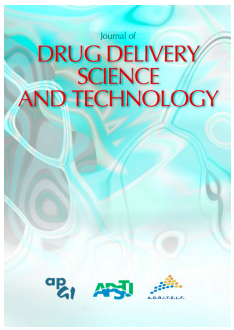

An approach for pH-independent release of poorly soluble ionizable drugs using hot melt extrusion

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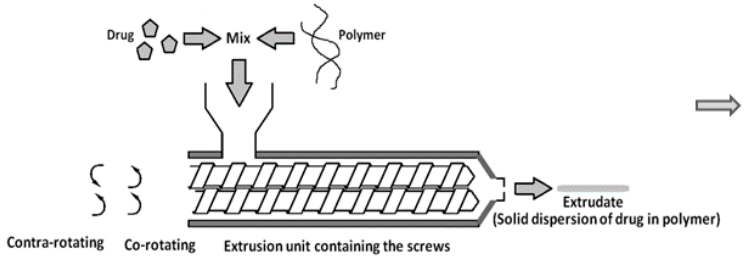
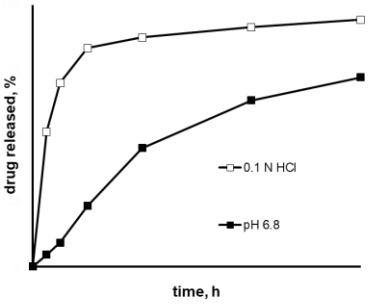
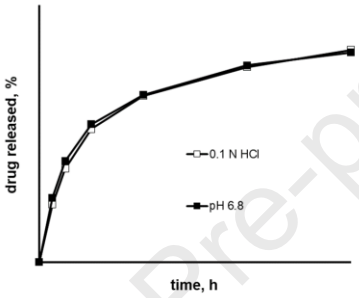


Itraconazole + Soluplus®

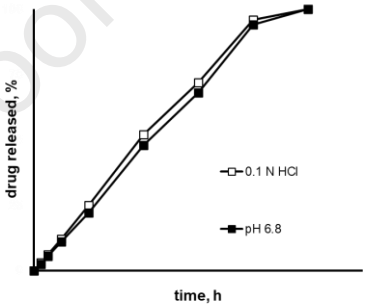


Itraconazole + Soluplus® Aqoat®AS-LF

Fast disintegrating tablet

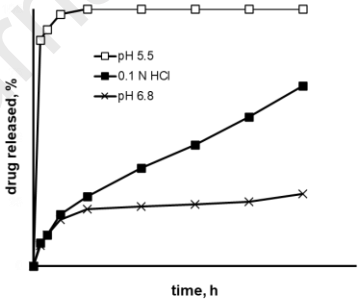


Erodable matrix tablet



Mefenamic acid+ Eudragit®E PO

Fast disintegrating tablet



Research article

An approach for pH-independent release of poorly soluble ionizable drugs using hot melt extrusion

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An approach for pH-independent release of poorly soluble ionizable drugs using hot melt extrusion

Abstract: Hot melt extrudates with combinations of Soluplus® and Aqoat® AS-L or Eudragit® EPO were investigated to improve drug release and to overcome the pH-dependent release of poorly water-soluble basic (itraconazole, ITZ) and acidic (mefenamic acid, MFA) drugs. The release of ITZ was improved in both 0.1 N HCl and PBS pH 6.8 by hot-melt extrusion with combinations of Soluplus®:Aqoat® AS-L and can be adjusted by varying the ratio of the polymers. At the ratio Soluplus®:Aqoat® AS®LF 75:25 an almost pH-independent release was achieved without any drop in the drug concentration within 24 h. A pH-independent and extended release (over 24 h) was obtained from milled extrudates when formulated in erodible matrix tablets using 15% Methocel® K15M as the carrier. The release of MFA from extrudates with Soluplus® was immediate only in PBS pH 6.8. From extrudates with cationic Eudragit® EPO the release of MFA was slow at 0.1 N HCl and PBS pH 6.8, due to poor drug solubility and insoluble Eudragit® EPO, respectively. However, in the medium with an intermediate pH of 5.5, both MFA and Eudragit® EPO are highly ionized, and the release was fast, complete, and stable within 24 h. These release behaviors could be to some degree applicable for immediate or enteric, but not for extended-release formulations.

Keywords: solid solution, hot-melt extrusion, Soluplus®, itraconazole, mefenamic acid, Aqoat® AS-L, Eudragit® EPO, pH-independent release.

1. Introduction

One important task in formulation science is to improve the oral bioavailability of poorly soluble drugs. Polymer-based solid solutions prepared by hot melt extrusion or spray drying are among the main formulation approaches [1-3]. These preparation methods aim to keep the drug in a dissolved state embedded in a polymeric matrix [1]. The solubility properties of the polymeric carriers determine the mechanism of drug release from these solid solutions [4-6]. Polymers affect the intermolecular interactions with the drug and can influence the degree of drug supersaturation and precipitation kinetics in the release media, as well as the transport of the drug through the mucus layer and intestinal membrane [7, 8].

Poorly soluble drugs can be classified as non-ionizable and ionizable (weak bases and weak acids) drugs [1, 9]. The solubility of ionizable drugs depends on the degree of ionization and, thus, is influenced by physiologic conditions and/or food intake, which affect the pH in the gastrointestinal tract [10, 11]. In addition, the release rate depends on gastrointestinal transit time [11, 12]. In general, weak bases are better soluble in an acidic (gastric fluids) environment, but can precipitate at higher pH (intestinal fluids) because of a decrease in solubility, which also negatively affects bioavailability [13]. Opposite pH-solubility considerations apply to weak acids [14].

Early attempts to improve the solubility of weak acidic drugs were associated with the use of pH-modifier. For example, orthophosphate/citric acid buffer was incorporated in an amorphous or semicrystalline furosemide-povidone solid dispersion. In this case, the dissolution rate of a weakly acidic drug was increased in acidic media and retarded in alkaline media [15-17]. Citric acid was used as a pH-modifier in an amorphous solid dispersion (ASD) of a weakly basic drug in polyvinyl pyrrolidone (PVP) in order to improve release and oral bioavailability [18]. A combination of PVP or PAA (polyacrylic acid) and cellulosic polymer was used in the formulation of celecoxib as ASD (prepared via solvent evaporation method). In this case, PVP or PAA was used to stabilize solid state due to the strong drug-polymer interaction and to control drug release, while HPMCAS or HPMC inhibited crystallization upon dissolution [19, 20]. Another combination of Eudragit® E PO and HPMC was used in ASD of indomethacin prepared via solvent evaporation method. The advantage of this combination vs. single polymers was a rapid supersaturation in acidic medium followed by the formation of new nanosized droplets which re-dissolved immediately when the pH was increased [21].

Hot melt extrusion is one of the most popular methods for the preparation of solid dispersions, often using polymer combinations. E.g. hot-melt coextrusion of ITZ with a Carbopol® 974P to the EUDRAGIT® L 100-55 polymer combination allowed for extended-release of supersaturated levels of ITZ following an acidic-to-neutral dissolution media pH transition [22]. A combination of EUDRAGIT® L 100-55 and hydroxypropyl cellulose (HPC) for ASD prepared by hot-melt extrusion improved the solubility of celecoxib compared with single polymers [23]. A synergistic effect to maintain the supersaturation level and enhance dissolution performance of nifedipine was demonstrated using combinations of HPMCAS(LG)-HPMCAS(HG) or HPMCAS(LG)-Eudragit®FS100 [24]. A rapid dissolution of efavirenz associated with its stable solid state was achieved with a combination of Soluplus® and enteric HPMCAS-HF in ASD prepared by hot-melt extrusion [25].

