The Use of a Hydrogel Matrix for Controlled Delivery of Niacin to the Gastrointestinal Tract for Treatment of Hyperlipidemia

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Summary

Hyperlipidemia treatment based on niacin requires gastrointestinal administration of relatively high doses. The recommended dietary allowance of niacin as vitamin B3 is 14 to 16 mg daily in adults, while the doses of niacin used in the treatment of hyperlipidemia are generally in the range of 1 to 3 g. Administration of such large doses requires a high concentration of the active compound in the tablet and proper control of the drug release. In this study, a hydrogel matrix based on poly(2-hydroxyethyl methacrylate) and polyvinylpyrrolidone was investigated as delivery vehicle for controlled NA release into the gastrointestinal environment. The prepared hydrogel matrices varied in used monomer and crosslinker types and concentrations. The content of NA in tablets was between 65-80 %. The release profiles of NA from tablets were examined under three different pH values (1, 4.5 and 6.8) over the time period of 30 h. The effects of the monomer ratio, the crosslinking of the polymer network, and the solubility of niacin during drug release under various pH are discussed. The results showed that the release time period can be achieved in a relatively wide range of time and can be adjusted according to the medical requirements.

Key words

Niacin • Hyperlipidemia • Hydrogel • Poly(2-hydroxyethyl methacrylate) • Polyvinylpyrrolidone • Controlled release

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Introduction

Niacin (NA, nicotinic acid, vitamin B3) is a lipid-modulating drug that decreases concentrations of all atherogenic apoB-containing lipoproteins, i.e. very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein (LDL) as well as lipoprotein[a] (Lp[a]). It reduces VLDL and triglyceride (TG) synthesis in the liver and inhibits release of free fatty acids from adipose tissue (Žák *et al.* 2006, Brown *et al.* 2009). NA, in addition to its hypolipidemic effects, exhibits a plethora of pleiotropic effects, of which the most important are anti-oxidative, anti-inflammatory, and anti-thrombotic (Florentin *et al.* 2011).

The NA lipid-modulating action is dose-dependent. At a dose of 2 g of NA, LDL-C is reduced by 15-18 %, TG by 30-40 %, and Lp[a] by 20 %. On the contrary, HDL-C rises by 25 % (Brown *et al.* 2009, Robinson 2010). Although earlier trials with NA as monotherapy or in combination with other lipid-lowering drugs have demonstrated significant clinical benefits in treating cardiovascular complications of atherosclerosis (Lavigne and Karas 2013), recent large randomized clinical studies – AIM-HIGH and HPS2-THRIVE – have been disappointing, demonstrating no further benefit

(decreased parameters of cardiovascular risk) of adding NA to existing statin therapy in patients with high cardiovascular risk (Boden *et al*. 2014, HPS2-THRIVE Collaborative group 2014). It must be emphasized that the designs of the AIM-HIGH and HPS-2/THRIVE trials are prone to some methodological limitations, which reduce the value of the published conclusions (Zeman *et al*. 2015). Therefore, we suppose that it would be appropriate to selectively evaluate the functioning of extended NA-release alone in a subgroup of patients suffering from low HDL-C and high TG. Therefore, the clinical evaluation of NA, especially with regard to its extended release formulations, is worthy of further research.

Both the side effects and the efficacy of NA formulations are controlled by two factors – the rate of absorption from the gastrointestinal tract and metabolic conversion in the liver. NA is metabolized along two distinct pathways in the liver. In the first pathway (low-affinity/high capacity), NA is conjugated with glycine to form nicotinuric acid (NUA). In the second pathway (high-affinity/low-capacity), NA is metabolized mainly into nicotinamide (NAM), and then into nicotinamide adenine nucleotide (NAD) and other metabolites, such as 6-hydroxy NAM, N-methyl NAM, and NAM-N-oxide (Žák *et al*. 2006). The adverse effects – of which flushing, and serious hepatotoxicity are the most frequent and dangerous – limit compliance with the treatment. NA-induced flushing is caused by increased prostaglandin D_2 (PGD2) synthesis in the epidermal Langerhans cells, which release PGD2. The immediate release of NA formulations, which are metabolized primarily in the conjugative pathway (low-affinity/high-capacity), are associated with cutaneous flushing. On the other hand, sustained-release NA formulations, which result from delayed absorption, are eliminated predominantly in the second pathway (high-affinity/low-capacity). The risk of hepatotoxicity, which increases after the administration of ultra-long-acting formulations, is associated with non-conjugative metabolites of NA (Brown *et al*. 2009). Therefore, the ideal formulation of NA should be administered only once a day with an optimal release rate and ratio of NUA (the first pathway metabolites) to NAM metabolites (the second pathway metabolites) in order to reduce flushing frequency and abolish liver toxicity.

In order to manage the required high content of the active compound in the tablet and the proper controlled release of the drug, hydrogel carriers based on poly(2-hydroxyethyl methacrylate) (PHEMA) and poly(*N*-vinylpyrrolidone) (PVP) (co)polymers were selected.

