissolve in the molten sucrose ester and might (at least partially) remain in this state upon cooling. During *wet granulation* riboflavin first dissolves in the granulation fluid (purified water) and then re-precipitates upon drying. This can be expected to result in a finer riboflavin particle distribution compared to that in granules prepared by *compression and grinding*. During the latter preparation technique, the vitamin remains in the solid state. At the end of the release experiments, all granules/granule fractions were white, indicating that riboflavin was completely released.

The specific surface area of the granules increased in the following ranking order: melt granulation ($0.05\ m^2/g$) < compression and grinding ($0.23\ m^2/g$) < wet granulation ($0.28\ m^2/g$), whereas the pore size decreased: melt granulation (1053 Å) > compression and grinding (315 Å) > wet granulation (214 Å). This is consistent with the observed variation of the granules' hardness: melt granulation (3.02 ± 0.76 N) > compression and grinding (1.15 ± 0.13 N) > wet granulation (0.76 ± 0.32 N). These differences can be attributed to the type and strength of the bonds created during granulation between the sucrose ester and vitamin particles. Importantly, granules prepared by melt granulation or compression and grinding were sufficiently stable to remain intact throughout the vitamin release experiments. In contrast, granules prepared by wet granu-

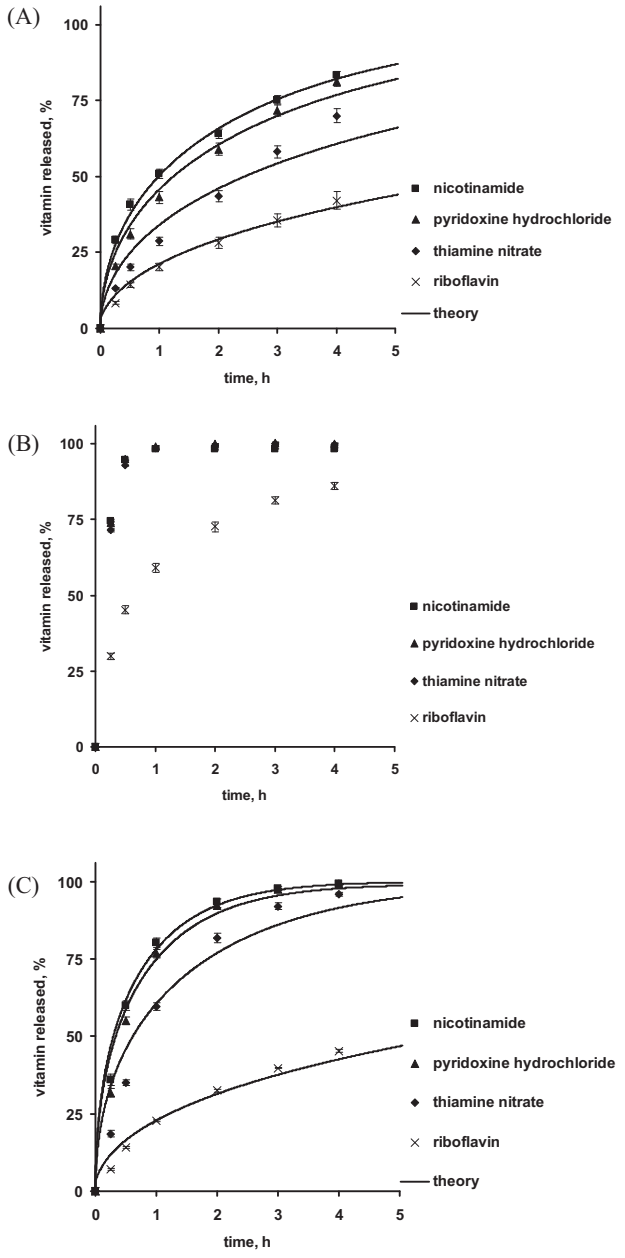

Fig. 2. Simultaneous controlled vitamin release from granules based on Sucrose Stearate S370 into phosphate buffer pH 6.8. Effects of the type of granule preparation technique: (A) melt granulation, (B) wet granulation, and (C) compression and grinding (sucrose ester content: 80%; total vitamin content: 5%, microcrystalline cellulose content: 15%, sieve fraction: 1.0–1.6 mm) (symbols: experimental results, curves: theory – Eq. (1)).

lation rapidly disintegrated upon exposure to the release media.

