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ORIGINAL ARTICLE

Simulated food effects on drug release from ethylcellulose: PVA–PEG graft copolymer-coated pellets

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Abstract

Background: Food effects might substantially alter drug release from oral controlled release dosage forms in vivo. *Methods*: The robustness of a novel type of controlled release film coating was investigated using various types of release media and two types of release apparatii. *Results*: Importantly, none of the investigated conditions had a noteworthy impact on the release of freely water-soluble diltiazem HCl or slightly water-soluble theophylline from pellets coated with ethylcellulose containing small amounts of PVA–PEG graft copolymer. In particular, the presence of significant amounts of fats, carbohydrates, surfactants, bile salts, and calcium ions in the release medium did not alter drug release. Furthermore, changes in the pH and differences in the mechanical stress the dosage forms were exposed to did not affect drug release from the pellets. *Conclusion*: The investigated film coatings allowing for oral controlled drug delivery are highly robust in vitro and likely to be poorly sensitive to classical food effects in vivo.

Key words: *Biorelevant media; coating; controlled release; food effects; pellets*

Introduction

Polymer-coated pellets are highly suitable as multiparticulate controlled drug delivery systems[1–3]. Different types of polymers are commercially available for the preparation of controlled release film coatings, including ethylcellulose, poly(acrylic acid) derivatives, and poly(vinyl pyrrolidine). They can be applied either from organic solutions or from aqueous dispersions[4]. Ethylcellulose is a particularly suitable coating material, because it is a good film former and generally regarded as nontoxic, nonallergenic, and nonirritant. To adjust desired drug release kinetics from ethylcellulose-coated dosage forms and to optimize long-term stability (in particular during open long-term storage under stress conditions), the addition of small amounts of PVA–PEG graft copolymer to aqueous ethylcellulose dispersion (aquacoat ECD) has recently been proposed[5–7]. Once these pellets get into contact with aqueous body fluids, water penetrates into the systems and dissolves the incorporated drug. The latter subsequently diffuses out of the dosage forms, the release rate being controlled by the composition and thickness of the film coating[8,9].

It has to be pointed out that the environmental conditions for drug release from coated pellets might significantly affect the underlying drug release mechanisms and resulting release patterns. For instance, the importance of osmotic effects (potentially leading to crack formation in the film coatings) can strongly depend on the osmolality of the surrounding bulk fluid. Also, the mechanical stress the coated pellets are exposed to might play a major role, determining whether the polymeric films remain intact during drug release or show crack formation. Furthermore, the presence of enzymes, surfactants, bile salts, carbohydrates, and fats might alter the film-coating composition with time (e.g., leading to polymer degradation or leaching of film compounds into the bulk fluid). Such changes can significantly alter drug release. In addition, variations in the pH of the aqueous environment might have an impact

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on the integrity and permeability of the polymeric membranes. It is well known that the environmental conditions for drug release within the gastrointestinal tract (GIT) can strongly vary inter-individually as well as intra-individually[10]. Obviously, the composition and quantity of ingested food can significantly alter the type and amount of bulk fluid surrounding the pellets during drug release throughout the GIT[11,12]. Furthermore, the transit times in the various GIT segments may strongly depend on the type and amount of ingested meals and beverages[13]. Consequently, the ingestion of food can affect the absorption of drugs from the GIT[14,15].

Obviously, the frequently used release media – 0.1 N HCl and phosphate buffer (pH 6.8 or 7.4) – simulating the contents of the stomach and intestine do not allow to appropriately monitor potential food effects on drug release from controlled delivery systems. Dressman and co-workers[16–20] proposed several interesting and much more 'biorelevant' aqueous media for in vitro drug release measurements: in particular, fast state simulating gastric fluid (FaSSGF), fed state simulating gastric fluid (FeSSGF), fast state simulating intestinal fluid (FaSSIF), and fed state simulating intestinal fluid (FeSSIF). These media allow for an estimation of the effects of the presence of pepsin, sodium taurocholate, lecithin, milk, and different types and amounts of ions in the GIT on drug release. However, little is yet known of the importance of potential food effects on the performance of polymer-coated, controlled release pellets.