PHEMA, a hydrogel polymeric material, is widely used in various medicinal applications such as contact lenses, intraocular lenses, and implants for various tissues (Horak 2004). Hydroxyethyl methacrylate hydrogels are generally considered non-toxic, and are found to be well accepted by the organism. The toxicity of PHEMA and polymerization residues (i.e. residual monomers, oligomers, crosslinkers, and initiators) have been investigated (Štol *et al*. 1988, Brynda *et al*. 1985, Cífková *et al*. 1988). Intradermal application of extracts from PHEMA-based polymers and compounds of polymerization mixtures, which can theoretically remain in resultant polymers, have revealed low irritation of the surrounding tissue.

PVP is approved for various medicinal applications (Irmukhametova *et al*. 2014, Bashir *et al*. 2013). In the past it was used as a plasma volume expander for trauma patients (Ravin *et al*. 1952). Nowadays, it is widely used in various pharmacological products, particularly in tablets or as a binder of pharmacologically active compounds (De Querioz *et al*. 2002, Bajpai and Sonkusley 2002). Iodine forms of PVP possess disinfectant properties and these complexes are also used in various products including solutions, ointments, liquid soaps, and surgical scrubs (Burks 1998). Due to the mass use of PVP, the total daily intake of the VP monomer has been defined at 50 µg per person (European Commission 2012). This amount includes all possible outputs from contact lenses, cosmetics, and other items. For pharmaceutical products, the maximum daily dose is 10 µg per person (Bühler 2005).

Heterogeneous hydrogel/solid compound systems, in which free radical polymerization proceeds in the presence of soluble particles, have been examined *via* the preparation of macroporous hydrogels. In this process, particles of defined sizes serve as porogen and after they dissolve the hydrogel is used as a scaffold with defined internal porosity (Přádný *et al*. 2010, Dinu *et al*. 2013). In the presented work, the hydrogel matrix serves as a delivery vehicle for NA, where the suitable ratio of monomers and crosslinking agents allows tablet behavior and drug release to be extensively controlled. The content of soluble particles and the swelling behavior of the hydrogel matrix along with its decomposition are major factors that affect the drug release profile. In the presented paper, we describe the optimization of such

a system for the controlled release of NA into the gastrointestinal environment under pH values of 1, 4.5, and 6.8. Commercially available Tredaptive and Niaspan are compared as reference release systems.

Methods

Experimental

N-vinylpyrrolidone (VP), 2-hydroxyethyl methacrylate (HEMA), ethylene glycol dimethacrylate (EDMA), NA (nicotinic acid, niacin), sodium, and azobisisobutyronitrile (AIBN) as an initiator were purchased from Sigma-Aldrich. The monomers, VP and HEMA, were distilled prior to reaction. Toluene (Lach-Ner, Czech Republic) was dried over 3Å molecular sieves overnight. The NA powder was sieved by the Analysette 3 SPARTAN (Fritsch, Germany) vibratory sieve shaker in order to exclude particles larger than 90 μm, which can create non-homogeneities in the hydrogel/drug tablet.

Preparation of 3,3'-ethylidene-bis(N-vinyl-2-pyrrolidone) (EBVP)

EBVP was synthetized according to the procedure subscribed in (Patent: GB1024400). 130 g of *N*-vinylpyrrolidone (1.16 mol) was mixed with 130 g of dried toluene and heated in an oil bath (120 °C) under reflux. To this stirred solution, 5.2 g of sodium (0.22 mol) was added. The solution was stirred and heated until all sodium was completely dissolved. Subsequently, the reaction mixture was cooled down to RT and toluene was decanted. A new portion of 130 g of toluene was added to the reaction residuum and the mixture was heated up under reflux until the residuum became fluid. The reaction mixture was cooled down again and toluene was decanted. Toluene phases were collected and extracted five times by water. After water evaporation the oily residuum was dissolved in chloroform and extracted again by water until the water phase became clean. The organic phase was dried over $MgSO_4$. Chloroform was removed under a vacuum. The residuum was dissolved in ethanol, concentrated, and crystallized.

White crystals were obtained and the melting point was determined at 123-125 °C under elemental analysis (found/calculated): C 67.84 %/67.71 %, H 8.29 %/8.12 %, N 11.17 %/11.31 %. NMR spectra were measured on Bruker Avance DPX 300, ^1H NMR (300 MHz, MeOD) δ 0.84 (3H, d), 1.92-1.99 (2H, m), 2.19-2.23 (2H, m), 2.5 (1H, sep), 2.92-2.98 (2H, quin), 3.39-3.40 (2H, q), 3.42-3.54 (2H, t), 4.45-4.55 (4H, t),

6.97-7.05 (2H, q)., ^{13}C NMR (300 MHz, MeOD) δ 12.53, 21.71, 35.93, 44.11, 46.20, 95.88, 130.14, 176.55. IR spectra were measured on Perkin Elmer PARAGON 1000 PC FT-IR spectrometer – 2972, 2890, 1686, 1625, 1386, 1320, 1206, 980 cm^{-1} N.

Tablet preparation

The reaction mixture containing the monomer, crosslinker, and initiator was bubbled by nitrogen to remove dissolved oxygen. NA powder was added and the mixture was homogenized and put into molds consisting of polyethylene syringes of 2 ml volume and 9 mm diameter. The reaction mixture was pressed to squeeze out gas and to reach compact matrix. The narrow ends of the syringes were stuffed with cotton wool to prevent the reaction mixture being drained. Polymerization was carried out in an oven at 75 °C for 16 h. The prepared material was removed from the syringe and cut into the desired shape and weight so that every formulation contained 1 g of NA. For simplifications, in further text these formulations are termed as tablets although this term is not exactly according to the pharmacopoeial standards. The tablet compositions varied in the type of monomers and their ratios (HEMA, VP, HEMA/VP 5/95 – 20/80), crosslinker concentration (0.15-0.5 % of EDMA for the PHEMA matrix, 0.05-0.5 % of EBVP for the PVP matrix), and NA content (65-80 % per tablet).