3.2. Simultaneous vitamin release

The symbols in Fig. 2 show the experimentally determined vitamin release kinetics from granules prepared by: (A) melt granulation, (B) wet granulation, or (C) compression and grinding. The systems consisted of 3.6% nicotinamide, 0.5% pyridoxine hydrochloride, 0.4% thiamine nitrate, 0.3% riboflavin, 80% sucrose ester and 15% microcrystalline cellulose (particle size 1.0–1.6 mm). Importantly, the release of the vitamins exhibiting very different aqueous solubility (Table 1) could be effectively and simultaneously controlled in the case of melt granulation and compression and grinding. In contrast, the release of the vitamins was rapid from granules prepared by wet granulation (except for riboflavin). This can at least partially be attributed to the lower mechanical stability of these systems (as discussed above), indicating that the strength of the inter-particle bonds created during wet granulation is much lower than in the two other cases. Thus, less hindrance for water and vitamin transport can be expected in these devices. Due to this rapid vitamin release, granules prepared by wet granulation were not further studied.

Interestingly, the rate of vitamin release generally decreased in the following ranking order: nicotinamide > pyridoxine hydrochloride > thiamine nitrate > riboflavin, irrespective of the type of preparation technique of the granules (Fig. 2). This ranking order corresponds well to: (i) the decrease in aqueous solubility, as well as to (ii) the increase in molecular weight of the vitamins/vitamin ions (Table 1) (note that in the case of salts, the respective ions diffuse).

In order to get deeper insight into the underlying mass transport phenomena, which are of importance for the control of vitamin release from these granules, Fick's second law of diffusion was used to quantify the observed nicotinamide, pyridoxine hydrochloride, thiamine nitrate and riboflavin release kinetics. However, as the granules prepared by wet granulation rapidly disintegrated upon exposure to the release medium, no effort was made to mechanistically model this type of delivery systems. The mathematical theory considers the following initial and boundary conditions:

(i) Perfect sink conditions are maintained for all vitamins throughout the experiment.
(ii) The vitamins are initially homogeneously distributed throughout the granules.
(iii) The geometry of the systems can be approximated by that of a sphere.
(iv) Vitamin diffusion with constant diffusivity is the dominant mass transport step.
(v) The granules remain intact during vitamin release.

Under these conditions the following analytical solution of Fick's second law can be derived using the method of Laplace transformation (Crank, 1975):

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left(-\frac{n^2 \cdot \pi^2}{R^2} \cdot D \cdot t\right) \quad (1)$$

here M_∞ and M_t denote the absolute cumulative amounts of vitamin released at infinite time and time t, respectively; R represents the radius of the granules and D the apparent diffusion coefficient of the vitamin within the system. If vitamin released leveled off below 100%, the experimentally determined plateau value was considered as the maximum amount of mobile compound.

The curves in Fig. 2 show the fittings of this theory (Eq. (1)) to the experimentally determined vitamin release kinetics from granules prepared by: (A) melt granulation, or (C) compression and grinding. Clearly, good agreement between theory and experiment was obtained in all cases, indicating that the diffusion of the vitamins through the granules is likely to be the release rate controlling mass transport step, irrespective of the type of preparation method (except for wet granulation) and type of vitamin. Based on these calculations, the following apparent diffusion coefficients of the vitamins in these granules could be determined: *Melt granulation*: D (nicotinamide) = 3.7 (±0.2) 10^{-8} cm^2/s, D (pyridoxine hydrochloride) = 2.9 (±0.3) 10^{-8} cm^2/s, D (thiamine cation in the case of thiamine nitrate) = 1.5 (±0.1) 10^{-8} cm^2/s, D (riboflavin) = 0.5 (±0.1) 10^{-8} cm^2/s. *Compression and grinding*: D (nicotinamide) = 12 (±1) 10^{-8} cm^2/s, D (pyridoxine hydrochloride) = 11 (±0.3) 10^{-8} cm^2/s, D (thiamine cation in the case of thiamine nitrate) = 5.8 (±0.4)