The major aim of this study was to evaluate the impact of (i) the presence of significant amounts of fats, carbohydrates, surfactants, bile salts, and calcium ions in the release medium; (ii) the differences in the mechanical stress the dosage forms are exposed to; and (iii) the gradual changes in the pH of the bulk fluids, on the resulting drug release kinetics from ethylcellulose : PVA–PEG graft copolymer-coated pellets. Diltiazem HCl and theophylline were used as freely and slightly water-soluble model drugs.

Materials and methods

Materials

Diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France); theophylline matrix pellets (70% drug content, diameter: 0.71–1.25 mm; FMC BioPolymer, Philadelphia, PA, USA); sugar cores (sugar spheres NF, diameter: 0.71–0.85 mm; NP Pharm, Bazainville, France); hydroxypropyl methylcellulose (HPMC, Methocel E 5; Colorcon, Dartford, UK); Ethylcellulose Aqueous Dispersion NF (Aquacoat ECD; FMC BioPolymer); poly(vinyl alcohol)–poly(ethylene glycol) graft copolymer (PVA–PEG graft copolymer, Kollicoat IR; BASF, Ludwigshafen, Germany); triethyl citrate (Morflex, Greensboro, NC, USA), calcium chloride ($CaCl_2$), sodium chloride (NaCl), isopropanolol, and lecithin (Alfa Aesar, Schiltigheim, France); pepsin, ethanol, methanol, acetic acid, and acetonitrile (Fisher Bioblock Scientific, Illkirch, France); and sodium taurocholate (donation from New Zealand Pharmaceuticals, Palmerston North, New Zealand) were used.

Preparation of coated pellets

Sugar starter cores were coated with an aqueous solution of diltiazem HCl (18.2%, w/w) and HPMC (0.9%, w/w) in a fluidized bed coater (Strea 1, Wurster insert; Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: inlet temperature = 40°C, product temperature = 40 ± 2°C, spray rate = 1 − 3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm, air flow rate = 100 m^3/h. The final drug loading was 10% (w/w).

Diltiazem HCl-layered sugar cores as well as theophylline matrix cores were coated with aqueous ethylcellulose dispersion containing small amounts of PVA–PEG graft copolymer in a fluidized bed coater (Strea 1, Wurster insert). The coating dispersions were prepared as follows: the aqueous ethylcellulose dispersion was plasticized overnight with triethyl citrate (25%, w/w, based on the ethylcellulose content). Aqueous PVA–PEG graft copolymer solution (3.7%, w/w, in the case of diltiazem HCl-layered sugar cores and 6.0%, w/w, in the case of theophylline matrix cores) was added so that a solid's content of 15% (w/w) was achieved in both cases. The respective blends were stirred for 30 minutes before coating. The process parameters were as follows: inlet temperature = 38°C, product temperature = 38 ± 2°C, spray rate = 2 − 3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm, and air flow rate = 100 m^3/h. After coating, the pellets were further fluidized for 10 minutes and subsequently cured for 24 hours at 60°C in an oven.

Drug release measurements

In media simulating the fast state and fed state

Drug release from ensembles of pellets was measured in a USP 30 paddle apparatus (AT 7; Sotax, Basel, Switzerland) (500 mL, 37°C, 100 rpm) (n = 3, if not otherwise stated). The 'standard' release media were 0.1 N HCl and phosphate buffer (pH 0.8) (USP 30) (complete medium change after 2 hours). The composition of more 'biorelevant' release media (as suggested by Dressman and co-workers[16,19]) is shown in Table 1: FaSSGF, FeSSGF, FaSSIF, and FeSSIF (complete medium change after 2 hours, total exposure time = 8 hours). Furthermore,

Table 1. Composition, pH, and surface tension of the more 'biorelevant' release media used for the drug release measurements shown in Figure 1.