Dissolution studies

Dissolution experiments proceeded according to standard simulation conditions of the gastrointestinal system, as stated in our list of reimbursed medicinal products (Český lékopis 2009). An ERWEKA DT 60 (Erweka, Germany) dissolution tester was used. Glass bottles were filled with either 900 ml of phosphate buffer (pH 6.8) (Sigma-Aldrich), acetate buffer (pH 4.5), or hydrochloride acid solution (pH 1) (Penta, Czech Republic). Six tablets were simultaneously tested at 37±1 °C. The shaking speed was set to 50 rpm. After set time periods (15 min, 1, 2, 4, 8, 12, 24 and 30 h), 200 μl of solution was removed to determine NA concentration. A decrease of solution volume was taken into account during calculations. Concentration of NA in solutions was quantified using the HPLC/DAD Shimadzu LC-20AD on a Purospher® STAR RP-18 column. The flow rate of the mobile phase (a mixture of citric buffer (0.05M) and acetonitrile 2/3 v/v) was set to 1.5 ml/min. Signals were detected at 262 nm. Calibration curves were individually measured for each pH value.

Results and Discussion

Various compositions of the hydrogel matrices were prepared and the effects of monomer type, crosslinker concentration, and incorporated compound content on their release profiles were investigated. The release experiments were carried out using buffers with pH values of 1, 4.5, and 6.8. The experiments proceeded for the time period of 30 h corresponding to the expected transition time in GIT: 3-5 h in stomach, 7-9 h in small intestine and 24-32 h in large intestine. The influence of pH was also evaluated. The NA release profiles were compared to the profiles obtained with the commercially available products, Tredaptive and Niaspan.

Influence of NA content in tablets

The expected daily therapeutic dose of NA for hyperlipidemia treatment is 2 g, where ingestion of two tablets corresponds to an amount of 1 g NA per tablet. The maximum dimensions of the tablets for convenient swallowing require at least 65 % of NA per tablet. Although the amount of the incorporated compound is not usually considered as a main factor affecting drug release, in the case of tablets containing such large drug concentration it can be an important factor.
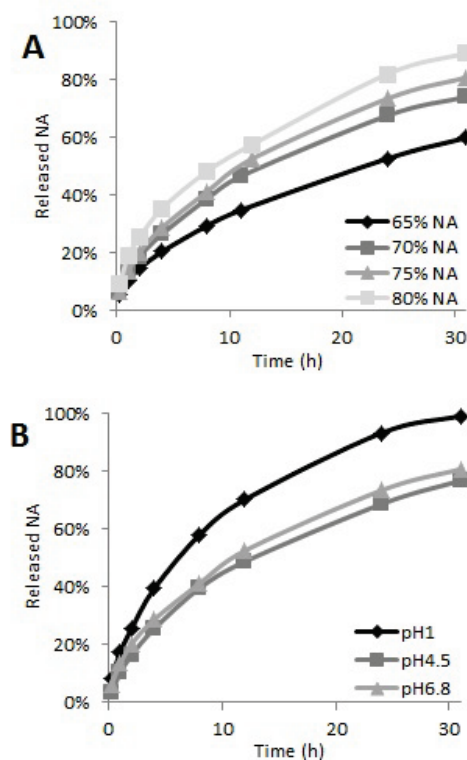

Fig. 1. NA release profiles from PHEMA-based tablets (HEMA/EDMA 99.5/0.5 w/w): **(A)** Influence of NA concentration in tablets (buffer pH 6.8); **(B)** Influence of buffer pH (75 % NA content in tablet).

Tablets based on a PHEMA matrix containing 65-80 % of NA were prepared and the NA release was observed under conditions corresponding to the gastrointestinal tract (i.e. under three different pH values). When various concentrations of NA were added to the insoluble hydrogel, NA release was driven particularly by the diffusion of dissolved NA through the liquid phase, presented in the interconnected pores arising after dissolution of the NA particles. Diffusion of NA in the swollen hydrogel was relatively slow and the difference in the NA release rate from various samples was caused particularly by the ratio of pore interconnection. In the case of the PHEMA-based matrix containing 65 % NA, the pores were not fully interconnected and within 30 h only 60 % of the incorporated NA was released. In the case of the 80 % NA tablet, the released amount reached almost 90 % within the same time period (Fig. 1A). The second apparent effect was the rate of dissolution of NA particles, which is dependent on pH. Although the shape of the curves obtained under various pH values exhibited almost similar profiles (Fig. 1B), the release amount of NA into buffer pH 1 was noticeably higher compared to pH values of 4.5 and 6.8, which corresponds to the faster dissolution of NA particles in an acidic environment. The difference in the dissolution between pH values of 4.5 and 6.8, which is close to NA pKa (4.85), was not as so apparent

Various contents of NA were incorporated into the PVP matrix with a low crosslink ratio (0.1 % EBVP), which provides soluble hydrogels. The dissolution rate of PVP hydrogel was close to the dissolution rate of NA, and therefore the influence of NA content on its release was almost suppressed (Fig. 2). The release of NA was relatively fast, especially into buffer pH 1, where, regardless of NA content, 100 % of NA was released within approx. 3 h. Evaluation of NA released into buffer pH 4.5 and 6.8 (Figs 2B and 2C) showed a slightly slower dissolution. The dissolution rate noticeably increased only in the case of tablets containing 80 % NA, as they disintegrated in an earlier stage of the experiment. The examined hydrogel/NA tablets release profiles similar to the commercial product, Tredaptive (see the added curve in Figure 2C).