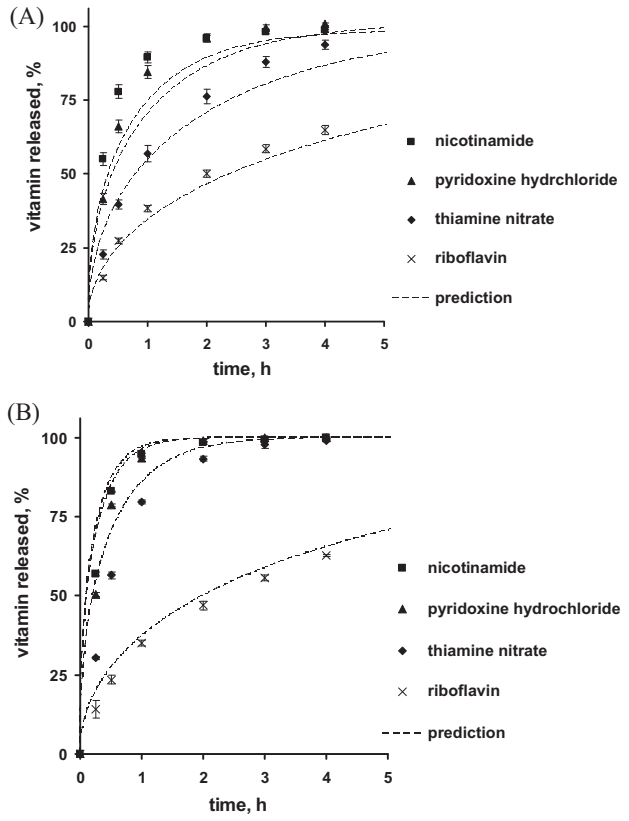

Fig. 3. Theoretically predicted vitamin release kinetics in phosphate buffer pH 6.8 (dashed curves) and independent experimental verification (symbols): nicotinamide, pyridoxine hydrochloride, thiamine nitrate, and riboflavin release from granules prepared by: (A) melt granulation, or (B) compression and grinding (sieve fraction = 0.5–1.0 mm; Sucrose Stearate S370; sucrose ester content: 80%, total vitamin content: 5%, microcrystalline cellulose content: 15%).

10^{-8} cm^2/s, D (riboflavin) = 0.6 (±0.01) 10^{-8} cm^2/s. The smaller diffusion coefficients of the vitamins in granules prepared by melt granulation compared to granules prepared by compression and grinding indicate a lower compound mobility in these systems.

However, it has to be pointed out that obtaining good agreement between theory and experiment when *fitting* a mathematical model to sets of experimental results is not a real proof of the validity of the applied theory. A much more reliable evaluation is based on the comparison of theoretically *predicted* compound release profiles and *independent* experimental results. Knowing the system specific apparent diffusion coefficients of the vitamins in the different granules types, Eq. (1) can be used to simulate *in silico* the effects of the system size on the resulting vitamin release kinetics. The dashed curves in Fig. 3 show the theoretically predicted release of nicotinamide, pyroxidine hydrochloride, thiamine nitrate and riboflavin from *smaller* granules prepared by melt granulation or compression and grinding. As in Fig. 2, the sucrose ester was Sucrose Stearate S370 and its content was 80%. In contrast to Fig. 2, the sieve fraction was 0.5–1.0 mm (instead of 1.0–1.6 mm). As it can be seen, the predicted vitamin release rates for the smaller granules were higher than the release rates of the larger particles, irrespective of the type of vitamin and type of preparation method (Fig. 3 versus Fig. 2). This can be attributed to the shorter diffusion pathway length. Then, in a second step, the respective granules were prepared in reality and the vitamin release kinetics into phosphate buffer pH 6.8 were determined experimentally (symbols in Fig. 3). Importantly, in all cases good to rather good agreement was observed between the theoretical predictions using Eq. (1) (dashed curves) and the independent experiments (symbols). This confirms the hypothesis that vitamin diffusion through the granule matrix is the dominant mass transport step controlling the release kinetics from this type of dosage forms. Furthermore, from a practical point of view, Eq. (1) can be used to facilitate device optimization: the granule size required to achieve a specific, desired vitamin release rate can be theoretically predicted.

3.3. Effects of the type of matrix former

Fig. 4 shows the effects of the type of matrix former on the resulting release kinetics: 50% Sucrose Stearate S370, Sucrose Stearate S1170, glyceryl dipalmitostearate, or glyceryl dibehenate and 45% ethylcellulose were used, the total vitamin content was 5%. The sieve fraction was 0.5–1.0 mm and all systems were prepared by melt granulation. As it can be seen, the type of matrix former affected the resulting vitamin release kinetics: Sucrose Stearate S1170:ethylcellulose-based systems showed the fastest release rates and glyceryl dipalmitostearate:ethylcellulose-based granules the slowest ones, irrespective of the type of vitamin. The fact that Sucrose Stearate S1170 led to faster compound release than Sucrose Stearate S370 can at least partially be attributed to the higher hydrophilicity of this sucrose ester (HLB = 11 versus 3). With increasing matrix hydrophilicity, the amount of water, which can penetrate into the granules is likely to increase, resulting in increased vitamin mobility. Again, Eq. (1) was fitted to the experimentally determined compound release kinetics (curves and symbols in Fig. 4) in order to better understand the underlying mass transport mechanisms. Clearly, good agreement was obtained in all cases, indicating that vitamin release is pre-dominantly controlled by diffusion, irrespective of the type of investigated matrix former. Based on these calculations, the following apparent diffusion coefficients were determined in granules prepared by melt granulation: D (nicotinamide) = 9.6 (±0.8) × 10^{-8} cm^2/s, D (pyridoxine hydrochloride) = 5.3 (±0.6) × 10^{-8} cm^2/s, D (thiamine nitrate) = 2.6 (±0.3) × 10^{-8} cm^2/s and D (riboflavin) = 2.5 (±0.2) × 10^{-9} cm^2/s in the case of *Sucrose Stearate S370:ethylcellulose*; D (nicotinamide) = 2.6 (±0.4) × 10^{-7} cm^2/s, D (pyridoxine hydrochloride) = 2.5 (±0.6) × 10^{-7} cm^2/s, D (thiamine nitrate) = 2.1 (±0.1) × 10^{-7} cm^2/s and D (riboflavin) = 1.1 (±0.2) × 10^{-8} cm^2/s in the case of *Sucrose Stearate S1170:ethylcellulose*; D (nicotinamide) = 7.3 (±0.4) × 10^{-8} cm^2/s, D (pyridoxine hydrochloride) = 4.1 (±0.1) × 10^{-8} cm^2/s, D (thiamine nitrate) = 4.0 (±0.1) × 10^{-8} cm^2/s and D (riboflavin) = 2.6 (±0.4) × 10^{-9} cm^2/s in the case of *glyceryl dipalmitostearate:ethylcellulose*; D (nicotinamide) = 9.8 (±1.0) × 10^{-8} cm^2/s, D (pyridoxine hydrochloride) = 7.1 (±0.8) × 10^{-8} cm^2/s, D (thiamine nitrate) = 4.2 (±0.3) × 10^{-8} cm^2/s and D (riboflavin) = 3.7 (±0.9) × 10^{-9} cm^2/s in the case of *glyceryl dibehenate:ethylcellulose*. Again, knowing these values the effects of the granule size on vitamin release can be quantitatively predicted for the different types of systems.