Extended drug release is often achieved using non-cross-linked, water-swellable polymers, e.g. hydroxypropyl methylcellulose (HPMC), that swell rapidly and form a continuous 'gel layer' over the dry core, which controls drug release [26]. The addition of basic or acidic ingredients is helpful for ionizable drugs (pH-dependent soluble) to control microenvironmental pH and, thus, to achieve pH-independent solubility along with the variable gastrointestinal pH media [27, 28].

Weakly basic ITZ (pKa 3.7) is a popular model poorly soluble drug in solid solutions [29, 30]. Recently published attempts to improve the solubility of ITZ used the hot-melt extrusion with different polymers e.g. ITZ (40 %) with HPMC, Eudragit® E100 or a mixture of Eudragit® E100 with Kollidon® VA64 [31]; ITZ (33 %) with Aqoat® AS-MG (HPMCAS) or Eudragit® L100-55 [32, 33]; ITZ (20 %) with Aqoat® AS-MMP (HPMCAS) [34]; ITZ (20 %) with Aqoat® AS-MG and surfactants [35, 36]; ITZ (25 %) with Kollidon VA64, Kollidon® 17P, Affinisol® HPMC, and Soluplus® [37, 38]; ITZ (33-50 %) with Kollicoat® Smartseal [39].

Weakly acidic (pKa 4.2) mefenamic acid (MFA) is another model poorly soluble drug [40]. Also with MFA, attempts to improve the solubility of MFA were done using hot-melt extrusion with polymers e.g. MFA (24-40 %) with Eudragit® E PO [41-43]; MFA (10-50 %) with Soluplus® and sorbitol [44-46] MFA (20-40 %) with AquaSolve™ (HPMCAS HG) and Kolliphor® P407 (poloxamer) [47].

Only a few studies have been published to prolong drug supersaturation following an acidic (gastric)-to-neutral (intestinal) pH change [22, 48]. In these studies, the supersaturation levels were not maintained long enough after pH change, and the drug tended to precipitate.

To achieve pH-independent release of a poorly soluble weak base (ITZ) or weak acid (MFA), the formulation with non-ionizable and ionizable carrier polymers can be useful. The neutral, amphiphilic PEG 6000-vinylcaprolactam-vinyl acetate graft copolymer (Soluplus®) has a Tg ~74 °C and was a suitable polymer for improving not only kinetic but also the thermodynamic solubility of poorly soluble drugs [49-51]. The enteric polymer Hydroxypropyl Methylcellulose Acetate Succinate HPMCAS (Aqoat® AS-L) with solubility at pH > 5 and relatively high Tg (120-135 °C) which gives excellent physical stability of its solid dispersions. Aqoat® AS-L can aggregate with drugs such as posaconazole or celecoxib and maintain their supersaturation [52, 53]. A cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate with a ratio of 2:1:1 (Eudragit® EPO) is soluble at pH <5 and having Tg ~45 °C has been also used frequently to maintain the supersaturation of MFA upon release from ASD, e.g. prepared by a cryogenic grinding method [41].

For the investigation of thermal properties of materials such as melting, and recrystallization, Differential scanning calorimetry (DSC) is a valuable technique. Furthermore, it is effective in determining the glass transition temperature of amorphous materials and the miscibility between solid dispersion components [49, 54]. Also, PXRD can be used to confirm the amorphous/crystalline nature of a sample. During X-ray measurement, the sample is exposed to x-rays at various angles; the diffraction patterns produced are then compared with reference standards for identification.

Crystal samples exhibit strong x-ray scattering and generate sharp characteristic peaks at specific collection angles in a diffractogram. While amorphous solids yield diffuse halo patterns due to their lack of long-range order symmetries [54].

Infra-red spectroscopy is well-established technique for compound identification and has been extensively used in the study of intermolecular interactions between solid dispersion components, including hydrogen bonding [55]. During the measurement, the sample is irradiated with a broad spectrum of infrared light. The absorption range for FTIR is between 400 and 4000 cm^{-1}. The region from 400-1000 cm^{-1} is the fingerprint region of the spectrum while the region between 1000 and 4000 cm^{-1} is related to specific functional groups [56]. For example, carbon oxygen double bound absorbs at wavelength around 1800-1600 cm^{-1} whereas, the absorption bands of hydroxyl groups are situated between 3650-3200 cm^{-1}. The measurements made by infra-red spectroscopy are very accurate and reproducible.

The aim of this study was to investigate approaches to achieve pH-independent release of poorly soluble ITZ or MFA from hot melt extrudates with the carrier polymers Soluplus®, Aqoat® AS-L or Eudragit® EPO.

2. Materials and Methods

2.1 Materials

The materials were used as received: ITZ (BASF SE, Ludwigshafen, Germany), MFA (Sigma Aldrich, Chemie GmbH, Steinheim, Germany), PEG 6000-vinylcaprolactam-vinyl acetate graft copolymer (Soluplus®; BASF AG, Ludwigshafen, Germany), hydroxypropyl methylcellulose acetate succinate (HPMCAS, Shin-Etsu Aqoat® AS-LF; ShinEtsu Chemical Co.,Ltd), aminoalkyl methacrylate copolymer E (Eudragit® E PO; Evonik Industries AG, Darmstadt, Germany), hydroxypropyl methylcellulose (HPMC, Methocel® K15M, Colorcon Ltd., Dartford Kent, UK), co-processed lactose monohydrate, povidone K30 and crospovidone (Ludipress®; BASF SE, Ludwigshafen, Germany), microcrystalline cellulose (Avicel® PH 102; FMC BioPolymer, Newark, USA), croscarmellose sodium (AC-Di-Sol®; FMC BioPolymers, Philadelphia, PA, USA), talc (Luzenac® pharma; Luzenac Europe, Toulouse, France).

2.2 Preparation of hot melt extrudates

Hot melt extrudates were prepared with drug:carrier ratio 1:3. The ingredients were mixed manually using a mortar and pestle for 5 min. Hot melt extrusion (HME) was performed in a twin-screw hot-melt extruder (Minilab HAAKE Rheomex CTW5, Thermo Scientific, Karlsruhe, Germany). Powder blends (approx. 10 g) were fed using a force feeder into the preheated barrel at 170 °C (above Tg of all used polymers) and screw speed 15 rpm. The first 3 g of extrudates from each batch were discarded and rest cut, having a uniform dimension (Ø 1.5 mm and length 5 mm), collected in dark glass vials, and stored in a desiccator at room temperature.

Milling of HME extrudates was performed in a cryo ball mill (Retsch MM 2000 small ball mill, Retsch GmbH, Haan, Germany) using liquid nitrogen. 2-3 g extrudates were filled into 10 ml metal jars filled with 2 metal balls (10 mm in diameter) and milled at 70-90 stokes/sec for 15-60 sec. Milled extrudates were then sieved in a vibratory sieve shaker (Analysette 3 PRO, Fritsch GmbH, Idar-Oberstein, Germany) using sieves 315 and 160 µm at an amplitude of 0.8 mm for 2 min to obtain the proper sieve fraction for further processing.