In the case of PVP hydrogels with critical crosslinker concentration, when the network was crosslinked just slightly above the border of complete dissolution, NA content had a predominant effect on the release profile. As shown in Figure 2D, all the NA from

the tablet with 80 % concentration released almost immediately, within approx. 30 min. The tablet containing the lowest NA concentration (65 %) released less than 50 % of NA within 12 h (the expected average time period for the gastrointestinal tract) and no more than 85 % within 30 h of the release experiment. These observations were made for all examined pH values. Apparently, in this particular hydrogel matrix

composition, the concentration of the incorporated active compound could be a main factor in controlling its release profile. In the case of PHEMA matrices, the critical crosslinker concentration was not obtained: 0.15 % of the crosslinker present in the HEMA monomer was above the limit and disintegration of tablets was not achieved.
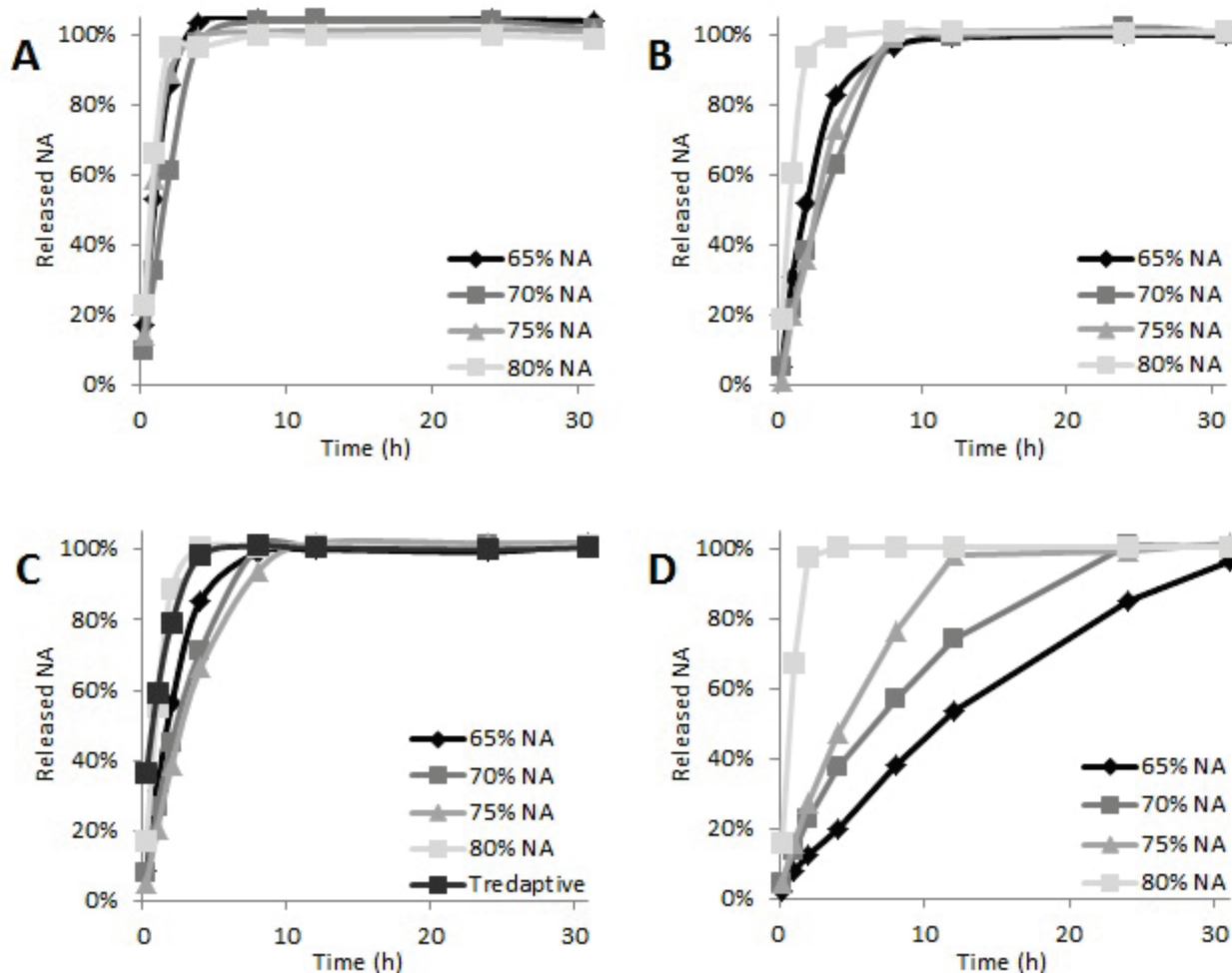

Fig. 2. Dependence of NA release profiles on NA concentration in PVP-based tablets: **(A)** Hydrogel matrix VP/EBVP 99.9/0.1 w/w, buffer pH 1; **(B)** Hydrogel matrix VP/EBVP 99.9/0.1 w/w, buffer pH 4.5; **(C)** Hydrogel matrix VP/EBVP 99.9/0.1 w/w, buffer pH 6.8; Tredaptive release profile added; **(D)** Hydrogel matrix VP/EBVP 99.8/0.2 w/w, buffer pH 6.8.

