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PII: S0378-5173(26)00388-1
DOI: https://doi.org/10.1016/j.ijpharm.2026.126940
Reference: IJP 126940

To appear in: *International Journal of Pharmaceutics*

Received Date: 19 February 2026
Revised Date: 29 April 2026
Accepted Date: 29 April 2026

Please cite this article as: T. Heinrich, R. Bodmeier, A. Dashevskiy, Effect of drug solubility, polymer, and filler on drug release from modified-release matrix tablets in hydroethanolic media, *International Journal of Pharmaceutics* (2026), doi: https://doi.org/10.1016/j.ijpharm.2026.126940

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Effect of drug solubility, polymer, and filler on drug release from modified-release matrix tablets in hydroethanolic media

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Keywords: hydroethanolic media; matrix tablets; modified release; solubility ratio; ethylcellulose; hydroxypropylcellulose; hypromellose (HPMC); Kollidon® SR; poly(ethylene oxide) (PEO).

Abstract

This study aimed to develop strategies to prevent accelerated drug release (alcohol-induced dose dumping) from modified-release matrix tablets in hydroethanolic media. Drugs with different solubility profiles (theophylline, propranolol HCl, paracetamol, and carbamazepine) were formulated with water-soluble or water-insoluble matrix formers, with optional addition of soluble or insoluble fillers. Drug release, medium uptake, and leaching were evaluated in 0.1 N HCl containing 0, 20, or 40% (v/v) ethanol. No release acceleration was observed for theophylline and propranolol HCl, which showed low solubility ratios between hydroethanolic and aqueous media (approximately 2). In contrast, paracetamol and carbamazepine (solubility ratio approximately 20) required formulation adjustments. For paracetamol, comparable release profiles across media were achieved using matrix formers with low medium uptake (e.g., Klucel® MXF or Kollidon® SR) or by incorporating a soluble filler such as lactose. For carbamazepine, the increased solubility in hydroethanolic media shifted the release mechanism from erosion-dominated to diffusion-dominated; similar release profiles were only obtained with hydrophilic polymers exhibiting relatively high erosion rates.

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1. Introduction

Alcohol-induced dose dumping remains an important concern for regulatory agencies and formulation scientists. In view of the risks associated with unintended rapid release after co-administration with alcoholic beverages, the FDA recommends additional in vitro testing of extended-release formulations in media containing 0-40% (v/v) ethanol, and profile similarity is commonly assessed using the f2 factor [1]. The clinical relevance of this issue was highlighted in 2005, when markedly increased Cmax values were reported for extended-release hydromorphone capsules administered with ethanol [2]. Since then, both commercial and non-commercial modified-release dosage forms have been investigated extensively [3].

Among oral extended-release systems, matrix tablets based on water-soluble or water-insoluble polymers are particularly common. It was showed that ethanol can accelerate or modify drug release from hydrophilic, lipophilic, and dual-matrix tablets depending on polymer type and formulation design. The study underscores the risk of alcohol-induced dose dumping in certain matrix systems[4]. For matrix tablets, hydroethanolic media can affect drug solubility, wettability, swelling, erosion, and mechanical properties [3]. It was demonstrated that hydro-alcoholic media can significantly alter the hydration and gel-layer formation of hypromellose (HPMC) matrix tablets, potentially affecting drug-release performance [5]

Because drug diffusion and polymer swelling/erosion occur simultaneously in hydrophilic matrices [4-14], the net ethanol effect is often formulation specific. For example, acetylsalicylic acid release from HPMC K4M tablets was related to increased drug solubility in hydroalcoholic media and possibly to a larger diffusional contribution, whereas tablet swelling was greater in non-ethanolic media [15]. In addition, erosion strongly depends on gel strength, which has been reported to increase for swollen HPMC tablets in hydroethanolic media [16]. Previous studies also showed broadly similar release behavior for some combinations of drugs, fillers, and HPMC grades [5], while other reports highlighted that soluble lactose may intensify ethanol effects compared with insoluble MCC [17], whereas soluble maltitol can slow release because of its lower solubility in 40% ethanol [18]. Comparable questions have been addressed for other hydrophilic polymers: no release acceleration was reported for PEO tablets containing metformin or gliclazide [19] or for HPC-based systems with tramadol [20]. The abuse-resistant Guardian® technology issued by Egalet corp. utilizes injection molding of PEO with morphine sulphate at high temperature and pressure to avoid preliminary drug release and accelerated release [21].

Theophylline tablets with xanthan gum were also studied with respect to polymer content and particle size; larger particles and lower polymer levels increased release in 40% ethanol, especially in mini-tablets because of the shorter diffusion pathway [22].

Water-insoluble polymers have been investigated less frequently for modified-release matrix tablets. For ethylcellulose, previous work mainly addressed films and demonstrated increased water permeation and swelling after ethanol addition [13]. Ethylcellulose in combination with guar gum was also used as a coating to obtain ethanol-resistant release from theophylline pellets [14] and corn starch-codeine phosphate pellets [23]. Likewise, tramadol tablets prepared with Kollidon® SR showed alcohol-resistant release behavior [24, 25]. In such insoluble matrix systems, drug release is generally dominated by diffusion through the hydrated polymer network [26].

A mechanistic understanding of alcohol-related dose-dumping risks and highlights the need to evaluate ethanol effects during formulation development. It was demonstrated that ethanol affects key biopharmaceutical processes—namely drug solubility, supersaturation, and intestinal absorption. Using a combination of solubility measurements, dissolution experiments, and in silico absorption modelling, it was demonstrated that ethanol can markedly increase the apparent solubility of certain drugs, alter supersaturation profiles, and consequently modify the predicted absorption kinetics. Importantly, the study showed that these ethanol-induced changes are highly drug-dependent and can either enhance or reduce absorption, meaning that alcohol consumption has the potential to compromise the intended performance of controlled-release formulations [27].

Taken together, the available literature does not yet provide broadly applicable formulation guidelines because most reports focus on specific drugs or individual formulations. The present study therefore goes beyond drug solubility alone and systematically examines how drug solubility, polymer type/viscosity, and filler properties jointly influence release from modified-release matrix tablets in hydroethanolic media. The specific aim was to identify combinations that are prone to ethanol-induced release changes and to derive practical formulation approaches to minimize or prevent such changes.

2. Materials and Methods

2.1. Materials:

Carbamazepine, paracetamol, and theophylline were obtained from BASF SE (Ludwigshafen, Germany), and propranolol HCl was obtained from IPCA Laboratories Limited (Mumbai, India). Hydroxypropylcellulose (HPC, Klucel® MXF, Ashland Inc., Wilmington, USA), ethylcellulose (EC, Ethocel® 10 FP), hypromellose (HPMC, Methocel® K100LV CR, K4M CR, and K100M CR; Colorcon Ltd., Dartford, UK), polyethylene oxide (PEO, Sentry Polyox® WSR 303 LEO NF Grade, Dow, Inc., Connecticut, USA), poly(vinyl acetate) and poly(vinyl pyrrolidone) (PVAc/PVP, Kollidon® SR, BASF SE, Ludwigshafen, Germany), poly(ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride) [1:2:0.1] (Eudragit® RS, Evonik Industries AG, Darmstadt, Germany), Patent Blue V (BASF SE, Ludwigshafen, Germany), lactose (Flowlac® 100, Meggle GmbH & Co. KG, Wasserburg am Inn, Germany), magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany), and ethanol (99.8%, Carl Roth GmbH + Co. KG, Karlsruhe, Germany) were used as received.