2.3 Differential scanning calorimetry (DSC)

Thermal properties of the samples were studied using differential scanning calorimetry (DSC) (DSC-822e Mettler-Toledo, Switzerland). Drug, drug:polymer physical mixture or drug:polymer8S9 milled extrudates were weighed accurately in a 40 µl aluminum pans and

sealed. The pans were subjected to heat under a nitrogen atmosphere and 10 ˚C/ min scanning rate. The melting point (Tm) was determined by the Stare® software.

2.4 Powder x-ray diffraction (PXRD)

Drug, drug:polymer physical mixture or drug:polymer(s) milled extrudates were tested using Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, λ = 0.15418 nm, 40 kV, 20 mA) fixed with a Philips PW 1710 diffractometer (Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). The scattered radiation of the samples was detected with a vertical goniometer (Philips PW 1820, Philips Industrial & Electro-acoustic Systems Division, Almelo, The Netherlands). A scanning rate of 0.02 2θ per sec over the range of 4-40 2θ at ambient temperature was used to determine each spectrum.

2.5 Fourier transform infra-red (FTIR) spectroscopy

FTIR spectroscopy measurements were performed with an Excalibur 3100 FTIR spectrophotometer (Varian Inc., Palo Alto, USA). The spectra from drug, drug:polymer(s) physical mixture, or drug:polymer(s) milled extrudates were obtained in the scan range of 600 to 4,000 cm^{-1} at a resolution of 4 cm^{-1} and an average of 16 scans, using a horizontal ATR accessory with a single reflection diamond crystal (Pike Miracle, Pike Technologies, Madison, USA) and Varian software (Resolution Pro® 4.0).

2.6 Aqueous solubility

100 mg of drug powder (x100 solubility excess) was suspended in 100 ml of 0.1 N HCl or PBS pH 6.8 and shaken in vials at 75 rpm using an incubator shaker at 37 ℃ for 24 h or until equilibrium was achieved. At specified times, samples were kept without shaking until complete precipitation and clear supernatant was additionally filtered using a 10 µm filter followed by 10 times dilution with methanol to avoid crystallization. The amount of dissolved drug was determined UV-spectrophotometrically at 258 or 289 nm for ITZ or MFA, respectively, using the calibration curves in methanol.

2.7 Preparation of immediate or extended release tablets

Tablets containing extrudates corresponding 100 mg ITZ or MFA, 108 mg of Ludipress® solely or respective mixture with 15 % Methocel® K15M and 2 mg magnesium stearate were prepared by first mixing of the materials in a mortar using a plastic card for 5 min

followed by tableting using instrumented tablet press EK0 (Korsch AG, Berlin, Germany) equipped with single round punches 8 mm at a compression force 5-15 kN. Weight of the tablets was 210 ± 10 mg and hardness 70 ± 10 N.

2.8 Drug release

The drug release was investigated under non-sink conditions (100 mg drug) using the USP rotating paddle method (VK 7010, Vankel Technology Group, Cary, USA) either in 900 ml 0.1 N HCl, PBS pH 6.8, pH 5.5, or, for a pH-change, in 750 ml 0.1 N HCl for 2 h followed by pH adjustment to pH 6.8 by adding 250 ml 0.2 M tribasic sodium phosphate at 37 °C, 100 rpm. At predetermined time points, samples were taken, filtered through 10 µm filters, and diluted with methanol to avoid crystallization. The amount of dissolved drug was determined UV-spectrophotometrically at 258 or 289 nm for ITZ or MFA, respectively, using the calibration curves in methanol. The amount of dissolved drug was measured UV-spectrophotometrically at 258 or 289 nm for ITZ or MFA, respectively. Drug release of each investigated sample was performed in triplicate and the mean values with standard deviation (error bars) were plotted.

3. Results and Discussion

The poorly water-soluble model drugs ITZ and MFA have a pH-dependent solubility, and they are practically insoluble even at a pH of higher solubility. Therefore, pH-independent solubilization is required for their immediate and extended-release formulations.

The solubility of ITZ was 9 µg/ml in 0.1 N HCl and approx. 1 ng/ml in PBS pH 6.8 [49]. The drug dissolution under the non-sink conditions (corresponding to 100 mg of drug in 900 ml medium) even in favorable media 0.1 N HCl was limited by the respective solubility and reached only approx. 10 % within 24 h (Fig. 1A).

The drug dissolution can be significantly improved by forming hot melt extrudates with Soluplus® while the drug: carrier ratio 1:3 was optimal in term of processability and performance [49]. Thus, complete release was achieved within 30 min, and the supersaturation was maintained for at least 24 h with the milled hot melt extrudates (Fig. 1B). The inhibition of recrystallization from a supersaturated solution of appropriate polymers was described by three mechanisms [57]. Firstly, crystal growth is prevented due to the adsorption of polymers on the undissolved drug crystals by specific interactions, thus, leading to reduced diffusion and entering of drug molecules to the correct position on the crystal surface. Secondly, by increasing the solubility of the drug through solubilization through polymers and nominally reducing the degree of supersaturation. The solubilization capacity of Soluplus® was demonstrated previously [49]. The third mechanism, associated with increased viscosity, was considered negligible due to the low polymer concentration in the release medium.

In comparison, the dissolution from the physical mixtures of ITZ an Soluplus® was similar to the dissolution of the pure drug; the drugs remained in their crystalline state in the physical mixture. Being fast and complete within 30 min in 0.1 N HCl (Fig. 1B), the release of ITZ from milled hot melt extrudates with Soluplus® levelled off by approximately 50% at PBS pH 6.8 (medium with lower drug solubility) (Fig. 2). Interestingly, no ITZ precipitation was observed after adjusting the pH of 0.1 N HCl to pH 6.8. After ITZ dissolved at low pH, its supersaturation in PBS pH 6.8 was maintained due to solubilization by Soluplus® (Fig. 2). The preparation of Soluplus® milled extrudates compressed into tablets is thus an appropriate approach for ITZ immediate release formulations.

Poorly soluble drugs, when formulated into extended-release oral dosage forms, might also require solubilization techniques. HPMC matrix tablets are popular for extended release dosage forms and, therefore, were used to prepare non-disintegrating erodible tablets with ITZ:Soluplus® milled extrudates. The release was extended only in the favorable acidic medium, but did not occur at unfavorable PBS pH 6.8 (Fig. 3). This is due to poor medium

256 accessibility in the case of non-erodible tablets, in addition to any limited release from milled
257 extrudates due to low solubility of ITZ at this pH (Fig. 2).

258 To achieve pH-independent modified release of a basic drug, a combination of retarding
259 neutral and acid polymers was a successful approach [58-60]. First, ITZ was hot melt extruded
260 with the enteric polymer Aqoat® AS-LF (HPMCAS) alone and formulated into immediate
261 release tablets. As expected, the ITZ release in 0.1 N HCl was very slow and incomplete after
262 24 h because the Aqoat® AS-LF is insoluble at this pH (Fig. 4). In contrast, the release was
263 rapid and complete in PBS pH 6.8 because of the dissociation and dissolution of the enteric
264 polymer. However, the supersaturation, reached after 1 h, could not be maintained, and gradual
265 precipitation of ITZ occurred detected by declined concentration curve of the time (Fig. 4). The
266 pH-dependent release with Aqoat® AS-LF extrudates was opposite to the release with
267 Soluplus® extrudates (rapid/slow release with Soluplus® in 0.1 N HCl/PBS pH 6.8,
268 respectively).