FaSSGF	FeSSGF	FaSSIF	FeSSIF
2.0 g NaCl	13.75 g NaCl	7.7 g KCl	—
3.2 g pepsin	4.05 g sodium acetate	3.9 g KH_2PO_4	1 g Na-taurocholate
—	—	0.55 g lecithin	2.75 g lecithin
7 mL HCl (37%)	1.03 g glacial acetic acid	NaOH q.s. pH 6.5	Glacial acetic acid q.s. pH 5.0
H_2O q.s. 1 L	H_2O q.s. 1 L	H_2O q.s. 1 L	H_2O q.s. 1 L
—	Skimmed milk (3.5% fat) 1 L	—	—
pH 1.6	pH 5.0	pH 6.5	pH 5.0
Surface tension 42.8 ± 0.1 mN/m	Surface tension 50.0 ± 0.2 mN/m	Surface tension 44.0 ± 0.1 mN/m	Surface tension 36.9 ± 0.1 mN/m

FaSSGF, fast state simulating gastric fluid, according to the USP 30; FeSSGF, fed state simulating gastric fluid, according to Jantratid et al.[19]; FaSSIF, fast state simulating intestinal fluid, according to Galia et al.[16]; FeSSIF, fed state simulating intestinal fluid, according to Jantratid et al.[19]

Table 2. Composition of the fat- and carbohydrate-containing release media used for the drug release measurements shown in Figure 2.

	Gastric fluid	Intestinal fluid
Carbohydrates (g)	33.3 (sacharose)	17.5 (glucose)
Fat (g)	16.6 (coconut oil) and 16.6 (corn oil)	15.3 g (sodium stearate) & 15.2 (sodium oleate)
Lecithin (g)	2.75	5.5
Sodium taurocholate (g)	1	3.2
Tween 80 (%, w/v)	0.1	0.05
Glycerol (mmol)	—	43.5
H_2O	q.s. 1 L	q.s. 1 L
HCl (32%, w/w)/NaOH	q.s. pH 5.0	q.s. pH 5.0
Surface tension (mN/m)	37.6 ± 3.6	28.2 ± 3.7

diltiazem HCl and theophylline release was determined in fat and carbohydrate-containing media (n = 6). Table 2 shows the compositions of the respective bulk fluids (complete medium change after 4 hours, total exposure time = 10 hours).

In media simulating gradual changes in the pH and being agitated in a different way

To better simulate the gradual changes in the pH of the contents of the GIT, also the USP apparatus 3 (Bio-Dis; Varian, Les Ulis, France) (200 mL in each vessel, 37°C, dipping speed: 20 dpm, n = 3) and the release media listed in Table 3 were used, according to Mehuys et al.[21]

In media containing different amounts of calcium ions

To estimate the impact of the calcium ion content of the release medium, drug release was also measured in 0.1 N HCl containing 0, 10, 25, and 50 mmol/L $CaCl_2$ in a USP paddle apparatus (AT 7, 900 mL, n = 3).

At pre-determined time points, 3-mL samples were withdrawn and analyzed for their drug content either by UV-spectrophotometry (diltiazem HCl/theophylline: λ = 236.9/270.4 nm in 0.1 N HCl and λ = 237.4/272.2 nm in phosphate buffer, pH 6.8, respectively) (UV 1650 PC, Shimadzu, Champs-sur-Marne, France) or by high-performance liquid chromatography (HPLC) analysis (in the case of

Table 3. Release media used to simulate the gradual changes in pH along the GIT.

GI segment	Exposure time	Medium	pH
Stomach	120 minutes	Hydrochloric acid media Ph. Eur.	1.2
Duodenum	15 minutes	Phosphate buffer Ph. Eur.	5.8
Duodenum	15 minutes	Phosphate buffer Ph. Eur.	6
Jejunum	120 minutes	Simulated intestinal fluid (sp) USP	6.8
Proximal ileum	30 minutes	Phosphate buffer Ph. Eur.	7.2
Distal ileum	60 minutes	10 mM phosphate buffer (pH adjusted with NaOH)	7.5

The drug release kinetics measured in these media are shown in Figure 3.