In a comparison of tablets based on various hydrogel matrices, the trend of faster NA release from tablets with higher NA content was not noticeably affected by the hydrogel swelling ratio (HEMA/EDMA 99.5/0.5 hydrogel contains approx. 40 % of water in its equilibrium state compared to more than 80 % for VP/EBVP 99.8/0.2 hydrogel). Generally, the diffusion of the releasing compound is influenced by the swelling degree of the hydrogel. However, in this heterogeneous

system, the release mechanism is driven mainly by the diffusion of NA in the water phase contained in the pores arising after dissolution of the NA particles. Therefore, the interconnection of the pores plays a crucial role. This corresponds with the fact that varying crosslinking ratios of PHEMA also have negligible effect on NA release (the influence of crosslinker concentration is discussed further).

Although the NA content was, in some particular

cases, a promising way of controlling the release profile and given that the highest NA content allowed the tablet dimensions to decrease (and consequently made them more convenient for ingestion), preparation of polymerization mixtures with more than 80 % of NA was complicated due to its consistency. As the polymerization mixtures with the lower amount of NA were more easily processed and polymerization proceeded using common syringes, reproducible results with higher NA content required extremely precise homogenization of polymerization components and polymerization using special molds with defined pressure. Therefore, the polymerization mixture with 75 % NA was found to be an optimal compromise between these two contrasting requirements and was used for all other release experiments.

Influence of crosslinker concentration in PHEMA matrices

The extent of crosslinking in the polymer network is generally considered a prevailing factor in controlling drug release profile, i.e. it influences the diffusion of the incorporated active compound through the polymer matrix and the decomposition of the carrier. The lower amount of polymer chain links increases the total swelling of the hydrogel matrix; therefore, the increased chains of flexibility should improve solid-state diffusion.

The series of tablets based on the PHEMA hydrogel matrix containing 75 % of NA were prepared with various amounts of EDMA crosslinker. The HEMA monomer contains some amount of EDMA (in our case 0.15 %), which was also the lowest concentration used in experiments. The highest concentration was prepared at 0.5 %. As shown in Figure 3A, there was no considerable effect of crosslinking the PHEMA hydrogel matrix upon NA release. It seems that the increased hydrogel swelling ratio along with the faster realization of the equilibrium swollen state had no considerable impact on faster NA release. During the expected time of the digestive system (12 h), no more than 50 % of incorporated NA was released. Therefore, it can be assumed that the diffusion of NA in the swollen hydrogel had a minor effect and also that no noticeable difference between hydrogels of various degrees of swelling was observed, as shown in Figure 3B. This is compared with the NA release from tablets based on the PHEMA hydrogel (water content approx. 40 %) and the PVP hydrogel (water content approx. 85 %).

After the release experiment (30 h), even the less crosslinked hydrogel matrix containing 0.15 % of EDMA did not completely disintegrate. The partly porous/partly NA particles containing the highly swollen hydrogel matrix of non-changed dimensions (Fig. 4A) were soft, pliable and still compact.
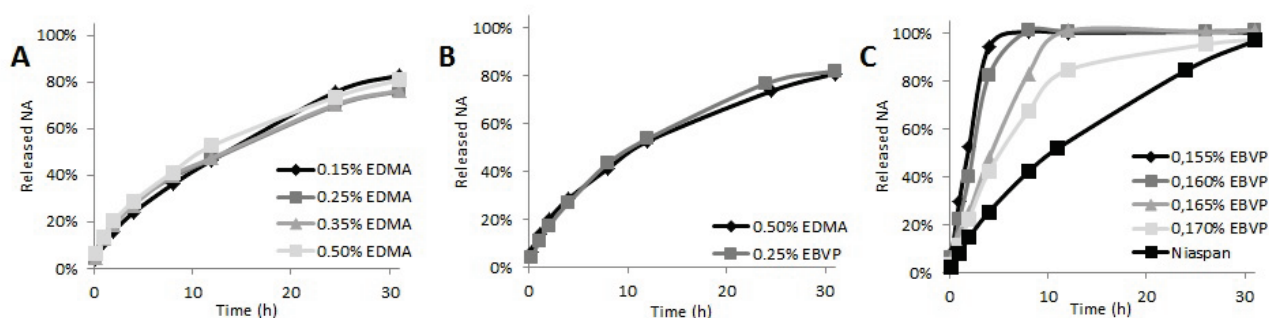

Fig. 3. Influence of crosslinking on the NA release profile from tablets (buffer pH 6.8, NA content 75 % in tablet): **(A)** Various EDMA concentrations in PHEMA matrices; **(B)** Comparison of PHEMA (0.5 % EDMA) and PVP (0.25 % EBVP) matrices; **(C)** Various EBVP concentrations in PVP matrices (Niaspan release profile added).