2.2. Methods:

2.2.1. Solubility determination

An excess of drug was added to 0.1 N HCl containing 0 or 40% (v/v) ethanol and shaken horizontally (80 rpm, 37 °C, n = 3). After 48 h, samples were withdrawn, centrifuged, and analyzed by UV spectrophotometry (UV HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at 319, 244, 235, and 255 nm for propranolol HCl, paracetamol, theophylline, and carbamazepine, respectively. The solubility ratio was defined as the ratio of drug solubility in media containing 40% and 0% ethanol.

The solubility of lactose was determined at room temperature by stepwise addition (30 min intervals) of the respective medium (starting with 3.5 ml) until complete dissolution of 1 g lactose with continuous agitation (80 rpm, n=3).

2.2.2. Tablet preparation

49.5 % drug, 49.5% polymer and 1% Mg stearate were blended in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 min and then manually compressed using a tableting press Korsch EK-0 (Korsch AG, Berlin, Germany) equipped with 7 mm round punch at a compression force of 25±2 kN. Tablets with fillers consisted of either 35% polymer, 30% drug, 33% lactose, 1% Mg stearate and 1% Aerosil® or 49.5% paracetamol, 24.5% Methocel, 24.5% filler and 1% Mg stearate. Drug-free matrix tablets consisting of 99% polymer and 1% Mg stearate were compressed with a 10 mm round punch.

2.2.3. Release testing

Release testing was conducted in 0.1 N HCl containing 0, 20 or 40% (v/v) ethanol in a USP II paddle apparatus (900 ml, 75 rpm, 37°C, n=2-3, VK 7010, Vankel Industries, Edison, NJ, USA) and the drug concentration was quantified on-line via UV-spectroscopy (Cary 50 Tablet, Varian Optical Spectroscopy Instruments, Mulgrave, Victoria, Australia) at the same wavelengths as for the solubility studies.

2.2.4. Drug diffusion through the polymeric gel

Paracetamol solution (800 µl, 6.8 mg/ml) prepared in 0 or 40% ethanol was placed into the chamber of a custom-built diffusion cell (diameter 10 mm; volume 3 ml). A drug-free Methocel® K4M tablet was placed on top to ensure direct contact with the medium while tightly sealing the chamber. The assembled diffusion cells were then immersed in the respective external medium in USP II paddle apparatus and proceeded as described for release testing,

2.2.5. Medium uptake, dry weight loss, and viscosity

Medium uptake was determined using drug-free matrix tablets placed in a USP-I basket apparatus (900 ml, 100 rpm, 37 °C, n = 2). Tablets were removed at predetermined time points, gently blotted with soft tissue, and weighed in the wet state (m_{wet}); they were then dried overnight at 105 °C and weighed again (m_{dry}). Medium uptake was calculated as $\frac{m_{wet} - m_{dry}}{m_{dry}}$. Dry weight loss (referred to as leaching) reflects the loss of soluble tablet components into the medium and was calculated as $\frac{m_{initial} - m_{dry}}{m_{initial}}$. The kinematic viscosity of a 5% (w/w) Kollidon® 30 solution was measured with a capillary viscometer (n = 3, SCHOTT AG, Mainz, Germany) at room temperature (19 °C).

2.2.6. Video monitoring of tablet swelling

Tablets were clamped between two transparent inert discs in 500 ml of the respective medium (37 °C; 0% or 40% (v/v) ethanol; n = 2), exposing only the radial surfaces to medium penetration in a set-up similar to that described previously [28]. Photographs were acquired with a camera coupled to image-analysis software (ICCapture, The Imaging Source Europe GmbH, Bremen, Germany). Swelling (%) was calculated from the increase in the projected 2D tablet area relative to the initial area, i.e., $[(A_t / A_0) - 1] \times 100$, using the FIJI platform [29].

2.2.7. Mathematical evaluation of release curves

The similarity of release curves between aqueous and hydroethanolic media was determined using the f2 factor. Release profiles with f2 values above 50 were considered similar [30].

Release curves were analysed by a modified method of Peppas and Sahlin [11]:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad \text{equation 1}$$

where the exponent $m = 0.45$ was chosen based on the geometric properties of the tablet, and the kinetic constants k_1(diffusional release) and k_2(case-II transport) were calculated from the experimental data points using ordinary least squares regression.

The quotient between these constants was used for the estimation of the average % of drug released via diffusion ($\overline{F}$) until 60%.

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$$\overline{F} = \frac{\sum_{t=0}^{t_{60\%}} \frac{1}{1 + \left(\frac{k_2}{k_1}\right) t^{0.45}}}{t_{60\%}}$$

equation 2

3. Results and discussion

Drug solubility in the release medium is one of the key parameters governing release from matrix tablets and can increase solubility in hydroethanolic media can promote faster release [7, 27]. All drugs investigated here were more soluble in 40% ethanol than in aqueous medium, although the magnitude of this increase, referred as solubility ratio, differed markedly among compounds (Table 1).

Table 1. Solubility of drugs in 0.1 N HCl containing 0 or 40% (v/v) ethanol.

Drug	**Solubility (mg/mL)**		**Solubility ratio $S_{40\%}/S_{0\%}$**
	0% EtOH	**40% EtOH**	
Propranolol HCl	142.2	302.5	2.1
Paracetamol	7.6	156.0	20.4
Theophylline	7.2	17.8	2.5
Carbamazepine	0.2	3.8	20.0

Accordingly, the effect of ethanol on release from matrix tablets containing 50% Methocel® K4M differed among the model drugs. The release rates of freely soluble propranolol HCl and slightly soluble theophylline were different from each other, but for each drug they were essentially independent of ethanol content (Figs. 1A-B). Their relatively low solubility ratios (approximately 2) were apparently insufficient to induce pronounced ethanol-related changes. In contrast, release of both paracetamol and carbamazepine was accelerated in 40% ethanol (Figs. 1C-D), consistent with their substantially higher solubility ratios (approximately 20). Therefore, subsequent experiments focused on these two drugs.