3.4. Influence of the sucrose ester concentration

Fig. 5 shows the effects of varying the sucrose ester (Sucrose Stearate S370) content in granules prepared by melt granulation (sieve fraction: 1.0–1.6 mm) from 20 to 80%, while keeping the total vitamin content constant at 5%. The microcrystalline cellulose content was decreased from 75 to 15%, accordingly. Clearly, an increase in the sucrose ester content led to decreasing vitamin release rates, irrespective of the type of vitamin. This can at least partially be attributed to the lipophilicity of Sucrose Stearate S370 (HLB = 3) and/or the fact that this sucrose ester forms denser matrices than microcrystalline cellulose under these conditions. From a practical point of view, desired vitamin release patterns can easily be adjusted by varying the sucrose ester content. Again, good

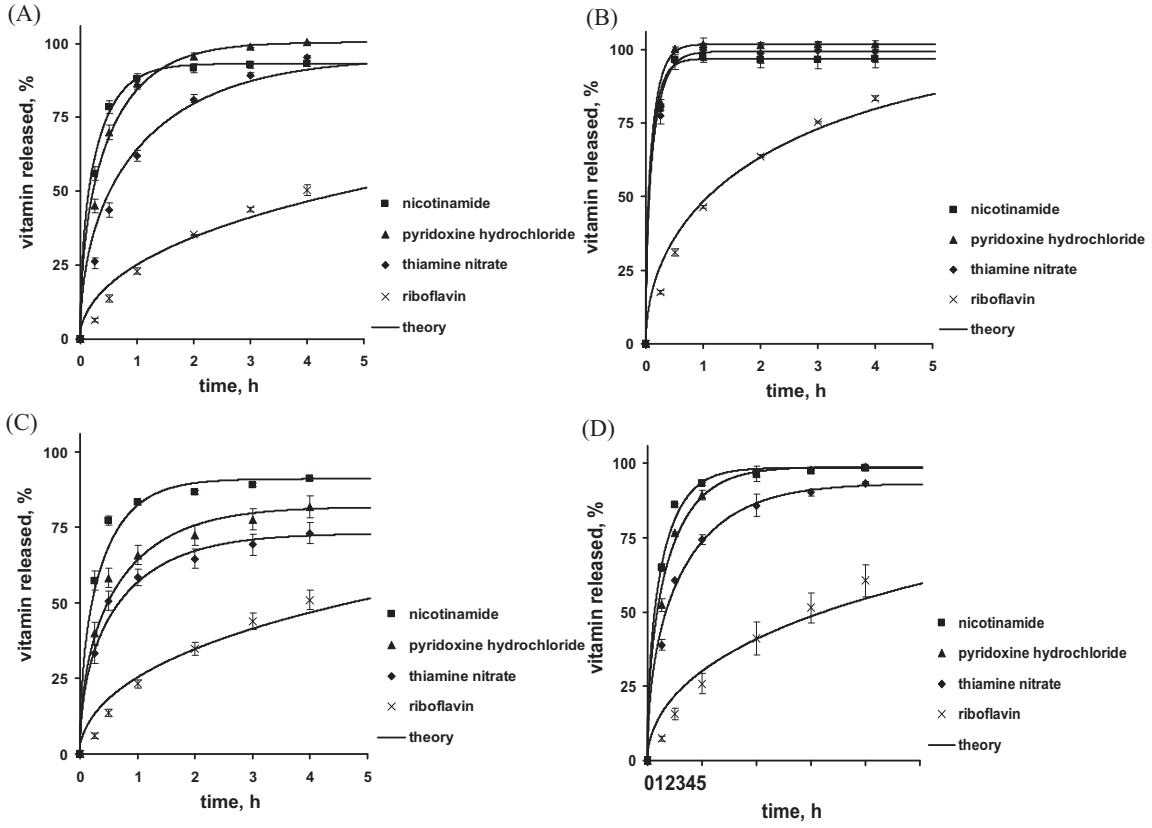

Fig. 4. Effects of the type of matrix former on simultaneous vitamin release from granules in phosphate buffer pH 6.8: (A) Sucrose Stearate S370:ethylcellulose 50:45, (B) Sucrose Stearate S1170:ethylcellulose 50:45, (C) glyceryl dipalmitostearate:ethylcellulose 50:45, and (D) glyceryl dibehenate:ethylcellulose 50:45 (total vitamin content: 5%, sieve fraction: 0.5–1.0 mm; melt granulation) (symbols: experimental results, curves: theory – Eq. (1)).

agreement was obtained between theory (curves) and experiments (symbols) when fitting Eq. (1) to the experimentally measured release kinetics shown in Fig. 5, irrespective of the sucrose ester content and type of vitamin. The apparent diffusion coefficients determined based on these calculations are plotted in Fig. 6 as a function of the Sucrose Stearate S370 content. Clearly, the compound mobility significantly deceased with increasing sucrose ester content, due to the reasons discussed above. Importantly, the knowledge of these values allows estimating the apparent vitamin diffusivities for other sucrose ester contents. Thus, the impact of the granule formulation as well as of the granule size on vitamin release can be theoretically predicted.

3.5. Influence of the type of filler