Influence of crosslinker concentration in PVP matrices

Compared to the PHEMA hydrogels, where the monomer still contains some amount of EDMA crosslinker, PVP hydrogels can be prepared without any crosslinker agent. In addition to the high hydrophilicity of VP, a fully dissolute hydrogel matrix can be prepared. When testing the NA release from non-crosslinked PVP

matrices, we found complete fast dissolution of the tablet and release of incorporated NA into the liquid media (Fig. 4B). It seems that the dissolution of PVP hydrogel was fast and that the swollen hydrogel layer covering the non-reacted core did not appear.

Further experiments proceeded with crosslinked PVP matrices; as a crosslinker, the bifunctional structural

analog EBVP was examined. A series of samples containing 75 % NA was prepared with 0.05 to 0.5 % EBVP. The concentration of 0.2 % EBVP was found to be critical for dissolution of the hydrogel matrix. Tablets with higher crosslinker concentration did not dissolve and the NA release profiles did not differ noticeably, which is very similar to the release profiles obtained with PHEMA hydrogels. Similar to the PHEMA matrices, the PVP hydrogel-based tablets remained compact over the course of the experiment, which can be potentially harmful in the gastrointestinal tract.

Various crosslinking of PVP matrices under the limit of 0.12 5 % EBVP had almost no effect on hydrogel decomposition and consequent NA release profile. NA released almost immediately, as with the non-crosslinked PVP matrix. The crosslinking effect was most apparent within the range of 0.15-0.2 % EBVP. With the appropriate crosslinker concentration, it was possible to adjust complete NA release between 5 and 20 h (Fig. 3C). During the release experiment, the hydrogel matrix swelled and a shell of swollen porous hydrogel appeared, covering the non-reacted dry core (Figs. 4C and 4D). The shell thickness was dependent on EBVP content, becoming thicker with increasing crosslinking. The dissolution rate of this shell decreased with increasing crosslinking, since, in the case of 0.2 % EBVP, it became insoluble so that by the end of the experiment the buffer remained a block of swollen porous hydrogel. In contrast, the hydrogels of lower EBVP concentration completely decomposed, which is preferable feature, however, the rapid NA release would cause side effects.
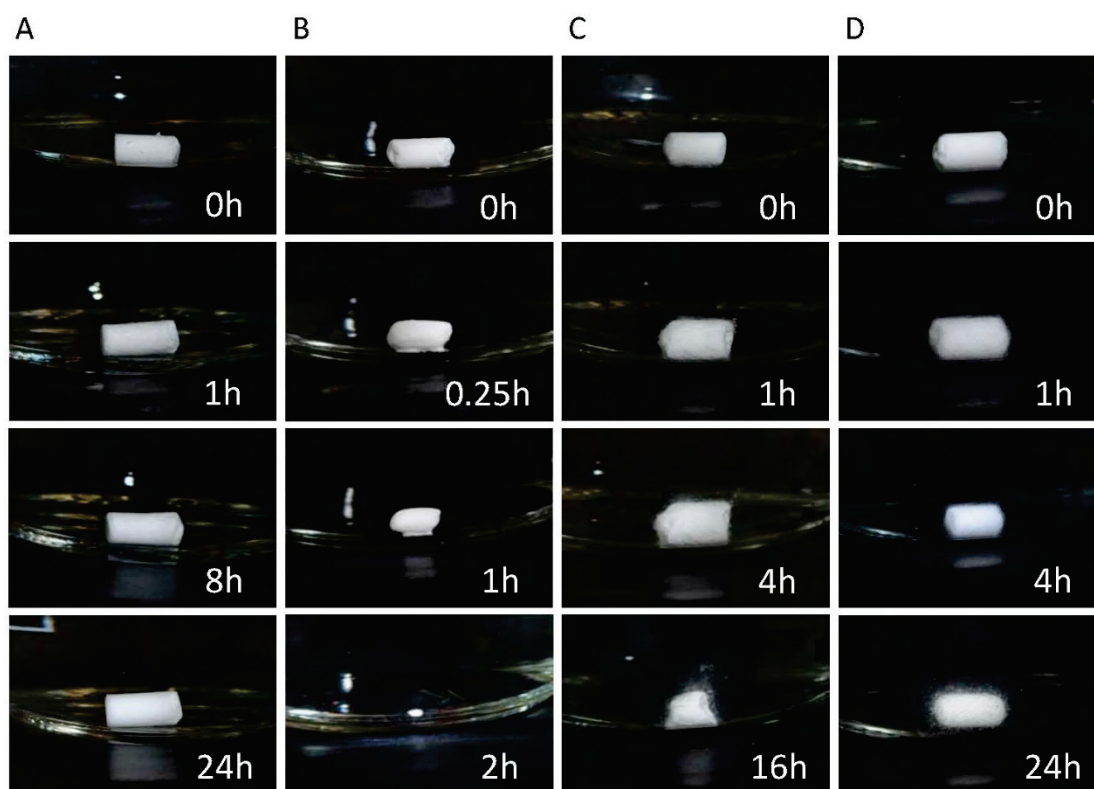

Fig. 4. Disintegration of tablets containing 75 % NA in buffer pH 6.8 using a hydrogel matrix: **(A)** HEMA/EDMA 99.85/0.15 w/w; **(B)** VP without crosslinker; **(C)** VP/EBVP 99.83/0.17 w/w; **(D)** VP/EBVP 99.8/0.2 w/w.