the following release media: FeSSGF, FaSSIF, FeSSIF, fat, and carbohydrate-containing fluids). Fifty microliters of the samples was injected into an HPLC apparatus (ProStar 410, Varian). A Synergi Hydro-RP C18 column (4 µm, 250 × 4.6 mm; Phenomenex, Torrance, CA, USA) was used and kept at 25 ± 2°C. In the case of diltiazem HCl, the mobile phase was a 5:4:1 blend of 50-mmol phosphate buffer (pH 6.0):acetonitrile:methanol (according to Schilling et al.[22]). The pH of the mobile phase was adjusted to pH 4.2 with phosphoric acid. The flow rate was 0.7 mL/min, and the drug was detected using UV spectrophotometry at λ = 237 nm (ProStar 325 UV–Vis detector, Varian). In the case of theophylline, the mobile phase was a 24:75:1 blend of ethanol:water:acetic acid (according to Aragão et al.[23]). The flow rate was 1 mL/min and the drug was detected using UV spectrophotometry at λ = 273 nm (ProStar 325 UV–Vis detector). Data collection and analysis were performed using the Galaxie SW software (Varian). In the case of protein-containing release media, the proteins were precipitated by the addition of 3 mL isopropanolol. The samples were subsequently centrifuged (Universal 320; Hettich, Tuttlingen, Germany) and filtered through a 0.45-µm PTFE filter before HPLC analysis. The surface tensions of the media were measured using the ring method (Lauda TD1, Lauda, Lauda-Koenigshofen, Germany) (n = 3).

Results and discussion

Drug release in media simulating the fast state and fed state

Diltiazem HCl and theophylline release from coated pellets in media simulating the contents of the stomach and intestine in the fast and fed states is shown in Figure 1 (solid curves). The compositions of the media (FaSSGF, FeSSGF, FaSSIF, and FeSSIF) are indicated in Table 1. For reasons of comparison, also drug release measured in the standard media 0.1 N HCl and 'phosphate buffer (pH 6.8) is shown in Figure 1 (dotted curves). Clearly, drug release was very similar in all types of bulk fluids, indicating that the presence of pepsin, lecithin, sodium taurocholate as well as milk (3.5% fat) does not significantly affect the resulting release patterns, irrespective of the type of drug. Thus, also in vivo the presence or absence of these compounds is not likely to alter drug release from this type of dosage forms.

Furthermore, the presence of significant amounts of fats and carbohydrates on drug release from ethylcellulose:PVA–PEG graft copolymer-coated pellets was studied. The resulting release kinetics of diltiazem HCl and theophylline upon 4 hours of exposure to saccharose, coconut oil, and corn oil containing simulated gastric fluid (for composition see Table 2) and subsequent 6-hour exposure to glucose, sodium stearate, and sodium oleate containing simulated intestinal fluid (for composition see Table 2) were monitored. Note that these media also contain lecithin and sodium taurocholate, but in higher concentrations than the above-described FeSSIF. The fat and carbohydrate contents were four times higher than that recommended for a single meal according to the German Federal Ministry of Food, Agriculture and Consumer Protection[24]. The consequences of the saponification of coconut oil (containing high amounts of saturated fatty acids) and