In order to fine-tune the resulting vitamin release kinetics, different types of fillers can be used, such as microcrystalline cellulose or ethylcellulose. Fig. 7 shows the simultaneous release of nicotinamide, pyridoxine hydrochloride, thiamine nitrate and riboflavin from granules prepared by melt granulation containing 86% Sucrose Stearate S370, 9% filler and 5% total vitamin (symbols = experimental results, curves = theory). The filled symbols show the release kinetics from granules containing ethylcellulose as filler, the open symbols show the release profiles from microcrystalline cellulose containing devices. Clearly, vitamin release was slightly faster in the case of microcrystalline cellulose. This might be attributable to a less restricted water penetration into the system (e.g., ethylcellulose can be used for moisture protective coatings, Bley et al., 2009). Importantly, in all cases again good agreement between the analytical solution of Fick's second law (Eq. (1)) and the experimental results was obtained (curves and symbols in Fig. 7). Thus, the underlying vitamin release mechanisms are not affected by the type of investigated filler. Again, the diffusion coefficients determined based on these fittings can be used to quantitatively predict the effects of the granules' dimensions on the resulting vitamin release patterns: D (nicotinamide) = 3.7 ($\pm$0.4) $\times 10^{-8}$ cm^2/s, D (pyridoxine hydrochloride) = 2.4 ($\pm$0.1) $\times 10^{-8}$ cm^2/s, D (thiamine nitrate) = 8.4 ($\pm$0.3) $\times 10^{-9}$ cm^2/s and D (riboflavin) = 3.9 ($\pm$0.2) $\times 10^{-9}$ cm^2/s in the case of *ethylcellulose*; D (nicotinamide) = 6.7 ($\pm$0.5) $\times 10^{-8}$ cm^2/s, D (pyridoxine hydrochloride) = 4.1 ($\pm$0.4) $\times 10^{-8}$ cm^2/s, D (thiamine nitrate) = 1.4 ($\pm$0.1) $\times 10^{-8}$ cm^2/s

Table 2
Effects of the initial total vitamin content (w/w, referred to the total system mass) on the apparent diffusion coefficient of nicotinamide, pyridoxine hydrochloride, thiamine chloride hydrochloride and riboflavin 5′-phosphate (in 10^{-8} cm^2/s) ($\pm$SD) in granules prepared by melt granulation upon exposure to phosphate buffer pH 6.8 (Sucrose Stearate S370; sucrose ester content: 80%; filler: microcrystalline cellulose, sieve fraction: 1.0–1.6 mm).