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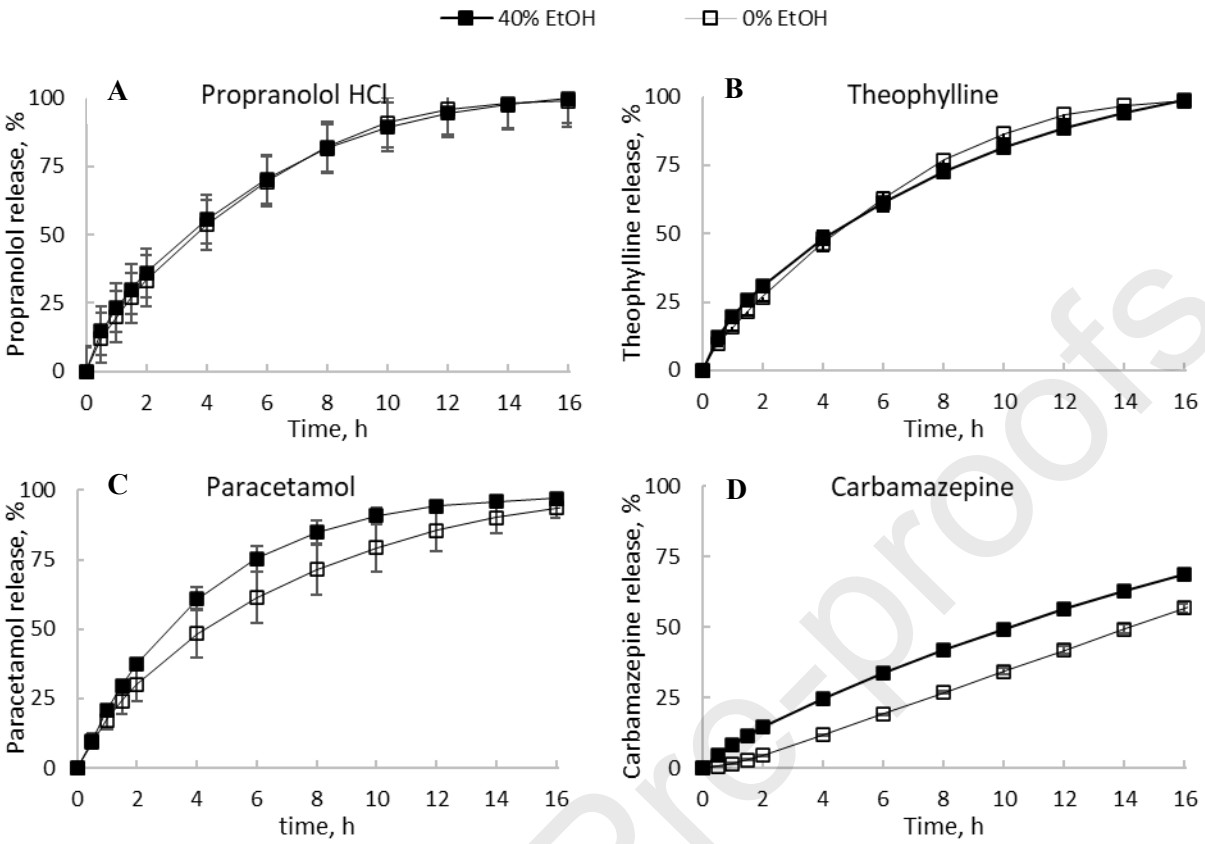

Fig. 1 Release of A) Propranolol HCl, B) Theophylline, C) Paracetamol and D) Carbamazepine from Methocel® K4M tablets in 0 or 40% ethanol.

Release acceleration for paracetamol was also observed from matrix tablets prepared with all investigated HPMC viscosity grades as well as with PEO WSR 303 (Fig. 2A-D). In contrast, the release profiles from HPC MXF matrices were considered similar (f2 = 54), and release in 40% ethanol was even slightly slower (Fig. 2E). Thus, HPC MXF appears to be a suitable polymer for paracetamol matrix tablets when minimizing ethanol-induced release changes is the primary objective.

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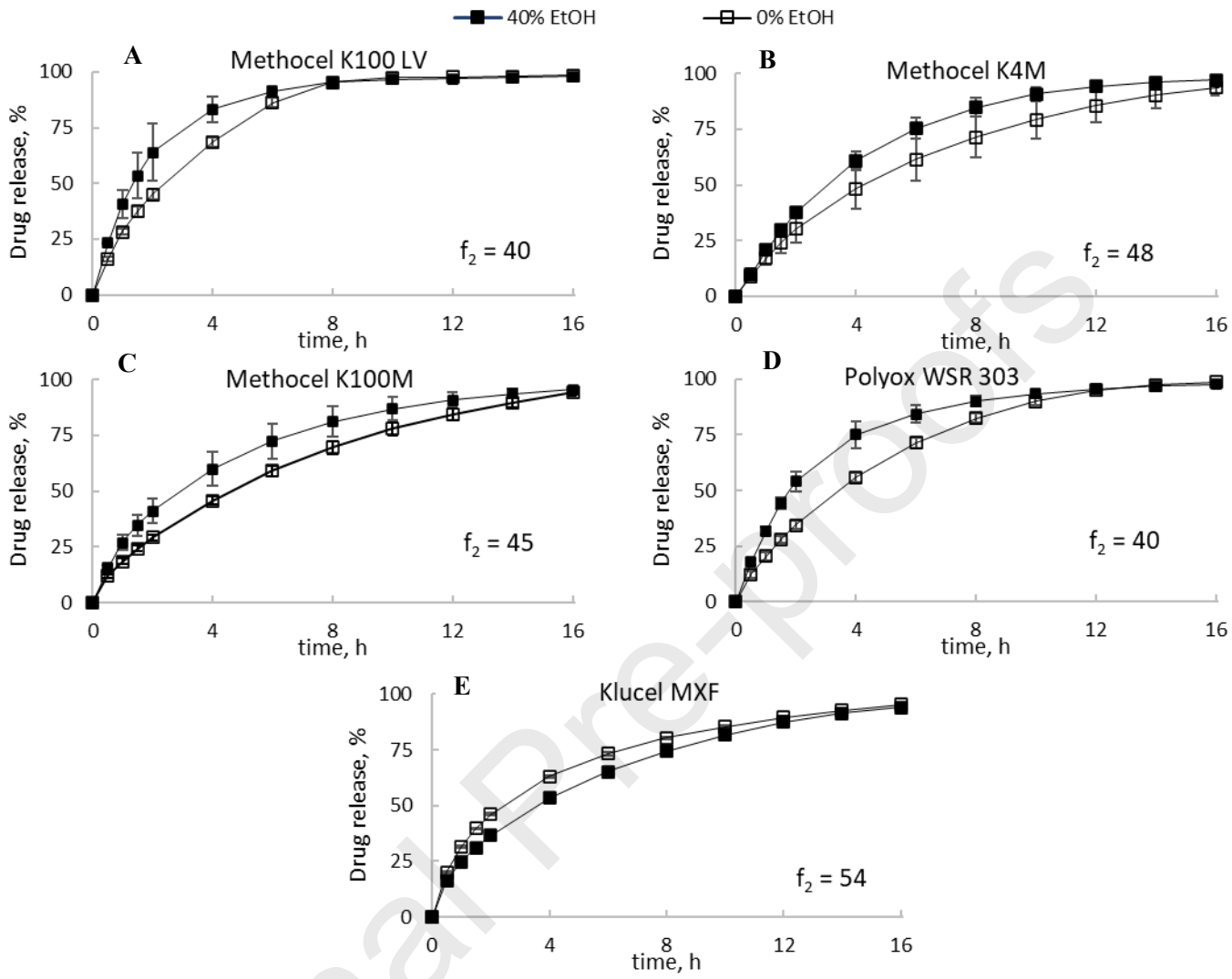

Fig. 2 Release of paracetamol from tablets with A) Methocel K100 LV, B) Methocel K4M, C) Methocel K100 M, D) Polyox WSR 303 and E) Klucel MXF in 0 or 40% ethanol.