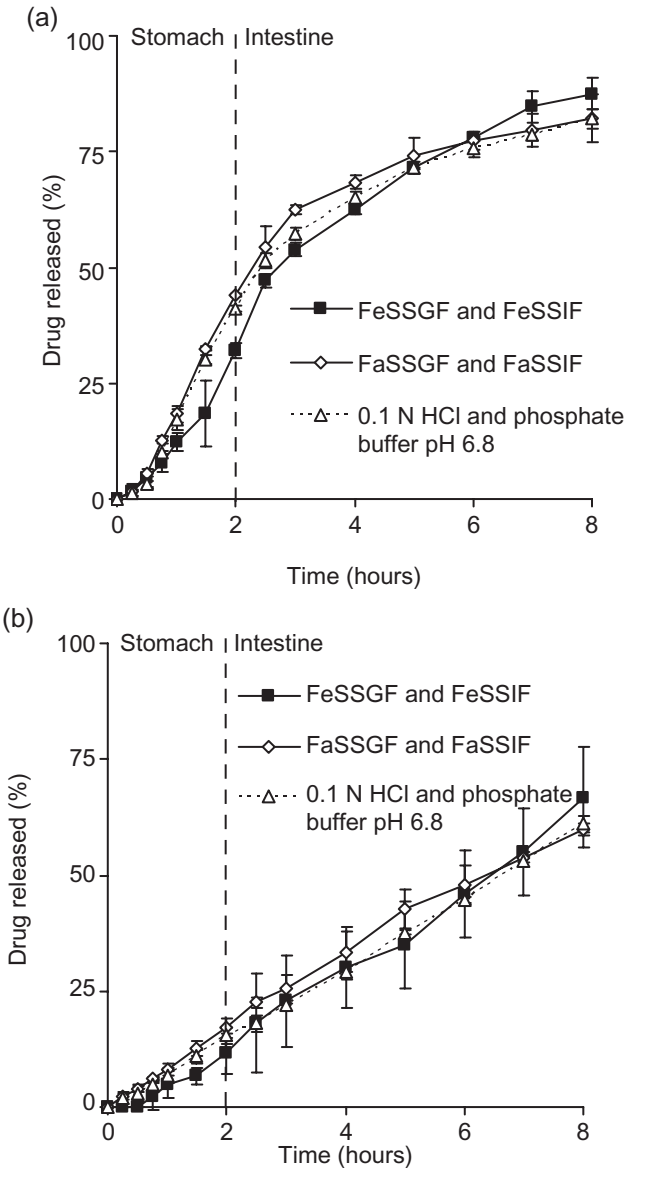

Figure 1. Drug release from (a) diltiazem HCl-layered sugar cores coated with ethylcellulose : PVA–PEG graft copolymer 90:10 (coating level: 30%) and (b) theophylline matrix cores coated with ethylcellulose:PVA–PEG graft copolymer 85:15 (coating level: 15%) in 'biorelevant' gastric and intestinal fluids in the fast and fed state (solid curves) (USP paddle apparatus, 500 mL, n = 3). For reasons of comparison, also drug release in the 'standard' release media '0.1 N HCl' and 'phosphate buffer pH 6.8' is shown (dotted curves).

corn oil (containing predominantly unsaturated fatty acids) within the intestine was simulated by adding saturated and unsaturated free fatty acids (sodium stearate and sodium oleate) and glycerol to the medium simulating the contents of the intestine. The resulting emulsions were stabilized by the addition of Tween 80. The presence of the latter also allowed adjusting physiological surface tensions (36–51 mN/m in gastric fluids[25] and 26–30 mN/m in intestinal fluids[26]) of the release media (37.6 and 28.2 mN/m, respectively). Lecithin acted as a natural emulsifier. The pH of both bulk fluids, simulating the contents of the fed stomach and fed intestine, was adjusted to 5.0 (according to Kalantzi et al.[18]; Jantratid et al.[20]; Dressman et al.[27]). Note also the elevated transit time in simulated gastric fluid in the fed state (4 hours, according to Davis et al.[28]). Diltiazem HCl and theophylline release from the investigated pellets into these fat- and carbohydrate-containing media are shown in Figure 2 (solid curves). For reasons of comparison, also drug release upon 2 hours of exposure to 0.1 N HCl and 8 hours of exposure to phosphate buffer (pH 6.8) was measured (dotted curves). Clearly, no significant changes were observed when adding significant amounts of fats, carbohydrates, and surfactants to the release media, irrespective of the type of drug. Thus, drug release from this type of delivery systems is also likely to be nonsensitive to such changes in vivo caused by food ingestion.

Effects of gradual changes in the pH and degree of agitation of the release medium

To more realistically simulate the gradual changes in the pH of the contents of the GIT and to better simulate the mechanical stress the coated pellets are exposed to because of GIT motility, the USP apparatus 3 (20 dpm) and the release media shown in Table 3 were used. The selected pH values and transit times were based on mean values reported in the literature[21,29–31]. The release kinetics of diltiazem HCl and theophylline from the investigated coated pellets under these conditions are shown in Figure 3 (solid curves). For reasons of comparison, also drug release upon 2 hours of exposure to 0.1 N HCl and 4 hours of exposure to phosphate buffer pH 6.8 in a USP paddle apparatus (500 mL, n = 3) are plotted (dotted curves). As it can be seen, the experimental conditions did again not significantly affect the resulting drug release rate, irrespective of the type of drug. Thus, also differences in the mechanical stress and differences in the pH of the surrounding bulk fluid the pellets are exposed to in vivo are not likely to alter drug release.