269 To overcome the pH-dependent release of ITZ from milled extrudates with either
270 Soluplus® or Aqoat® AS-LF, a combination of both polymers in different ratios was
271 investigated to potentially achieve pH-independent release. The release of ITZ in both 0.1 N
272 HCl and PBS pH 6.8 can be adjusted by varying the ratio of Soluplus®:Aqoat® AS-LF. An
273 increase in the Aqoat® AS-LF resulted in a slower ITZ release in 0.1 N HCl and a faster release
274 in PBS pH 6.8 (Fig. 5).

275 In order to understand the state of ITZ in hot melt extrudates, DSC investigations were
276 242 performed (Fig. 6). ITZ is a crystalline drug with a Tm = 169 ˚C which slightly shifted in
277 the physical mixture with investigated polymers as it was already demonstrated previously
278 [49]. On the other hand, in milled extrudates with Soluplus®, Aqoat® AS-LF, Soluplus®:Aqoat®
279 AS-LF in different ratios, no melting peak was detected that confirms dissolved state of ITZ in
280 the respective polymeric matrix. Also, no drug peaks were detected on the X-ray diffractograms
281 of milled extrudates with Soluplus®, Aqoat® AS-LF, and Soluplus®:Aqoat® AS-LF as carriers
282 (Fig. 7).

283 To evaluate the drug-polymer molecular interaction in extrudates FTIR spectroscopy
284 was used (Fig. 8)**.** As it was demonstrated previously [49], in the spectrum of ITZ stretching
285 modes C=O, C=N and C-N were recorded at approximately 1699, 1512, and 1452 cm^{-1},
286 respectively. Soluplus® demonstrated 2 peaks, namely, at 1732 and 1629 cm^{-1}, originating from
287 the stretching of ester carbonyl and C=O stretching for tertiary amid respectively. Aqoat® AS-
288 LF showed 1 peak at 1734 cm^{-1} originating from the stretching of carbonyl group. The spectrum

of ITZ physical mixture with both polymers contained all peaks described for individual components. The spectra of extrudates demonstrated almost the same characteristic peaks for pure polymers. However, the carbonyl group observed in the pure ITZ was stretched and overlapped with C=O stretching vibration of both polymers. Thus, intermolecular interactions between ITZ and the polymers could have occurred during hot melt extrusion which was more pronounced for counter-ionic Aqoat® AS-LF containing extrudates.

Since the milled hot melt extrudates with Soluplus®: Aqoat® AS-LF in ratio 75:25 demonstrated most pH independent release (Fig. 5), it was further formulated in HPMC matrix tablets with Methocel® K15M. With this approach, a pH-independent and extended over 24 h release was achieved (Fig. 9).

Another representative of ionizable drugs MFA was investigated and, to improve the aqueous solubility and, hence, the dissolution of acidic drugs, a basic polymer, e.g. Eudragit® E PO alone or in combination with Soluplus® was used to form solid solutions via hot melt extrusion.

Two polymorphic forms of MFA were described in literature [61, 62]. The thermal behavior of MFA investigated in this study was similar to the described Form 1 [61]. In this case, upon heating, Form 1 turned at 170.7 °C to Form 2 which melted at 229.5 °C. No melting peaks were observed by DSC from MFA physical mixture and milled extrudates with different polymers (Fig. 10 A, C, E). Probably, the drug was dissolved in the molten polymer/s before reaching its melting temperature. Since, DSC could not be used for the clarification of physical state of MFA in extrudates, PXRD was applied as an additional method. Pure MFA has numerous diffraction peaks indicating its crystalline nature. Also, in the physical mixture with investigated polymers, the diffraction peaks of MFA were observed, although in lower intensity. On the other hand, with milled extrudates with up to 33% drug loading no diffraction peaks were detected (Fig. 10 B, D, F) confirming amorphous state of MFA.

The equilibrium solubility of MFA Form 1 and 2 in water was reported as equal, namely, approx. 40 µg/ml [62]. However, the solubility of MFA, as an acidic drug, is pH dependent e.g. 0.4 or 29.6 µg/ml at pH 1.2 or 6.8, respectively, as reported [40], as well as 7 or 33 µg/ml at pH 5.5 or pH 6.8, respectively, as determined in this study. The drug release under non-sink condition (corresponding to 100 mg of drug in 900 ml medium) levelled off by only approx. 38 % within 24 h even in favorable media PBS pH 6.8 (Fig. 11A) which corresponds to the drug solubility in the respective media. Also, the release of MFA from extrudate with Soluplus® can be significantly improved in favorable PBS pH 6.8 (nearly complete release) or

at pH 5.5 (levelled off at approx. 20 %). However, the release from the extrudate was still negligible in 0.1 N HCl (Fig. 11B).

The release of MFA in 0.1 N HCl solution was improved when MFA:Eudragit® EPO milled extrudates were formulated into immediate release tablets. This is due to salt formation between MFA and Eudragit® EPO. The release profile in unfavorable 0.1 N HCl, however, was still slow for immediate release formulations (Fig. 12 A). Simultaneously, the release of MFA from such extrudates was limited by approx. 20 % also in the favorable PBS pH 6.8 (Fig. 12 A). At this pH, approx. 85 % Eudragit® EPO is ionized (pKa 7.6) and, thus, the MFA is embedded in insoluble matrix. Eudragit® EPO is highly ionized and soluble in the medium with intermediate pH 5.5 and the release was fast, complete, and stable within 24 h (Fig. 12 A). Using a combination of Soluplus® and Eudragit® EPO, the release at pH 5.5 and 6.8 was almost equal, however, levelled off at approx. 50 % (Fig. 12 B). This is, probably, due to reduced amount of Eudragit® EPO needed for above mentioned salt formation.

The novelty of this study is the combination of approaches of improving the aqueous solubility and overcoming of pH dependent solubility of ionizable drugs by hot melt extrusion.

4. Conclusions

The problem of pH-dependent release of basic ITZ from milled extrudates was overcome by hot-melt extrusion with the non-ionizable Soluplus® and acidic Aqoat® AS-LF. Achieved supersaturation of ITZ in the release medium was maintained over 24 h. The pH-independent extended release was achieved by the formulation milled ITZ extrudates into erodible matrix tablets. Hot melt extrusion of MFA with either Soluplus® or Eudragit® EPO improved the dissolution rate only at certain pHs. This approach can be used for the development of immediate release or enteric-like, but not for the extended-release formulation of acidic APIs.