	10%	12%	16%
Nicotinamide	7.0 ($\pm$2.0)	7.5 ($\pm$0.3)	8.1 ($\pm$1.2)
Pyridoxine hydrochloride	3.8 ($\pm$1.4)	3.8 ($\pm$0.2)	4.9 ($\pm$0.9)
Thiamine chloride hydrochloride	3.9 ($\pm$1.3)	4.0 ($\pm$0.4)	4.9 ($\pm$1.0)
Riboflavin 5′-phosphate	1.3 ($\pm$0.2)	1.1 ($\pm$0.4)	1.7 ($\pm$0.4)

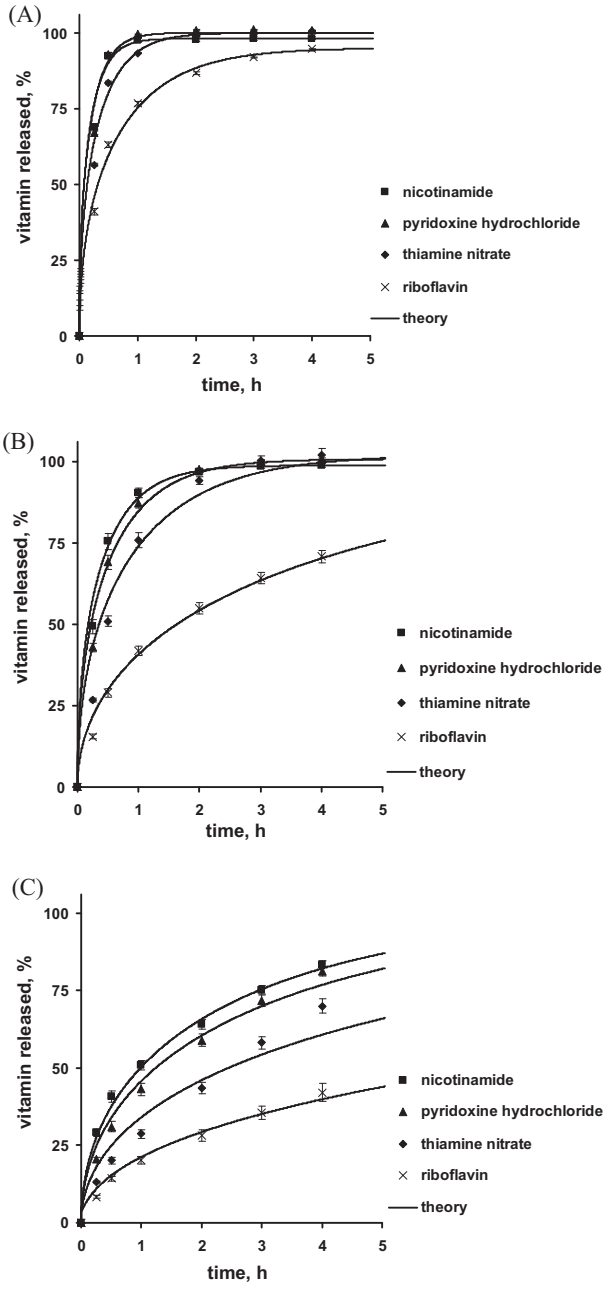

Fig. 5. Simultaneous vitamin release from Sucrose Stearate S370-based granules prepared by melt granulation in phosphate buffer pH 6.8, initially containing: (A) 20%, (B) 50%, or (C) 80% sucrose ester (total vitamin content: 5%, filler: microcrystalline cellulose, sieve fraction: 1.0–1.6 mm) (symbols: experimental results, curves: theory – Eq. (1)).

and D (riboflavin) = 4.1 (± 0.2) $\times 10^{-9}$ cm^2/s in the case of *microcrystalline cellulose*.

3.6. Impact of the total vitamin content

Fig. 8 shows the effects of increasing the total initial vitamin content on the resulting release kinetics of: (A) nicotinamide and thiamine chloride hydrochloride, and (B) pyridoxine hydrochloride and riboflavin-5′-phosphate from granules prepared by melt granulation in phosphate buffer pH 6.8. The sucrose ester (80%) was Sucrose Stearate S370, the filler microcrystalline cellulose. The total vitamin content was increased from 10 to 16%. As it can be seen, this resulted in a slight increase in all compound release rates, which can

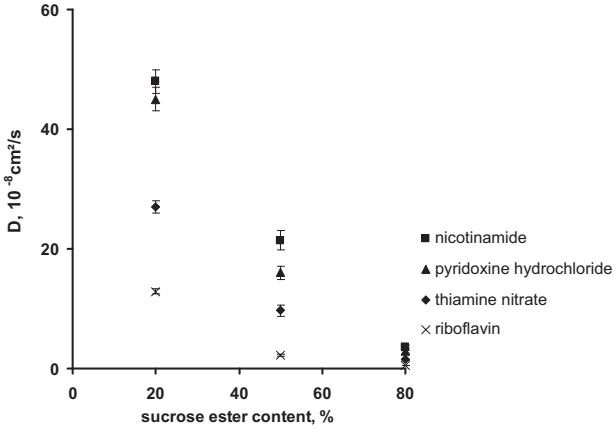

Fig. 6. Dependence of the apparent vitamin diffusion coefficients of nicotinamide, pyroxidine hydrochloride, thiamine nitrate and riboflavin in Sucrose Stearate S370-based granules prepared by melt granulation (measured upon exposure to phosphate buffer pH 6.8) on the initial sucrose ester content (sieve fraction: 1.0–1.6 mm).