Although with the appropriate EBVP concentration it was possible to achieve complete NA release within the relatively wide range of time, from a therapeutic point of view (to get closer to the Niaspan release profile, see the curve added in Figure 3C) it was desirable to suppress NA release in the early stage of the experiment. Therefore, the combination of HEMA and VP monomers was examined.

The HEMA monomer at a concentration of 5-20 % was added to the VP monomer; the monomer mixture with the addition of 75 % NA was polymerized using 0.17 % EBVP related to the VP monomer. It seems that the weak PHEMA network (crosslinked with 0.15 % EDMA in the monomer) hindered decomposition of the PVP network, suppressed convection of liquid media, and prolonged NA release in the early stage of the experiment

when compared with the pure PVP matrix (Fig. 5A). A more linear release profile was achieved whenever the duration of total NA amount released was comparable with Niaspan. There was no considerable difference between the release profiles obtained with various HEMA concentrations. Also, the difference in NA release into buffers of various pH values was not noticeable. However, at 10 and 20 % of HEMA content, it is not possible to completely avoid residual solid hydrogel fragments, which can, regardless of their softness, be a source of problems in the intestine. Therefore, an optimal NA release delivery system was arranged for the hydrogel matrix with the addition of 5 % of HEMA (Fig. 5B).
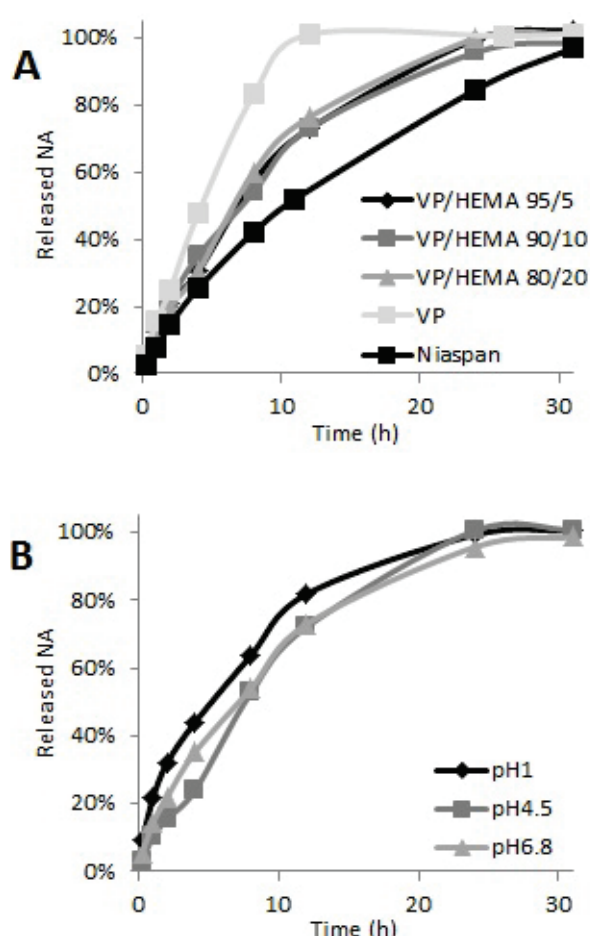

Fig. 5. NA release profiles from PVP/PHEMA-based tablets (75 % NA content in tablet): **(A)** Influence of the VP/HEMA monomer ratio (buffer pH 6.8, 0.15 % EDMA, 0.17 % EBVP, Niaspan release profile added); **(B)** Influence of buffer pH (VP/HEMA 95/5, 0.15 % EDMA, 0.17 % EBVP).

Conclusions

A hydrogel matrix for controlled delivery of NA to the gastrointestinal tract for the treatment of hyperlipidemia was explored and optimized. Monomer mixtures based on HEMA and VP were prepared with various compositions, various crosslinker content, and various amounts of active compounds. The release profiles were examined under various pH values in accordance with the gastrointestinal environment.

The concentration of NA in tablets was between 65 and 80 %. The optimal level was found to be 75 % when taking into account final dimensions of the tablet and the convenient processibility of the polymerization mixture (reproducibility of the preparation). In combination with the soluble hydrogel matrix, NA concentration was found to be an efficient way of controlling NA release.

The hydrogels consisting of HEMA monomers were, due to residual EDMA crosslinker content, insoluble under examined conditions. Contrary, PVP-based matrix solubility (decomposition) was dependent on crosslinking density. The bifunctional structural analog EBVP was found to be appropriate for controlling crosslinking of the PVP network and consequent tablet dissolution and NA release. In order to delay the release in the early stage of the experiment, a combination of VP and HEMA monomers was found to be efficient.

The NA release profiles were explored and the influence of the hydrogel matrix composition on the processes during NA release was considered. NA release of commercially available Tredaptive and Niaspan was compared and it can be concluded that with the presented system both NA release profiles can be reached. It seems that the release time period of the total amount of NA as well as of the release profiles in earlier or later stages of tablet immersion can be controlled and adjusted according to medical requirements.

Conflict of Interest
There is no conflict of interest.

References

BAJPAI SK, SONKUSLEY J: Hydrogels for oral drug delivery of peptides: synthesis and characterization. *J Appl Polym Sci* **83**: 1717-1729, 2002.

BASHIR A, SUDHAIR A, ZAFAR I, BASHIR S, JAVID A: Synthesis of cross linked PVP hydrogels and its use for the control release of anti-asthmatic drugs. *Middle East J Sci Res* **14**: 273-283, 2013.