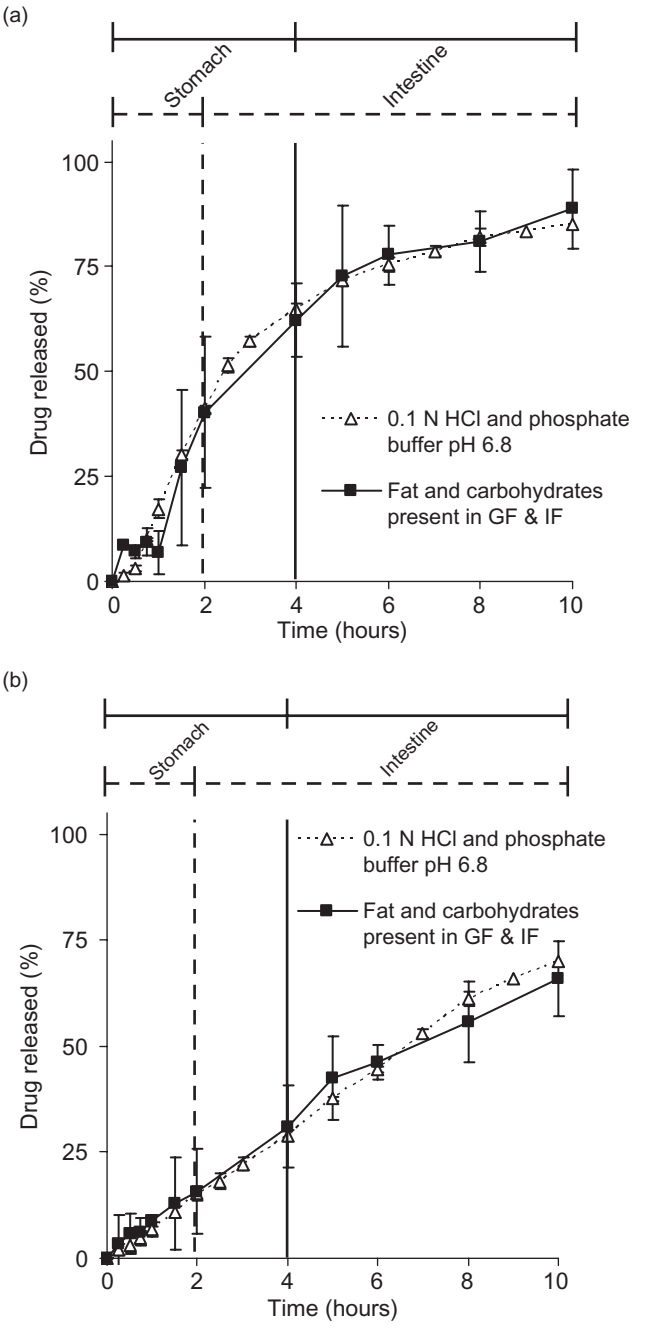

Figure 2. Drug release from (a) diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG graft copolymer 90:10 (coating level: 30%) and (b) theophylline matrix cores coated with ethylcellulose:PVA–PEG graft copolymer 85:15 (coating level: 15%) in fat- and carbohydrate-containing media (solid curves, GF = gastric fluid, IF = intestinal fluid). For reasons of comparison, also drug release in the 'standard' release media 0.1 N HCl and phosphate buffer (pH 6.8) is shown (dotted curves). All experiments were conducted in the USP paddle apparatus (500 mL, n = 6).