Medium uptake is one part of the overall release mechanism and depends on both the release medium and the polymer used to prepare the matrix tablets. For the drug-free tablets, the rate of medium uptake was largely independent of ethanol concentration, but it increased in the order Klucel® MXF < Methocel® K4M < PEO WSR 303 (Fig. 3). This trend is consistent with the overall difference between the dissolution profiles in aqueous and hydroethanolic media, as reflected by the corresponding f2 values for the drug-containing tablets (Fig. 2). In other words, the influence of increased drug solubility in hydroethanolic medium became more pronounced in matrices that allowed higher medium uptake.

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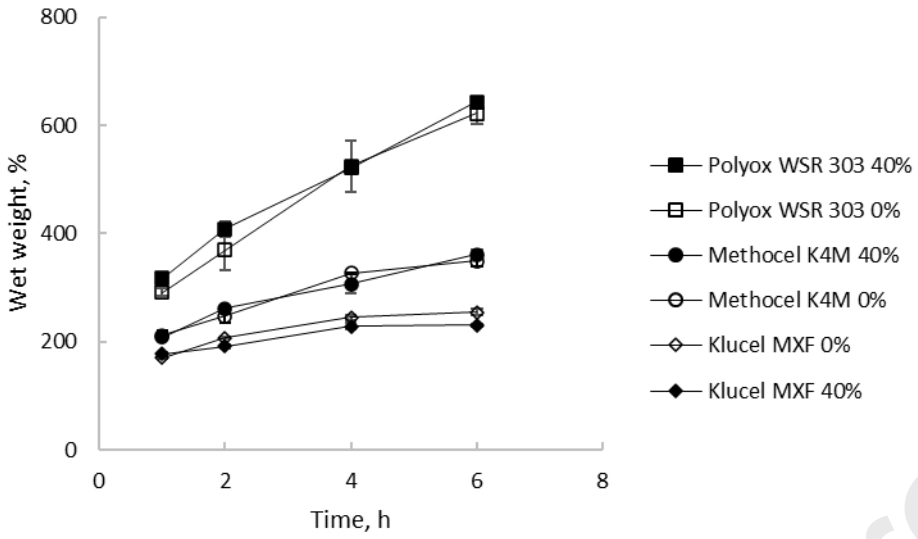

Fig. 3 Medium uptake of drug-free polymer tablets after immersion in 0 or 40% ethanol.

Polymer relaxation is another important step in drug release from hydrophilic erodible matrix tablets [31] and can be assessed by tablet swelling. Methocel® K4M tablets swelled less in hydroethanolic medium than in aqueous medium (Fig. 4), even though the medium uptake over the time of investigation was similar (Fig. 3). This combination suggests altered polymer relaxation and gel development in the presence of ethanol, indirectly indicating a denser gel structure. Consistent with this interpretation, diffusion of paracetamol through drug-free Methocel® K4M tablets was slower in 40% ethanol (data not shown), and increased gel strength in hydroethanolic media has been reported previously [14]. Thus, the data support a cautious mechanistic interpretation in which slower polymer relaxation, together with the increased solubility of paracetamol, contributes to the observed release acceleration.

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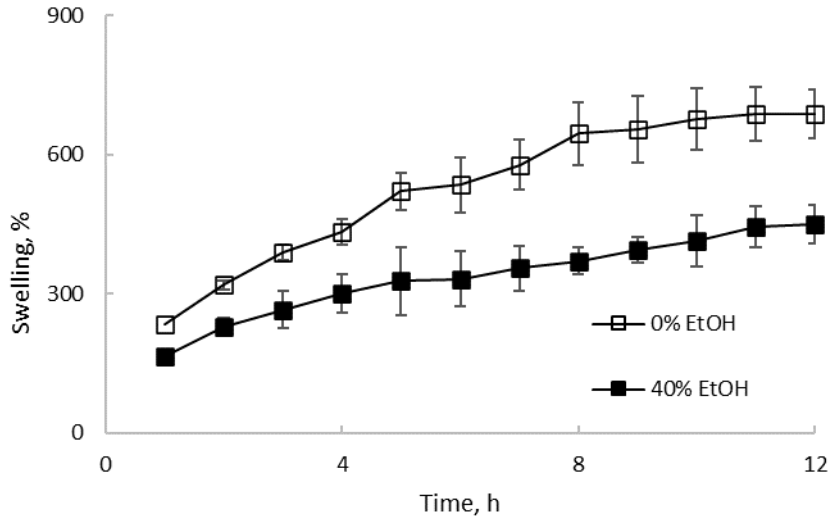

Fig. 4 Swelling of Methocel® K4M tablets.

Drug release from matrix tablets can be modified by the addition of fillers. Soluble fillers such as lactose can increase diffusion by reducing tortuosity and increasing porosity of the polymer network. The solubility of lactose decreased from 209.3 to 84.2 and 41.2 mg/ml as the ethanol content increased from 0 to 20 and 40%, respectively. Thus, the reduced lactose solubility in hydroethanolic media can partly compensate for the increased drug solubility. In fact, the release of paracetamol from PEO WSR 303 and Methocel K4M matrix tablets containing lactose was similar in 0, 20, and 40% ethanol (Fig. 5). However, nonspecific effects associated with dilution of either the drug or the matrix former by filler addition also had to be considered.

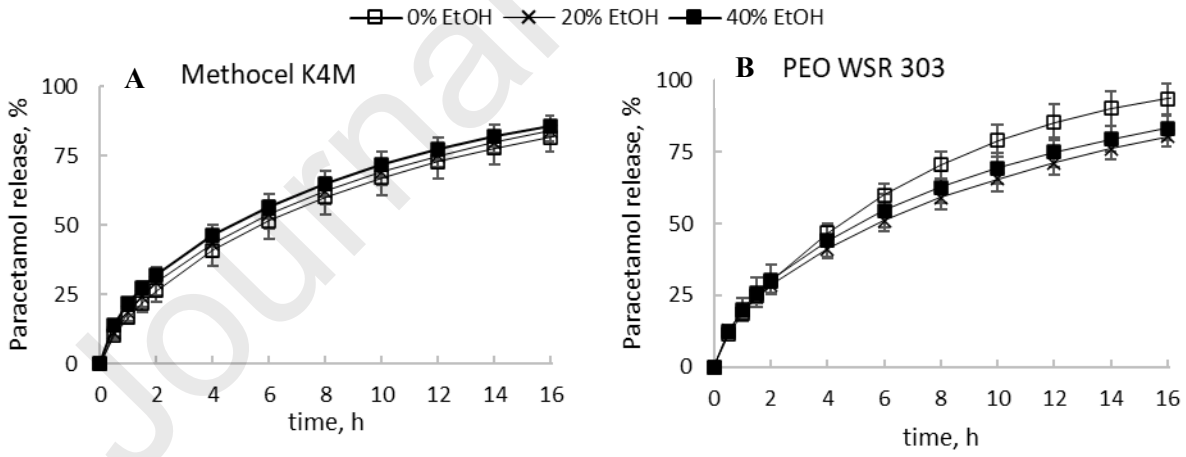

Fig. 3 Release of paracetamol from tablets with lactose and 35% A) Methocel K4M and B) PEO WSR 303 0, 20 or 40% ethanol. f_2-factor presented for media with 0 vs. 40% ethanol.