5. Acknowledgements

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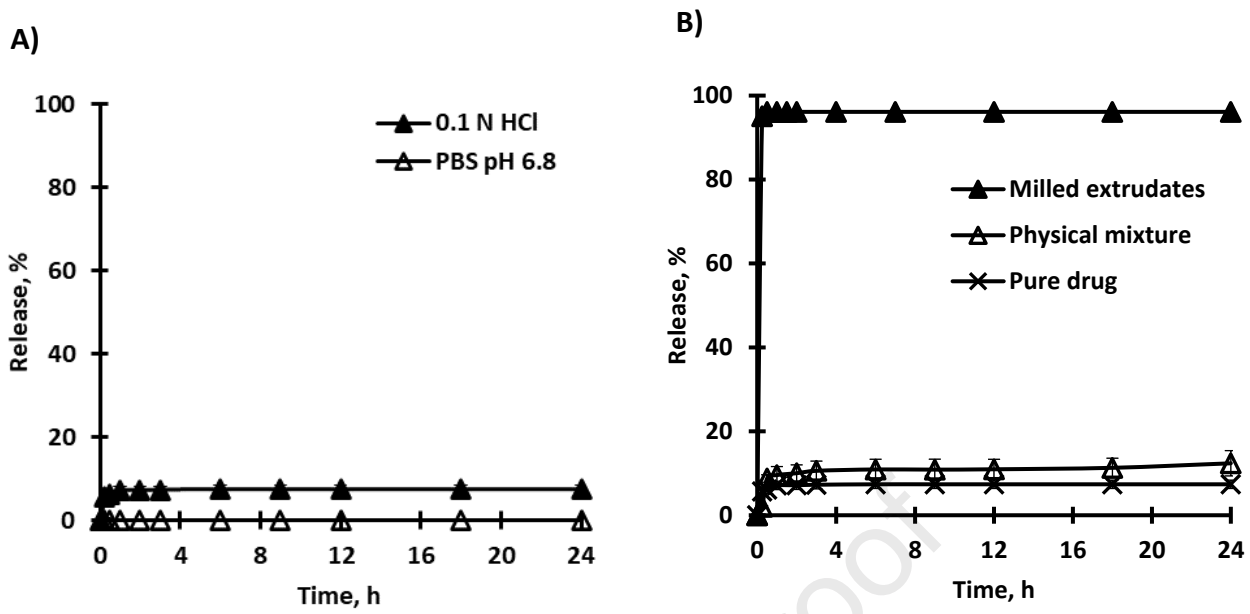

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520 **Figure. 1** Release of ITZ A) powder in different release media and B) powder, physical
521 mixture and ITZ:Soluplus® (1:3) milled extrudate in 0.1 N HCl.

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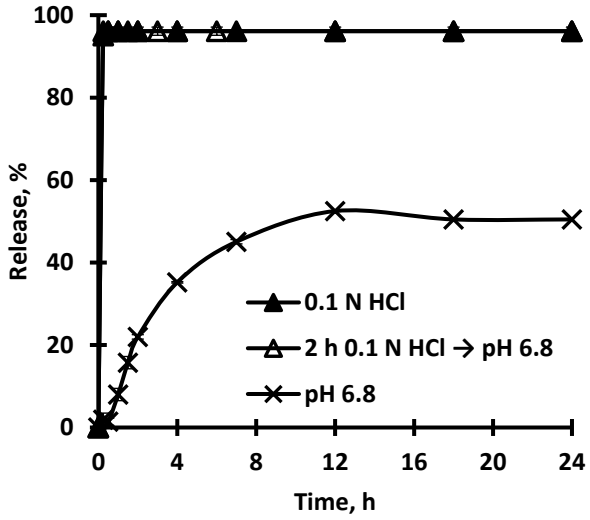

Figure. 2. Effect of pH on drug release from ITZ:Soluplus® (1:3) milled extrudate.

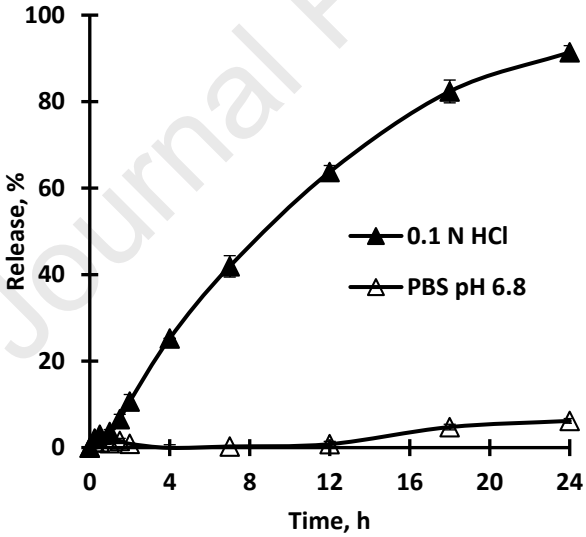

Figure. 3. Effect of pH on ITZ release from ITZ:Soluplus® (1:3) milled extrudate formulated into erodible Methocel® K15M matrix tablets.

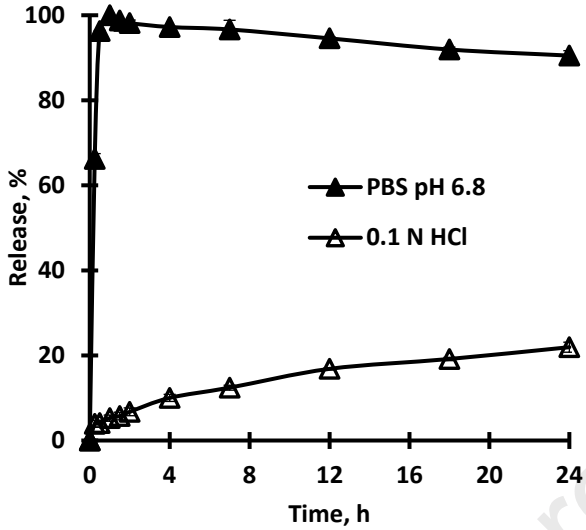

Figure. 4. Effect of pH on ITZ release from ITZ:Aqoat® AS-LF (1:3) milled extrudates.

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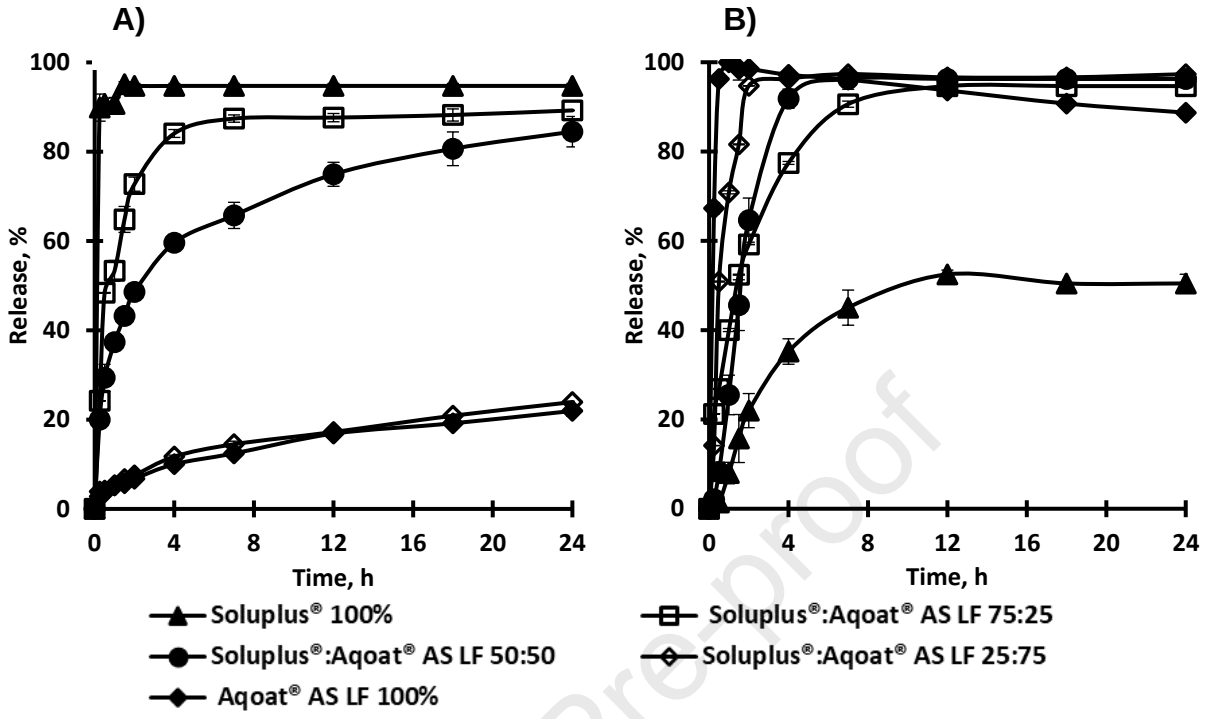