Impact of calcium ions

The properties of certain polymers used in controlled drug delivery systems are known to be sensitive to the presence of calcium ions in the bulk fluid. In particular, the permeability of a polymeric network for a drug might significantly be affected by the calcium ion concentration in the release medium. For this reason,

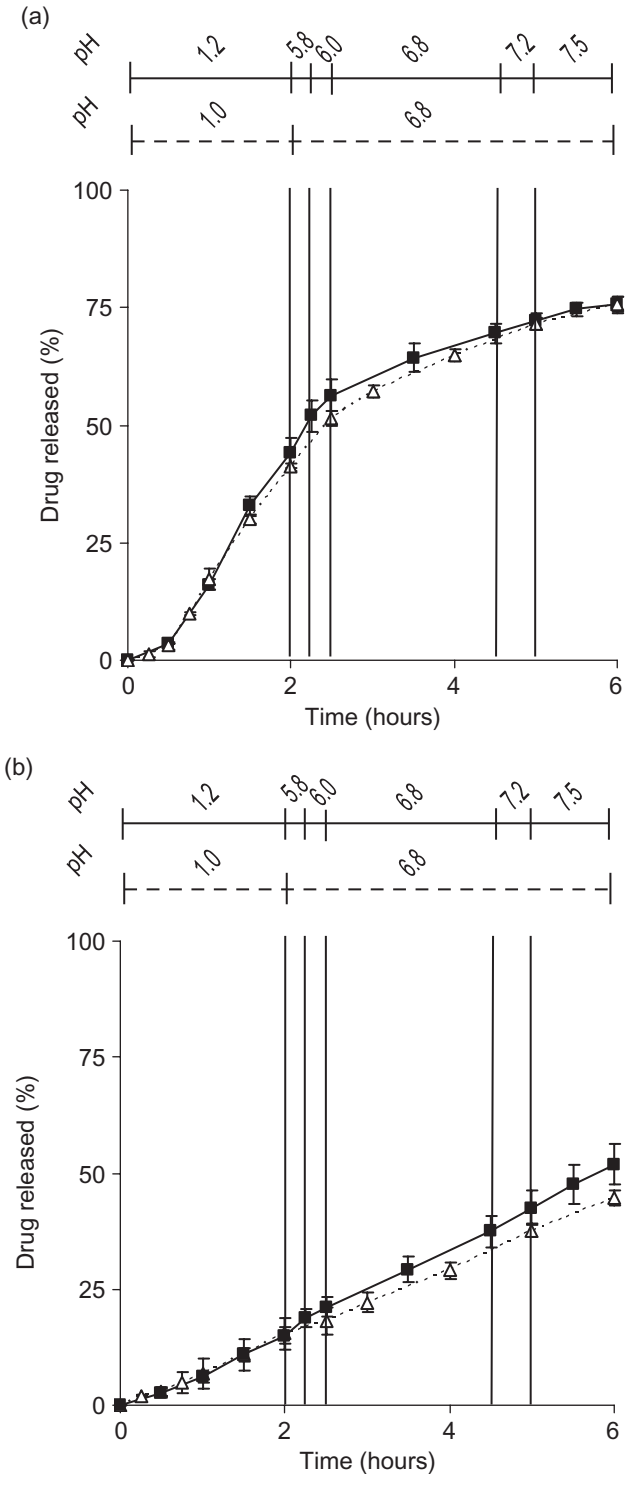

Figure 3. Drug release from (a) diltiazem HCl-layered sugar cores coated with ethylcellulose:PVA–PEG graft copolymer 90:10 (coating level: 30%) and (b) theophylline matrix cores coated with ethylcellulose:PVA–PEG graft copolymer 85:15 (coating level: 15%) in a USP apparatus 3, simulating gradual changes in the pH of the release medium (solid curves) (200 mL in each vessel, 20 dpm, $n = 3$). For reasons of comparison, also drug release in the 'standard' release media 0.1 N HCl and phosphate buffer (pH 6.8) in a USP paddle apparatus (500 mL, $n = 3$) is shown (dotted curves).