BODEN WE, PROBSTFIELD JL, ANDERSON T, CHAITMAN BR, DESVIGNES-NICKENS P, KOPROWICZ K, MCBRIDE R, TEO K, WEINTRAUB W: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* **365**: 2255-2267, 2011.

BROWN BG, CANNER PI, McGOVERN ME, GUYTON JR, CARLSON LA: Nicotinic acid. In: *Clinical Lipidology. A Companion to Braunwald's Heart Disease*. CM BALLANTYNE (ed), Saunders, Elsevier, Philadelphia, 2009, pp 298-314.

BRYNDA E, ŠTOL M, CHYTRÝ V, CÍFKOVÁ I: The removal of residuals and oligomers from poly(2-hydroxyethylmethacrylate). *J Biomed Mat Res* **19**: 1169-1179, 1985.

BÜHLER V: *Polyvinylpyrrolidone Excipients for Pharmaceuticals: Povidone, Crospovidone and Copovidone*. Springer, Berlin, 2005, 266 p.

BURKS RI: Povidone-iodine solution in wound treatment. *Phys Ther* **78**: 212-218, 1998.

CÍFKOVÁ I, BRYNDA E, MANDYS V: Irritation effects of residual products derived from p(HEMA) gels. II. Compounds extracted from hydrogels. *Biomat* **9**: 372-375, 1988.

DE QUERIOZ AAA, VARGAS RR, HIGA OZ, RIBEIRO RR, VITOLO M: Lactam-amide graft copolymers as novel support for enzyme immobilization. *J Appl Polym Sci* **84**: 767-777, 2002.

DINU MV, PRADNY M, DRAGAN ES, MICHALEK J: Morphogical and swelling properties of porous hydrogels based on poly(hydroxyethyl methacrylate) and chitosan modulated by ice-templating process and porogen leaching. *J Polym Res* **20**: 1-10, 2013.

FLORENTIN M, LIBEROPOULOS EN, KEI A, MIKHAILIDIS DP, ELISAF MS: Pleiotropic effects of nicotinic acid: beyond high density lipoprotein cholesterol elevation. *Curr Vasc Pharmacol* **9**: 385-400, 2011.

HORÁK D: Application of poly(2-hydroxyethylmethacrylate) in medicine. In: *Leading Edge Research on Polymers and Composites*. YB MONAKOV, GE ZAIKOV, AA DALINKEVICH (eds), Nova Science Publishers, New York, 2004, pp 155-191.

HPS2-THRIVE COLLABORATIVE GROUP, LANDRAY MJ, HAYNES R, HOPEWELL JC, PARISH S, AUNG T, TOMSON J, WALLENDSZUS K, GRAIG M, JIANG L, COLLINS R, ARMITAGE J: Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* **371**: 203-212, 2014.

IRMUKHAMETOVA GS, SHAIKHUTDINOV EM, RAKHMETULLAYEVA RK, YERMUKHAMBETOVA BB, ISHANOVA AK, TEMIRKHANOVA G, MUN GA: Nanostructured hydrogel dressings on base of crosslinked polyvinylpyrrolidone for biomedical application. *Adv Mat Re* **875-877**: 1467-1471, 2014.

LAVIGNE PM, KARAS RH: The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J Am Coll Cardiol* **61**: 440-446, 2013.

PATENT: GB1024400: *Improvements in or relating to pyrrolidone derivatives*. 1966.

PŘÁDNÝ M, ŠLOUF M, MARTINOVÁ M, MICHÁLEK J: Macroporous hydrogels based on 2-hydroxyethyl methacrylate. Part 7: Methods of preparation and comparison of resulting physical properties. *E-Polymers* **43**: 1-10, 2010.

RAVIN HA, SELIGMAN AM, FINE J: Polyvinyl pyrrolidone as a plasma expander – studies on its excretion, distribution and metabolism. *N Engl J Med* **247**: 921-929, 1952.

ROBINSON JG: Pharmacologic treatment of dyslipidemia and cardiovascular disease. In: *The John Hopkins Textbook of Dyslipidemia*. PO KWITEROVICH Jr (ed), Lippincott, Williams & Wilkins, Philadelphia, 2010, pp 266-276.

SCF: European Commission, Scientific Committee on Food: Opinion of the Scientific Committee on Food on the safety of N-vinyl-2-pyrrolidone residues in polyvinylpyrrolidone and polyvinylpolypyrrolidone (insoluble polyvinyl-pyrrolidone) when used as food additives. 2002.

ŠTOL M, CÍFKOVÁ I, BRYNDA E: Irritation effects of residual products derived from poly(2-hydroxyethyl-methacrylate) gels. I. Testing of some model compounds. *Biomat* **9**: 273-276, 1988.

ŽÁK A, ZEMAN M, VECKA M, TVRZICKÁ E: Nicotinic acid: An unjustly neglected remedy (in Czech). *Čas Lék Čes* **145**: 825-831, 2006.

ZEMAN M, VECKA M, PERLÍK F, HROMÁDKA R, STAŇKOVÁ B, TVRZICKÁ E, ŽÁK A: Niacin in the treatment of hyperlipidemias in light of new clinical trials: has niacin lost its place? *Med Sci Monit* **21**: 2156-2162, 2015.