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593 **Figure 5.** Effect of Soluplus®:Aqoat® AS-LF ratio on ITZ release in A) 0.1 N HCl , B) PBS
594 pH 6.8 from milled extrudates with ITZ:polymer(s) (1:3).

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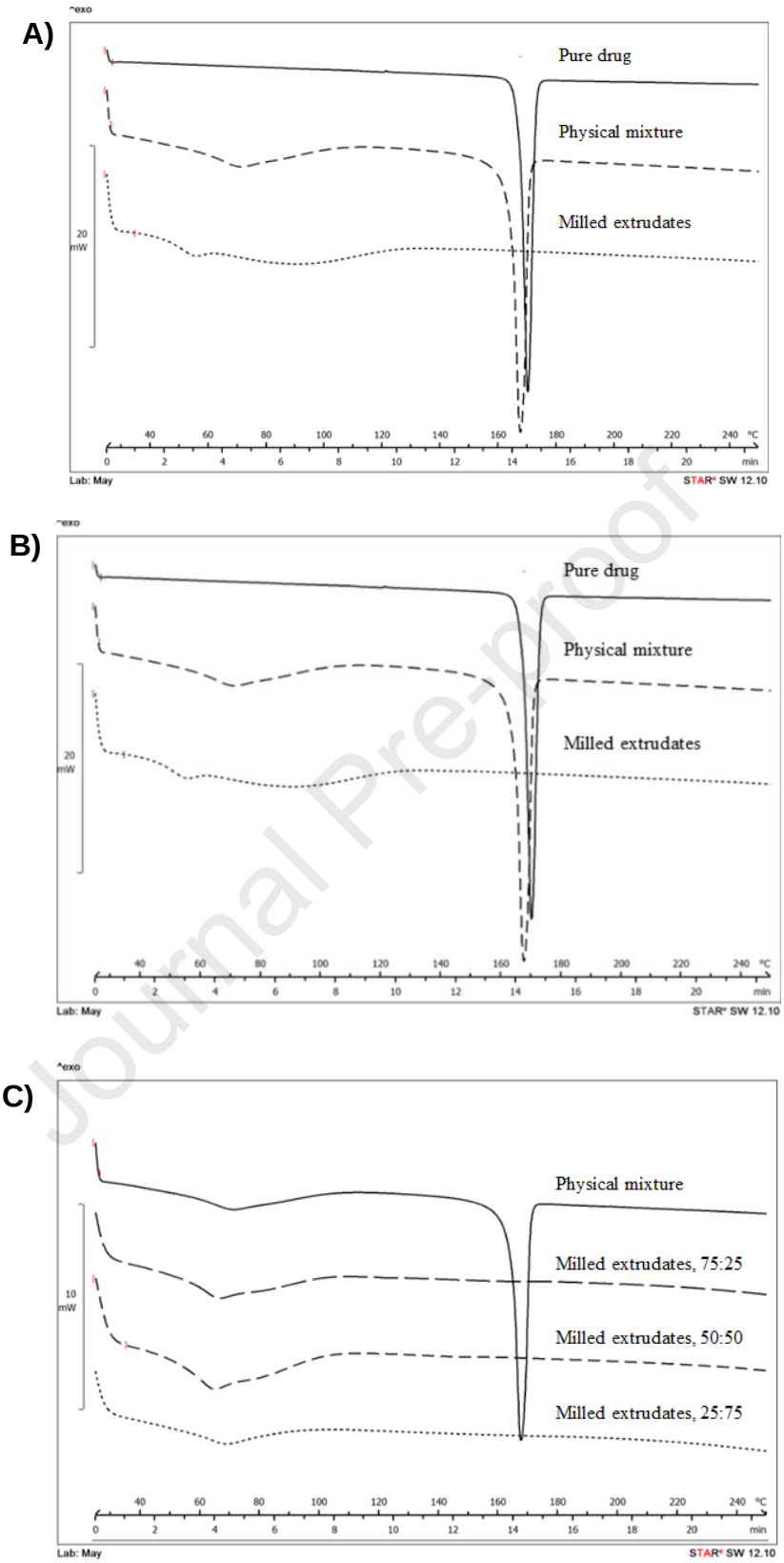

Figure 6. DSC thermograms of ITZ, its physical mixtures and milled extrudates with different carriers A) ITZ:Soluplus® (1:3) [49], B) ITZ:Aqoat® AS-LF (1:3) and C) Soluplus®:Aqoat® AS-LF in different ratios (ITZ:polymers ratio 1:3).

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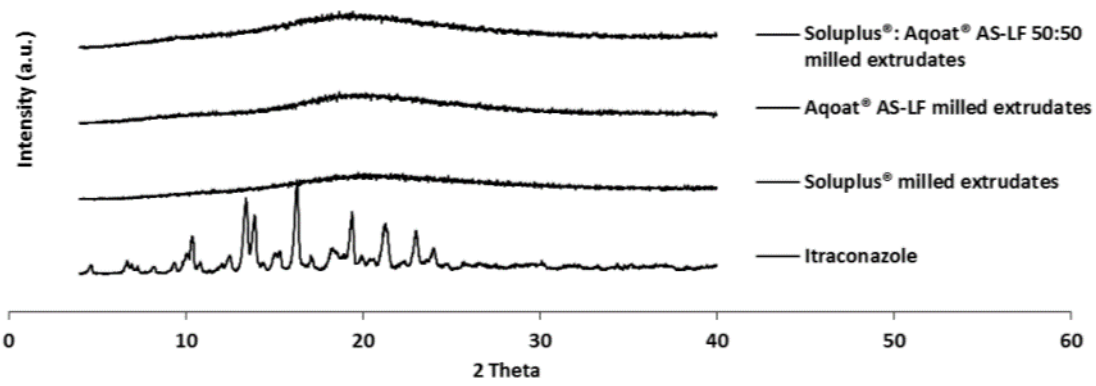

634 **Figure 7**. X-ray diffractograms of ITZ and its milled extrudates with different carriers
635 Soluplus®, Aqoat® AS-LF and Soluplus®:Aqoat® AS-LF (50:50). ITZ: carrier ratio 1:3.