probably be attributed to the increased hydrophilicity of the granules with increasing total vitamin content. Interestingly, in all cases Eq. (1) could be used to quantitatively describe the experimentally measured nicotinamide, thiamine chloride hydrochloride, pyridoxine hydrochloride and riboflavin-5′-phosphate release kinetics (curves and symbols in Fig. 8). Based on these calculations, the apparent vitamin diffusion coefficients listed in Table 2 could be determined. As it can be seen, the diffusivities generally increased with increasing total vitamin content. Using these values and Eq. (1), the resulting release patterns can be predicted for arbitrary granule sizes.

3.7. Importance of the type of release medium

The impact of the type of release medium (phosphate buffer pH 6.8 versus 0.1 M HCl versus water) on the release of nicotinamide and thiamine chloride hydrochloride is illustrated in Fig. 9. The symbols represent the experimentally determined release kinetics, the curves the fitted theory (Eq. (1)). As it can be seen: (i) the impact of the type of release medium is only limited in these cases, and (ii) diffusion is the dominant

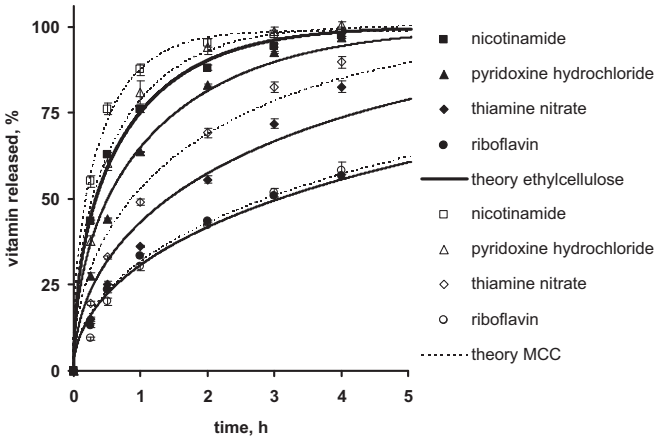

Fig. 7. Simultaneous vitamin release from Sucrose Stearate S370-based granules prepared by melt granulation, containing 9% ethylcellulose (closed symbols and solid curves) or 9% microcrystalline cellulose (open symbols and dotted curves) (release medium: phosphate buffer pH 6.8; sucrose ester content: 86%; total vitamin content: 5%, sieve fraction: 0.5–1.0 mm) (symbols: experimental results, curves: theory – Eq. (1)).