diltiazem HCl and theophylline release from the ethylcellulose:PVA–PEG graft copolymer-coated pellets was studied in 0.1 N HCl containing 0, 10, 25, and 50 mmol/L calcium ions. It has to be pointed out that these concentrations represent extreme conditions: Even upon ingestion of 1 L calcium-rich beverages, the Ca^{2+} concentration in the GIT has been reported to be in the range of 5–30 mmol/L[32]. As it can be seen in Figure 4, the resulting drug release kinetics is virtually overlapping,

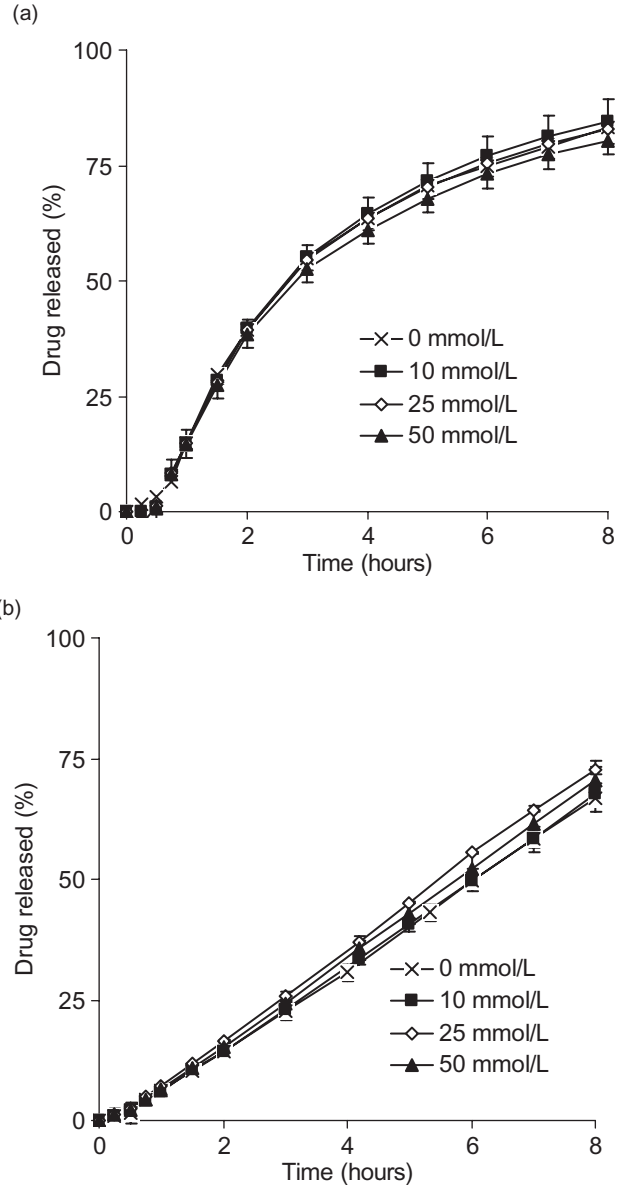

Figure 4. Effects of the calcium ion concentration in the release medium (0.1 N HCl) on (a) diltiazem HCl release from drug-layered sugar cores coated with ethylcellulose:PVA–PEG graft copolymer 90:10 (coating level: 30%) and (b) theophylline release from drug matrix cores coated with ethylcellulose:PVA–PEG graft copolymer 85:15 (coating level: 15%). All experiments were conducted in the USP paddle apparatus (900 mL, $n = 3$).

irrespective of the type of drug and calcium ion concentration. Thus, also this parameter, which might significantly vary in vivo, does not alter the release rate from this very robust type of delivery systems.

Conclusion

In vitro drug release from pellets coated with ethylcellulose containing small amounts of PVA–PEG graft copolymer is not sensitive to potential changes in the fat, carbohydrate, surfactant, bile salt, pepsin, lecithin, and calcium ion content of the surrounding bulk fluid nor to alterations in the mechanical stress and pH values the systems are exposed to. Thus, corresponding food effects in vivo are unlikely to be significant for this very robust type of controlled release formulations.

Acknowledgments

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Declaration of interest

Two of the authors are employees of FMC BioPolymer, the supplier of the investigated aqueous ethylcellulose dispersion.

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