For comparison, Methocel® K4M matrix tablets were also prepared in which part of the original drug load was replaced by either water-insoluble MCC or water-soluble lactose. In both cases, filler addition reduced the amount of matrix former and therefore increased release (Fig. 6). Insoluble fillers such as MCC can disturb polymer entanglement during swelling [32] and accelerate matrix erosion [7], thereby also accelerating drug release in non-ethanolic media (Fig. 6B). Consequently, for Methocel® K4M tablets the release profiles in 0 and 40% ethanol

became much closer after addition of either lactose or MCC (Fig. 6), although the underlying reasons differ for the two fillers.

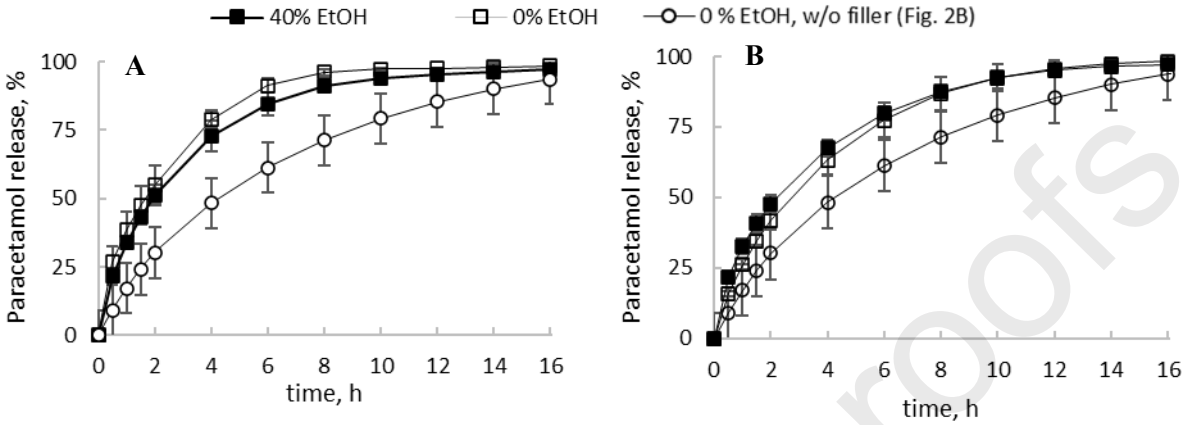

Fig. 4 Release of paracetamol from tablets with A) lactose and B) MCC and 24.5% Methocel® K4M in 0 or 40% ethanol.

For hydrophilic erodible matrices, the relative contributions of diffusion and erosion depend strongly on the HPMC viscosity grade [33, 34]. In the present study, tablets prepared with 50% of the lower-molecular-weight Methocel® K100LV released carbamazepine completely within 10 h and, importantly, almost independently of ethanol content (Fig. 7A). Similar behavior was also observed for other drug:polymer ratios (e.g., 30:70 and 70:30; data not shown). This finding is consistent with a comparatively strong erosion contribution, which limits the impact of the ethanol-induced increase in carbamazepine solubility.

In contrast, release of very slightly soluble carbamazepine from erodible matrix tablets containing Methocel® K4M or K100M, PEO WSR 303, or Klucel® MXF was accelerated in hydroethanolic medium (Fig. 7B-D), consistent with the high solubility ratio of carbamazepine (Table 1).

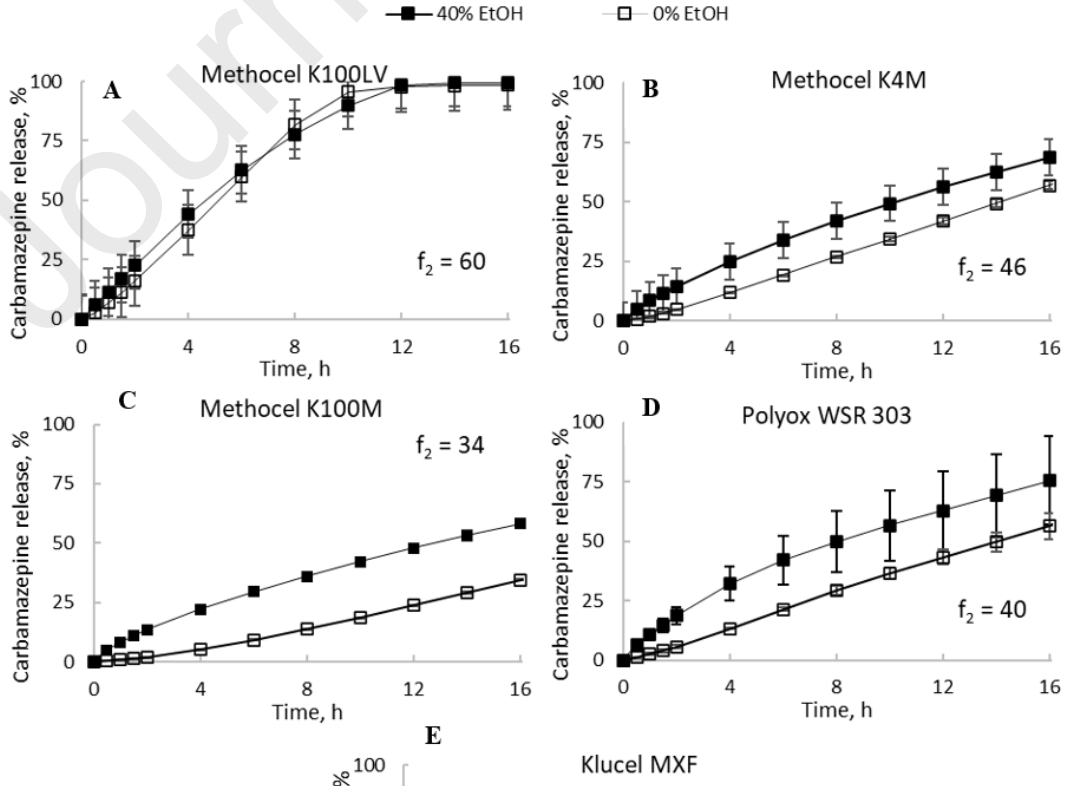

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Fig. 5 Carbamazepine release from tablets containing A) Methocel K100 LV, B) Methocel K4M, Methocel K100M, D) Polyox WSR 303 and Klucel MXF in 0 or 40% ethanol.

A mathematical treatment of the release data according to Equation 1 demonstrated that the release mechanism of paracetamol did not change markedly, as indicated by the nearly unchanged fraction released via diffusion in aqueous and hydroethanolic media (Table 2). In contrast, carbamazepine showed a clear shift: in aqueous medium the release was more erosion dominated, whereas in hydroethanolic medium the diffusional contribution increased substantially (Table 2). This difference is attributable to the markedly increased solubility of carbamazepine in 40% ethanol. The diffusional fraction in 40% ethanol also increased with increasing HPMC viscosity grade and the associated decrease in erosion. Consequently, ethanol-related release acceleration for carbamazepine appears least likely for low-viscosity matrices with sufficiently pronounced erosion, while Methocel® K100LV represents a notable exception within the overall comparison.

Table 2. Effect of ethanol concentration on f2 value and Peppas–Sahlin model parameters for paracetamol and carbamazepine release (data fitted up to 60% release).

Paracetamol

Polymer	f2 (0 vs 40%)	k1	k2	R^2	% diffusion
K100LV	40.4	0%: 3.27 40%: 6.24	0%: 0.21 40%: 0.07	0%: 0.99 40%: 0.97	0%: 62 40%: 91
K4M	47.7	0%: 2.18 40%: 3.24	0%: 0.11 40%: 0.12	0%: 0.99 40%: 0.98	0%: 59 40%: 70
K100M	45.3	0%: 2.87 40%: 4.51	0%: 0.08 40%: 0.03	0%: 0.99 40%: 0.99	0%: 72 40%: 92

WSR 303	39.9	0%: 2.52 40%: 5.59	0%: 0.17 40%: 0.03	0%: 0.99 40%: 0.97	0%: 57 40%: 94
MXF	54	0%: 4.87 40%: 3.75	0%: 0.01 40%: 0.05	0%: 0.98 40%: 0.99	0%: 97 40%: 85

Carbamazepine

Polymer	**f2 (0 vs 40%)**	**k1**	**k2**	**R^2**	**% diffusion**
K100LV	60.3	0%: 0.01 40%: 0.01	0%: 0.27 40%: 0.31	0%: 0.97 40%: 1.00	0%: 5 40%: 7
K4M	45.8	0%: 0.01 40%: 0.64	0%: 0.11 40%: 0.12	0%: 0.98 40%: 1.00	0%: 2 40%: 31
K100M	33.7	0%: 0.04 40%: 0.92	0%: 0.07 40%: 0.08	0%: 0.96 40%: 1.00	0%: 5 40%: 45
WSR 303	39.5	0%: 0.05 40%: 1.15	0%: 0.11 40%: 0.12	0%: 0.99 40%: 1.00	0%: 5 40%: 46
MXF	36.8	0%: 0.01 40%: 0.89	0%: 0.09 40%: 0.09	0%: 0.98 40%: 1.00	0%: 2 40%: 43

Notes: R^2 refers to the fit of experimental data up to 60% drug release. % diffusion was calculated using Equation 2.

The change in release behaviour of carbamazepine from Methocel K4M tablets in hydroethanolic media was macroscopically visualized. Free particles detaching from the polymer were clearly seen in aqueous, but not in hydroethanolic media (Fig. 8). The particles moved outwards also in 40% ethanol, but, due to the higher solubility, gradually dissolved before reaching the tablet boundary.

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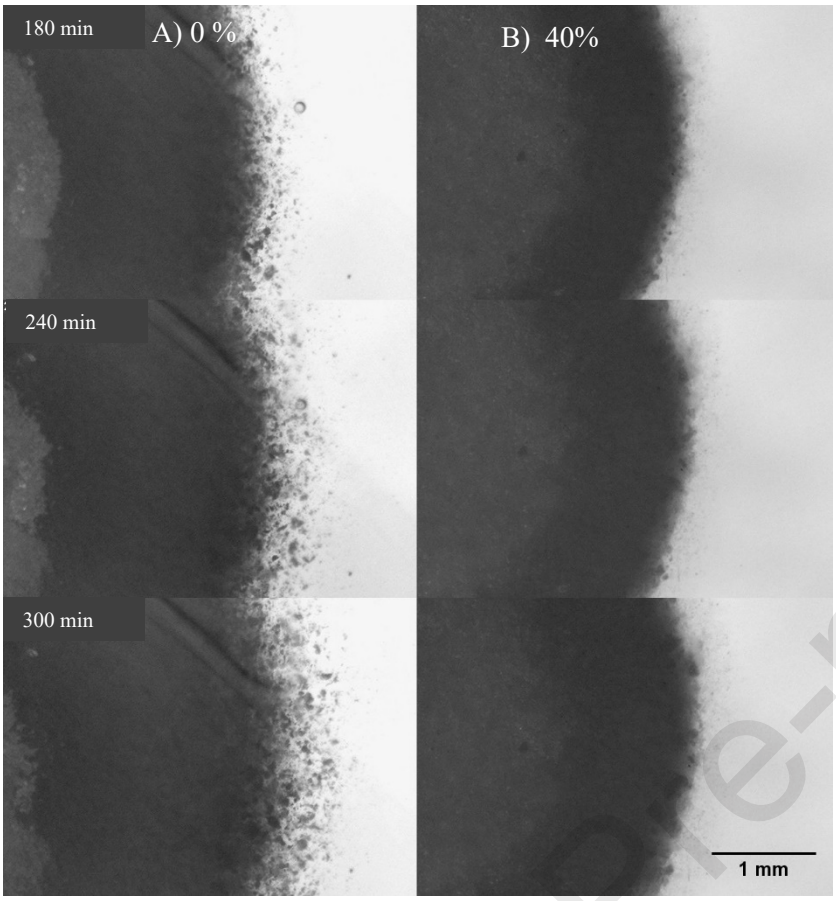

Fig. 8 Photograph of Methocel K4M tablet A) 0% and B) 40% ethanol upon release.

3.2 Insoluble polymers

For insoluble polymer matrices that remain intact in the release medium, drug release is expected to occur predominantly via diffusion. In contrast, tablets prepared with Eudragit® RS disintegrated in 40% ethanol; accordingly, their release was strongly accelerated (Fig. 9A) and this formulation was not considered further.

The behavior of insoluble ethylcellulose (EC) in hydroethanolic media has been studied widely for coating applications [14, 35], but much less for matrix tablets. Release of paracetamol from EC matrix tablets was accelerated in 40% ethanol (Fig. 9B). EC is soluble only in hydroethanolic mixtures above about 50% ethanol [36], but it can already swell in media with lower ethanol contents. Accordingly, the EC tablets remained intact but swelled more strongly in 40% ethanol than in aqueous medium (Fig. 10A), which can explain the enhanced diffusion [31]. A similar trend was observed for dry weight loss, considered as leaching of solid ingredients upon dissolution (Fig. 10B).

Kollidon® SR has previously been used successfully as a matrix former for opioid formulations with nearly unchanged release in hydroethanolic media [25], and this behaviour was also confirmed here for paracetamol (Fig. 9C). Kollidon® SR combines insoluble poly(vinyl acetate) with soluble poly(vinyl pyrrolidone) (PVP), both of

which interact differently with water and hydroethanolic media. Consequently, the viscosity of the liquid absorbed into the tablets is expected to differ between media; for example, a 5% PVP solution in 40% ethanol was approximately 2.5-fold more viscous than in aqueous medium (2.55 vs. 6.39 $\frac{mm}{s}$, respectively). Therefore, pore formation in the Kollidon® SR matrix, as indicated by medium uptake and dry weight loss/leaching, was more pronounced in 0% ethanol than in 40% ethanol (Fig. 10A-B). This trend counterbalanced the increased solubility of paracetamol in 40% ethanol and explains the nearly similar drug release profiles in both media (Fig. 9C).

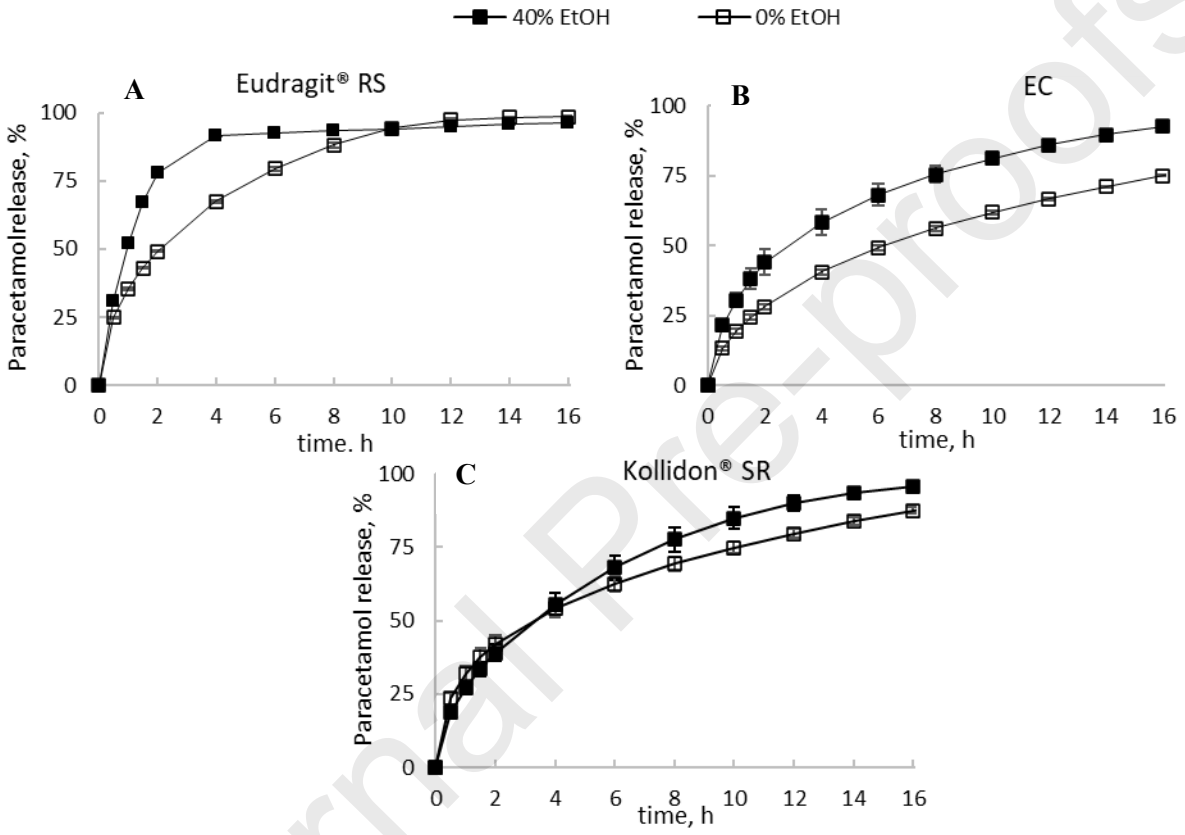

Fig. 9 Release of paracetamol from tablets with A) Eudragit® RS, B) EC and C) Kollidon® SR.

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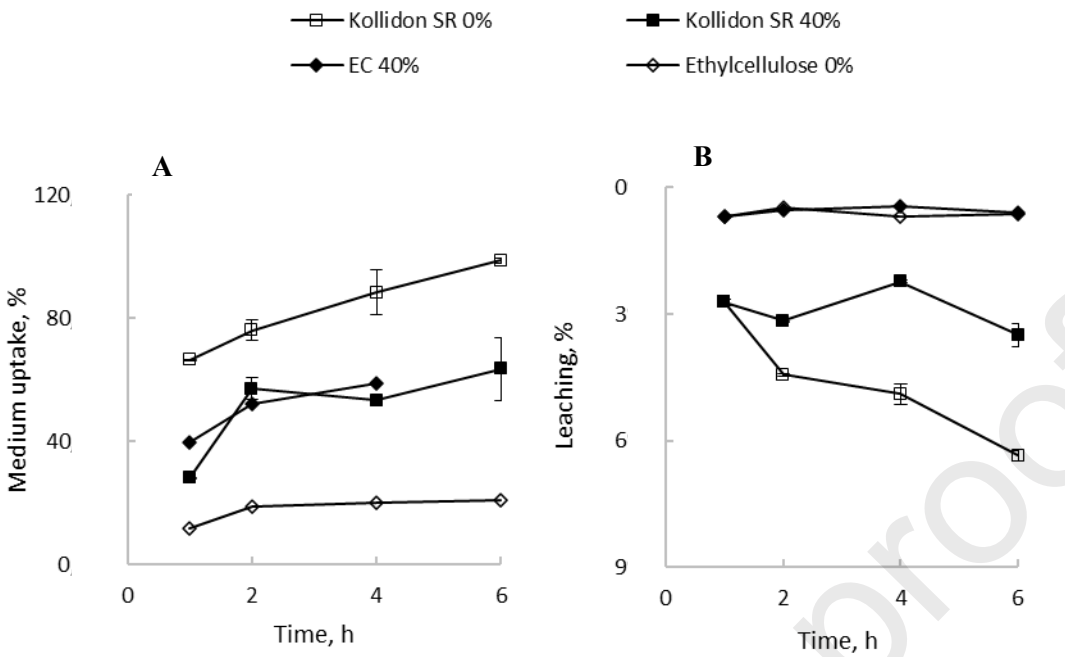

Fig. 10 A) Medium uptake and B) dry weight loss (leaching of soluble components) of EC and Kollidon® SR tablets after immersion in 0 or 40% ethanol.

A similar, or even slightly lower, release in hydroethanolic medium was also achieved for EC tablets after inclusion of lactose (Fig. 11). This behavior can be explained by two opposing nonlinear effects. First, the reduced solubility of lactose with increasing ethanol content lowers pore formation and thereby counteracts the increased solubility of paracetamol. Second, ethanol can increase medium permeation through EC, as reported previously for EC films [13]. At 40% ethanol these two effects were approximately balanced, leading to nearly identical release profiles, whereas at 20% ethanol the first effect seems to dominate and release was even slightly lower than in 0% ethanol (Fig. 11).

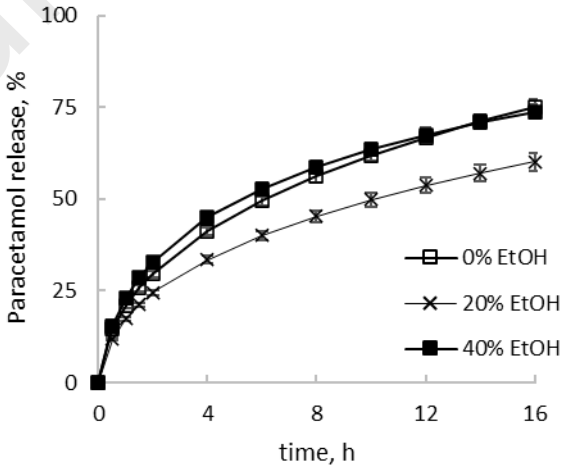

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Fig. 11 Release of paracetamol from tablets with lactose and 35% EC in 0, 20 or 40% ethanol.