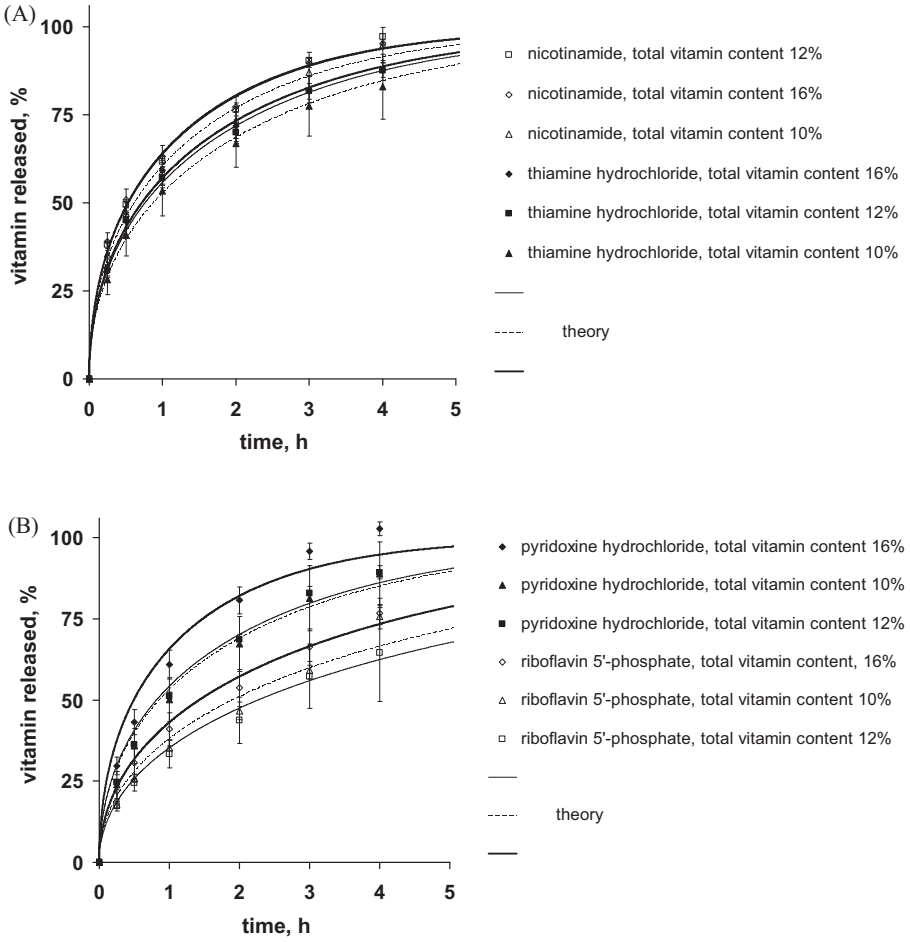

Fig. 8. Effects of the initial total vitamin content on the release of: (A) nicotinamide and thiamine hydrochloride, and (B) pyridoxine hydrochloride and riboflavin 5′-phosphate release in phosphate buffer pH 6.8 from Sucrose Stearate S370-based granules prepared by melt granulation (sucrose ester content: 80%; filler: microcrystalline cellulose, sieve fraction: 1.0–1.6 mm) (symbols: experimental results, curves: theory – Eq. (1)) (thick curves: 16%, thin curves: 12%, dotted curves: 10%, w/w, referred to the total system mass).

mass transport step, irrespective of the type of bulk fluid the granules are exposed to. The apparent diffusivities in phosphate buffer pH 6.8, water and 0.1 M HCl were determined to be 6.8 $(\pm 0.6) \times 10^{-8}$ cm^2/s, 7.4 $(\pm 0.4) \times 10^{-8}$ cm^2/s and 6.4 $(\pm 0.3) \times 10^{-8}$ cm^2/s for *nicotinamide*, and 5.1 $(\pm 0.9) \times 10^{-8}$ cm^2/s, 3.9 $(\pm 0.2) \times 10^{-8}$ cm^2/s and 5.0 $(\pm 0.4) \times 10^{-8}$ cm^2/s for *thiamine chloride hydrochloride*, respectively. Again, knowing these values and using Equation 1, the resulting vitamin

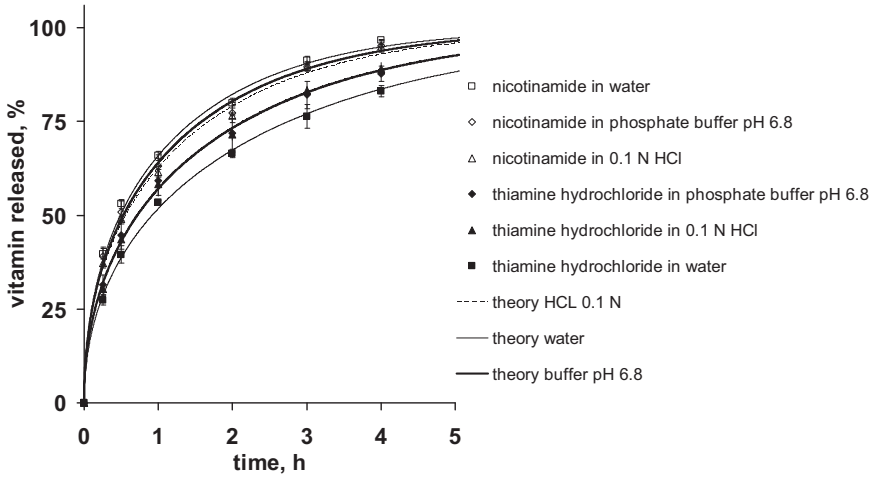

Fig. 9. Effects of the type of release medium on nicotinamide and thiamine hydrochloride release from Sucrose Stearate S370-based granules prepared by melt granulation (sucrose ester content: 80%; total vitamin content: 16%, microcrystalline cellulose content: 4%; sieve fraction: 1.0–1.6 mm) (symbols: experimental results, curves: theory – Eq. (1)) (thick curves: phosphate buffer pH 6.8, thin curves: water, dashed curves: 0.1 N HCl).

release patterns can be quantitatively predicted for arbitrary device dimensions.

4. Conclusion

Sucrose ester- or triglyceride-based granules can be used to simultaneously control the release of multiple vitamins, exhibiting very different water-solubility and molecular weights. Interestingly, vitamin diffusion seems to be the dominant mass transport mechanism in most cases. Thus, appropriate analytical solutions of Fick's second law can be used to quantitatively predict the effects of the granule size and composition on the resulting compound release kinetics. This can significantly help to facilitate device optimization.

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