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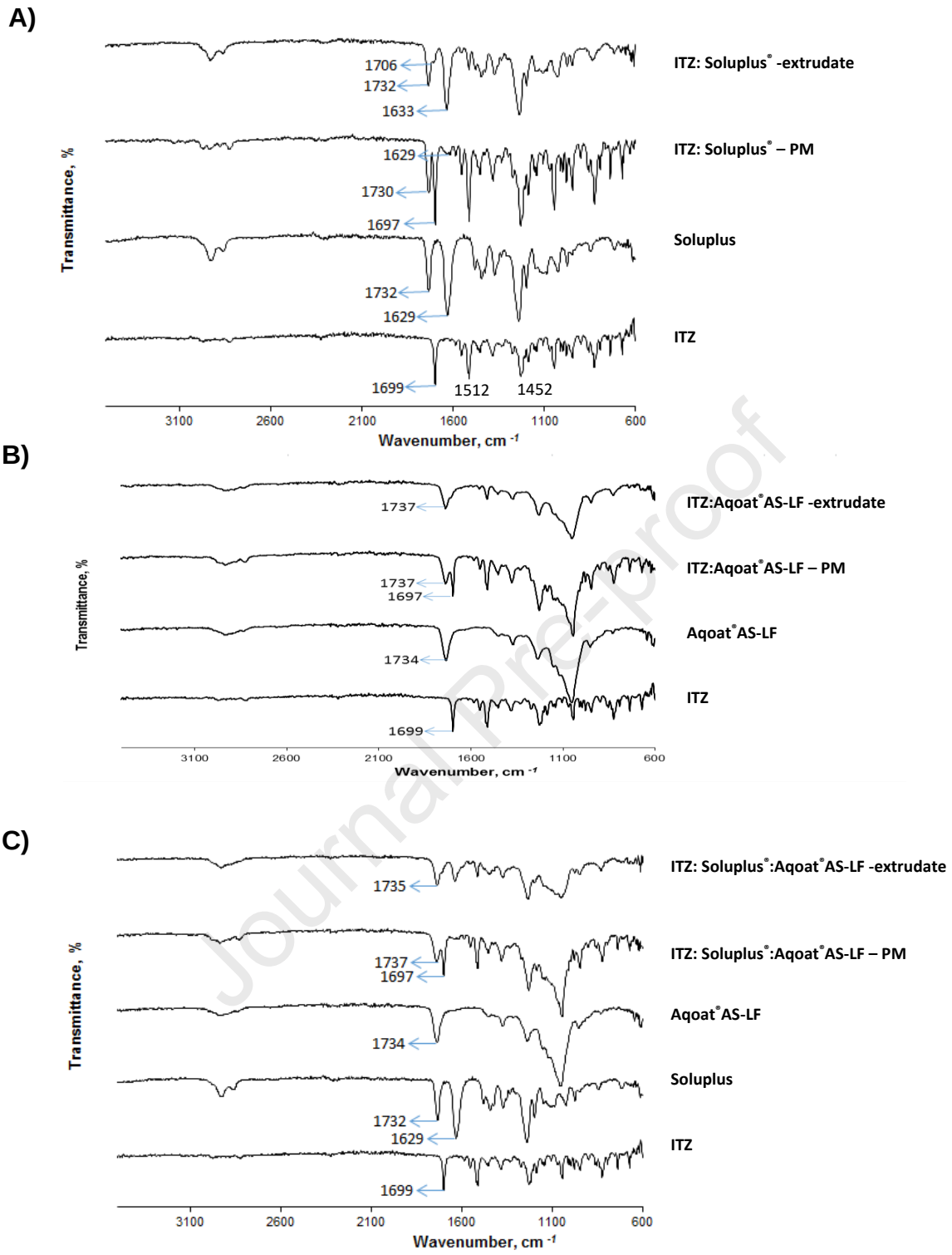
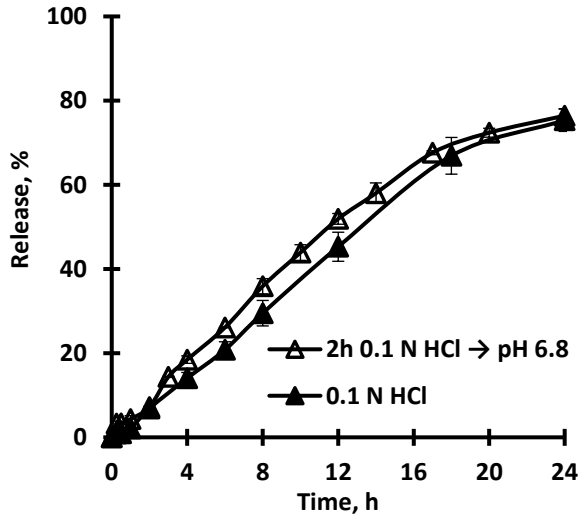


Figure 8. FTIR spectra of ITZ, its physical mixture and milled extrudates with different polymers A) Soluplus® [49], B) Aqoat®AS-LF, C) Soluplus®:Aqoat®AS-LF. ITZ:polymer(s) ratio 1:3.



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669 **Figure 9.** Effect of pH on ITZ release from Soluplus®:Aqoat®AS-LF (25:75) and
670 ITZ:polymers 1:3 milled extrudates formulated into erodible Methocel® K15M matrix tablets.
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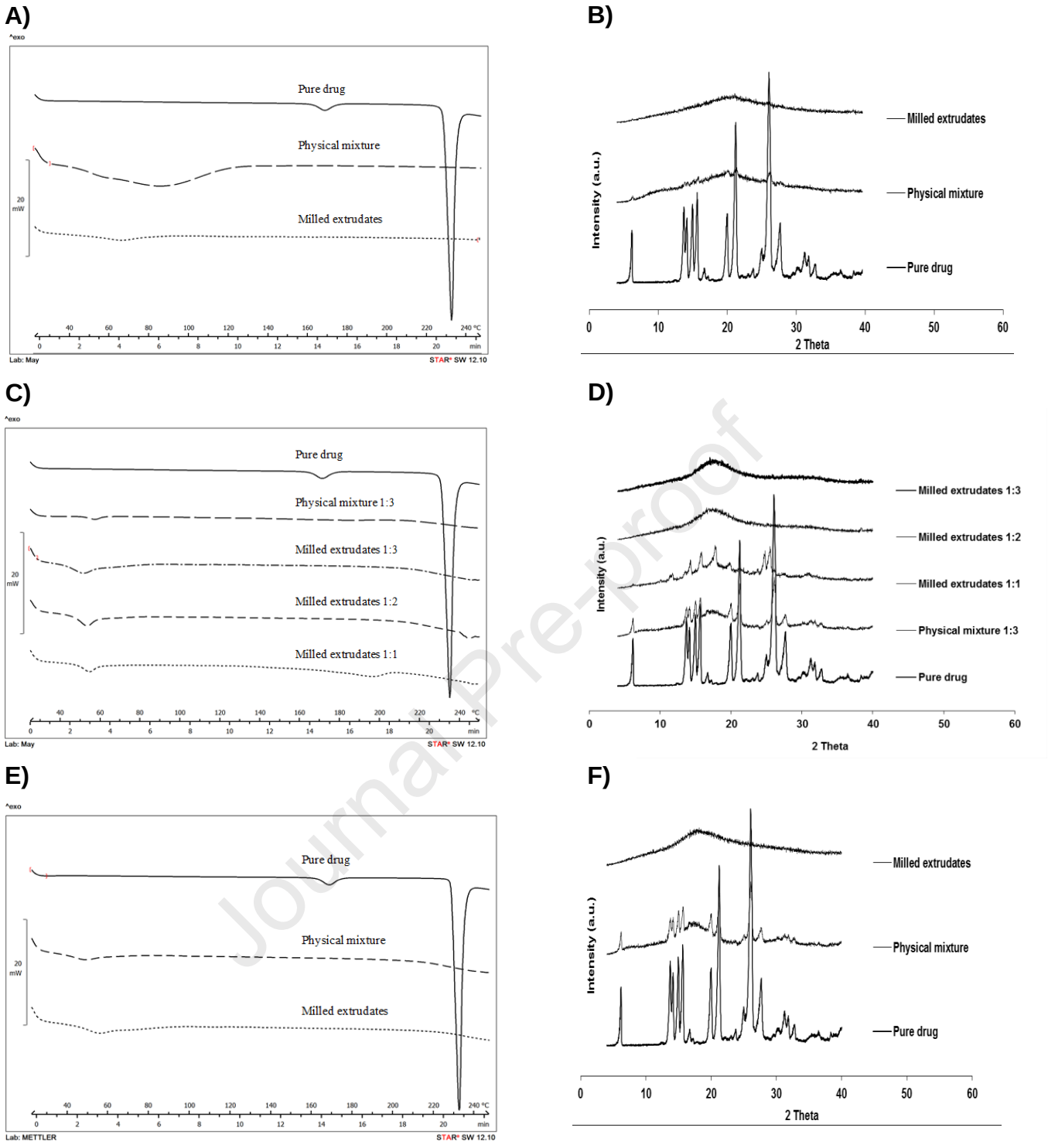