Release of carbamazepine from both Kollidon® SR and EC tablets was strongly accelerated in 40% ethanol (Fig. 12). Because release from these intact insoluble matrices is diffusion driven, the pronounced increase in carbamazepine solubility in hydroethanolic media directly accelerates transport through the matrix. Kollidon® SR nevertheless showed somewhat closer - although still not similar - release profiles, despite the lower dry weight loss/leaching of PVP in 40% ethanol (Fig. 10B).

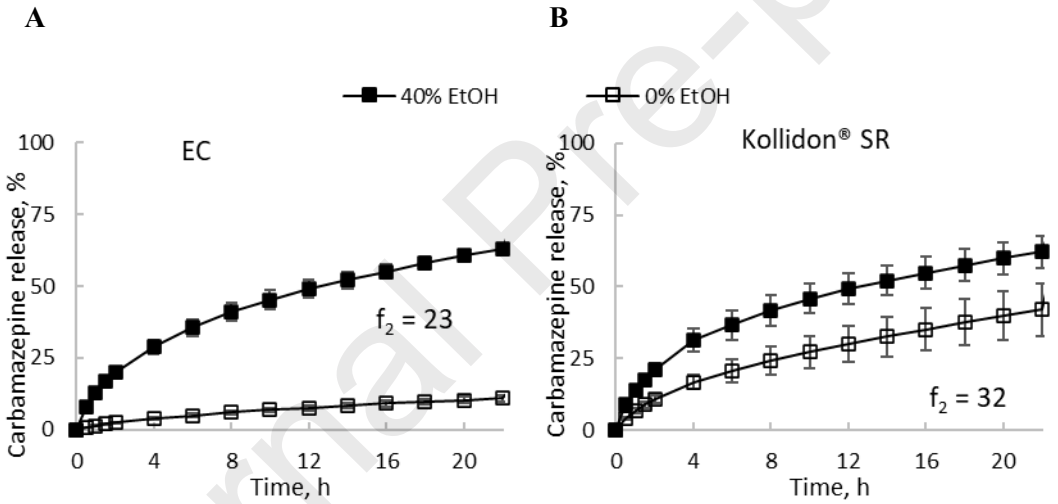

Fig. 12 Release of carbamazepine from tablets prepared with A) EC or B) Kollidon® SR in 0% or 40% ethanol.

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As described above for paracetamol, lactose addition was not sufficient to obtain similar carbamazepine release profiles from either Kollidon® SR or EC tablets (Fig. 13). Lactose increased the overall carbamazepine release rate, but it did not improve profile similarity between 0 and 40% ethanol. In both media, lactose is more soluble than carbamazepine and is, therefore, expected to dissolve more rapidly, whereas for paracetamol the relationship between lactose and drug solubility is different, especially in 40% ethanol. Thus, the compensatory effect of lactose appears to be limited to drugs with comparatively high aqueous solubility.

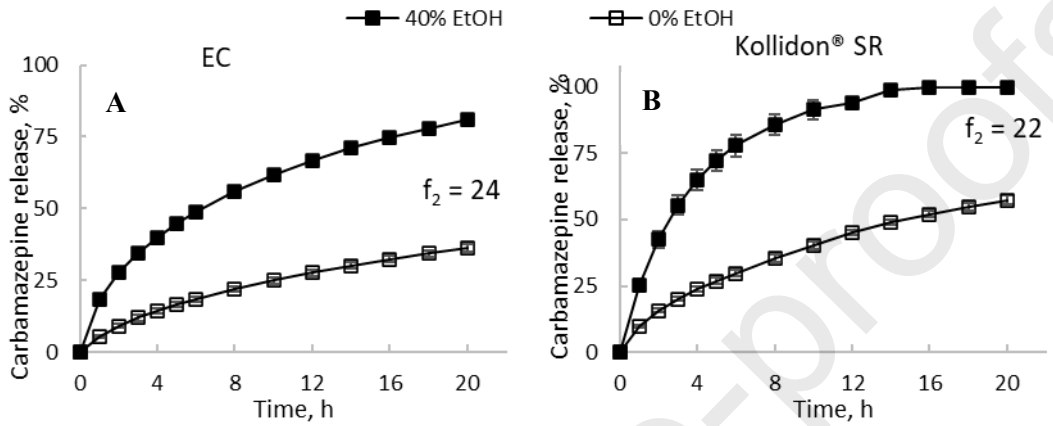

Fig. 13 Release of carbamazepine from tablets with lactose and 35% insoluble matrix polymers A) EC and B) Kollidon® SR in 0 or 40% ethanol.

4. Conclusion

For drugs with a low solubility ratio between hydroethanolic and aqueous media, pronounced release acceleration in hydroethanolic media is not expected for water-soluble matrix tablets. For paracetamol, similar release profiles across media were achieved either by using matrix formers with comparatively low medium uptake (e.g., Klucel® MXF or Kollidon® SR) or by incorporating lactose as a soluble filler. For carbamazepine, the markedly higher solubility in hydroethanolic media shifted release toward a stronger diffusional contribution; similar profiles were therefore only obtained with hydrophilic polymers showing relatively high erosion rates. Overall, the data indicate that ethanol resistance of matrix tablets depends on the interplay between drug solubility changes, polymer-controlled medium uptake/erosion, and filler properties rather than on a single formulation variable.

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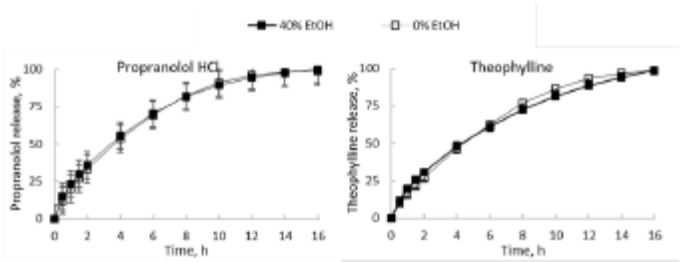
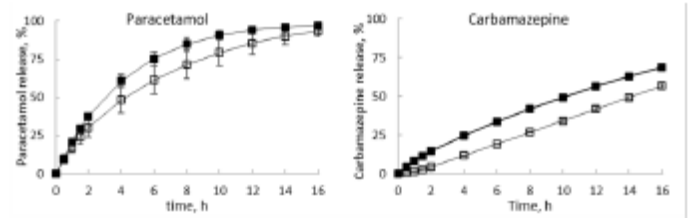
Methocel® K4M – different drugs

No ethanol induced release acceleration when Solubility ratio $S_{40\%}/S_{0\%} = 2$

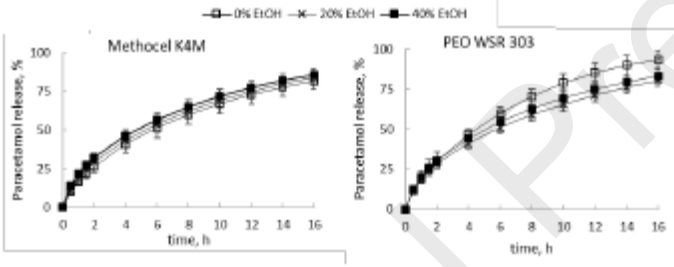


Ethanol induced release acceleration when Solubility ratio $S_{40\%}/S_{0\%} = 20$



Paracetamol – different matrix

no ethanol induced release acceleration with lactose as a poreformer



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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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