Figure 10. DSC thermograms (A, C, E) and X-ray diffractograms (B, D, F) of MFA as physical mixtures and milled extrudates with Soluplus® (A, B), Eudragit® EPO different ratios (C, D) and Soluplus:Eudragit® EPO (50:50).

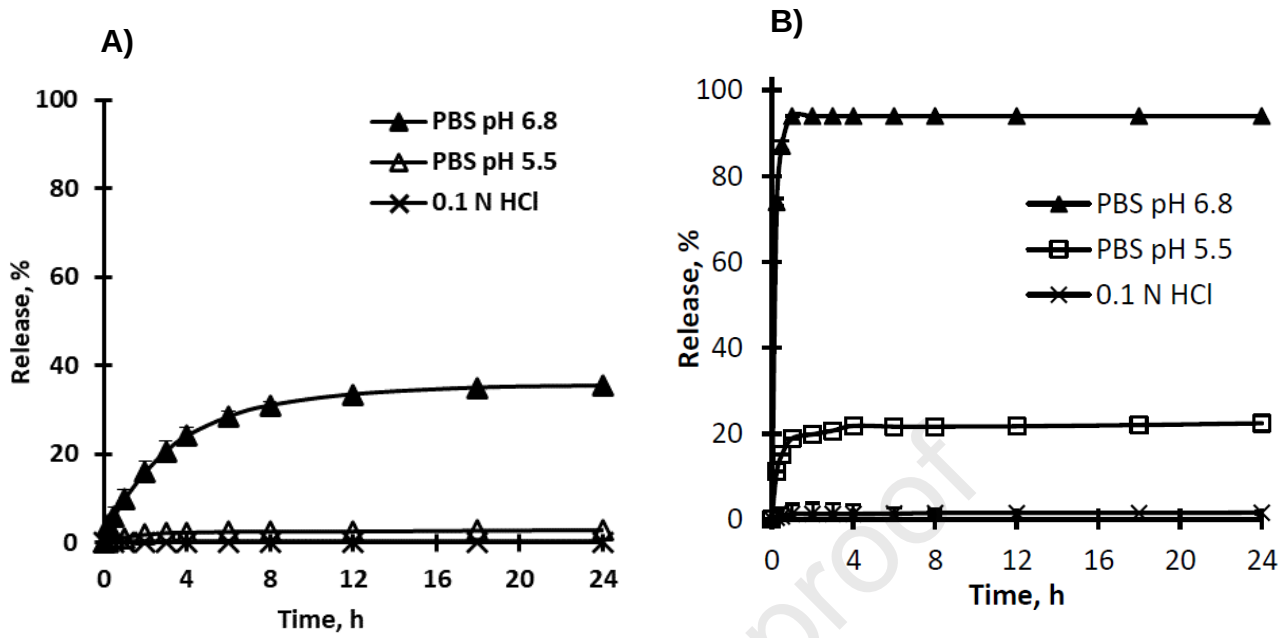

Figure 11. Effect of pH on mefenamic acid release A) drug powder and B) milled extrudate ITZ:Soluplus ratio 1:3.

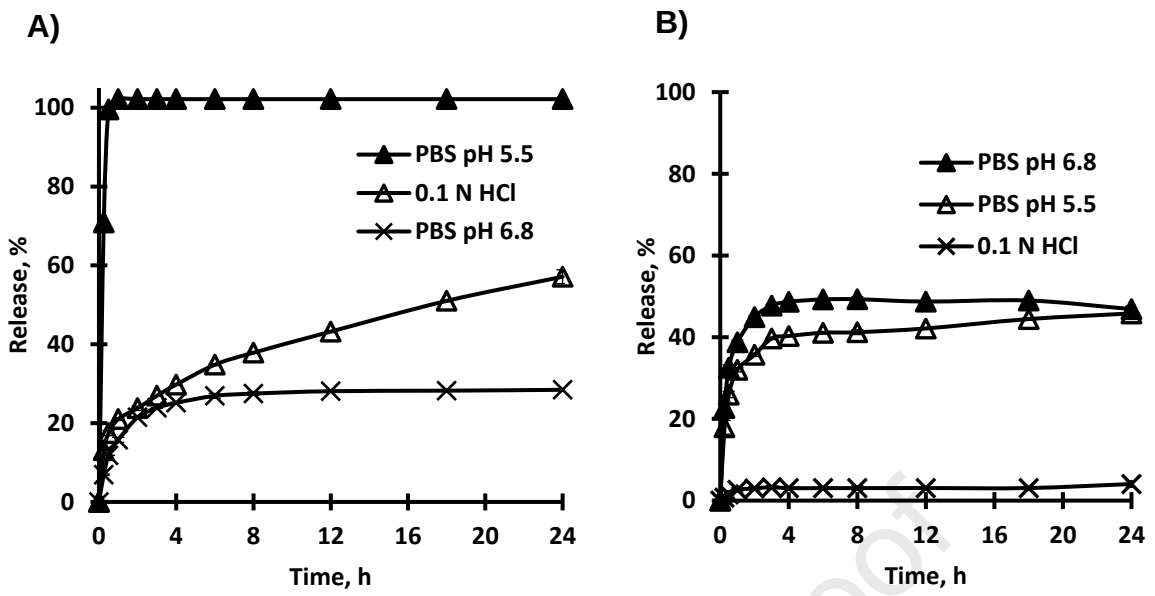

Figure 12. Effect of pH on MFA release from A) MFA: Eudragit® EPO (1:3) and B) Soluplus:Eudragit® EPO (50:50) milled extrudates.

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: