

Journal Pre-proofs

Original article

The effect of alcohol on ionizing and non-ionizing drug release from hydrophilic, lipophilic and dual matrix tablets

Václav Lochař, Alena Komersová, Kevin Matzick, Barbora Slezáková, Martin Bartoš, Jitka Mužíková, Samir Haddouchi

PII: S1319-0164(19)30169-0
DOI: <https://doi.org/10.1016/j.jsps.2019.11.020>
Reference: SPJ 974

To appear in: *Saudi Pharmaceutical Journal*

Received Date: 19 July 2019
Revised Date: 21 October 2019
Accepted Date: 29 November 2019

Please cite this article as: Lochař, V., Komersová, A., Matzick, K., Slezáková, B., Bartoš, M., Mužíková, J., Haddouchi, S., The effect of alcohol on ionizing and non-ionizing drug release from hydrophilic, lipophilic and dual matrix tablets, *Saudi Pharmaceutical Journal* (2019), doi: <https://doi.org/10.1016/j.jsps.2019.11.020>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 The Author(s). Published by Elsevier B.V. on behalf of King Saud University.



The effect of alcohol on ionizing and non-ionizing drug release from hydrophilic, lipophilic and dual matrix tablets

Václav Lochař^a, Alena Komersová^{a*}, Kevin Matzick^a, Barbora Slezáková^a, Martin Bartoš^b,
Jitka Mužíková^c, Samir Haddouchi^d

^aDepartment of Physical Chemistry, Faculty of Chemical Technology, University of Pardubice,
Studentská 95, 532 10 Pardubice, Czech Republic

^bDepartment of Analytical Chemistry, Faculty of Chemical Technology, University
of Pardubice, Studentská 95, 532 10 Pardubice, Czech Republic

^cDepartment of Pharmaceutical Technology, Charles University, Faculty of Pharmacy in
Hradec Králové, Akademika Heyrovského 1203, 500 05 Hradec Králové, Czech Republic

^dSPS Pharma Services, 3 Rue Châteaubriand, 45071 Orléans, France

*Corresponding author at: Department of Physical Chemistry, Faculty of Chemical Technology,
University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic

Fax: +420 466 037 068

E-mail address: alena.komersova@upce.cz

The effect of alcohol on ionizing and non-ionizing drug release from hydrophilic, lipophilic and dual matrix tablets

Abstract

The aim of this work was to investigate and quantitatively evaluate the effect of presence of alcohol on *in vitro* release of ionizing and non-ionizing drug from hydrophilic, lipophilic and hydrophilic-lipophilic matrix tablets. The Food and Drug Administration (FDA) recommends *in vitro* dissolution testing of extended release formulations in ethanolic media up to 40% because of possible alcohol-induced dose dumping effect. This study is focused on comparison of the dissolution behavior of matrix tablets (based on hypromellose and/or glyceryl behenate as retarding agent) of the same composition containing different type of drug – ionizing tramadol hydrochloride (TH) and non-ionizing pentoxifylline (PTX). The dissolution tests were performed in acidic medium (pH 1.2) and in alcoholic medium (20%, 40% of ethanol) and the changes of tablets were observed also photographically.

It was found that the alcohol resistance of the hydrophilic-lipophilic formulations with TH and the hydrophilic-lipophilic formulations with PTX containing a higher amount of hypromellose does not reflect the alcohol resistance of the formulations with pure hypromellose or glyceryl behenate. Both hydrophilic-lipophilic formulation with TH and more lipophilic formulation with PTX show significant alcohol dose dumping effect.

Keywords: hypromellose, glyceryl behenate, alcohol, tramadol hydrochloride, pentoxifylline, dissolution

1. Introduction

The major factors affecting the drug release in the gastrointestinal tract include also the presence of alcohol. The pure ethanol inhibits the gastric emptying (Franke et al., 2004) and it has been also described that some oral extended release dosage forms exhibit more rapid drug release in the presence of ingested ethanol due to a higher solubility of the drug and/or excipients in hydro-alcoholic media (Walden et al., 2007). Intense interest in the effect of alcohol on the drug release from controlled release formulations is connected with „The Case Palladon“ in July 2005 (FDA, 2005a; FDA, 2005b). In the light of this case, research in the field of extended release formulations containing opioids was focused on resistance of these formulations to alcohol. Due to the presence of alcohol in the gastrointestinal tract, the drug release mechanism can be changed or lost and rapid drug release in a short time period can cause high concentration of a drug in the blood – „alcohol-induced dose dumping effect“. Because the extended release formulations contain a larger amount of API than immediate release tablets, their dissolution kinetics in alcohol presence have to be carefully tested for propensity of dose dumping. This study is focused on the effect of alcohol on the dissolution behaviour of matrix tablets containing hypromellose or glyceryl behenate or combination of both of them (hydrophilic-lipophilic matrix tablets). Hypromellose (HPMC) is a hydrophilic polymer which in contact with the dissolution medium quickly hydrates, forms a gel layer and subsequent water penetration allows the extended drug release (Colombo et al., 1996; Bettini

et al., 1994). Drug release from these types of matrix tablets dependent on the physico-chemical properties of HPMC and drug (such as viscosity grade of HPMC used, tablet geometry, particle size of drug and polymer, drug solubility), on drug/HPMC ratio and type of filler and/or binder (Bettini et al., 1994; Li et al., 2005; Rodriguez et al., 2000). Glyceryl behenate is a lipophilic substance which can be used for the preparation of lipophilic or dual matrix tablets (Aburahma et Badr-Eldin, 2014). This excipient in concentrations up to 3 % is used as a lubricant; for drug release prolongation it is necessary to increase its concentration to above 10 % (Driver, 2017). In dual matrix based on glyceryl behenate and hypromellose, the ideal ratio is about 10 % glyceryl behenate and 15 % HPMC (Gattefossé 1). The release mechanism of the active ingredient from the matrices with glyceryl behenate is prevalently diffusion due to the multiplicity of porosity and the establishment of mini-channels (Li et al, 2006). An advantage of these matrices is the independence of drug release on pH (Gattefossé 2), which has been reported also for hypromellose (Dow Chemical Company). The effect of hydroalcoholic solution on textural and rheological properties of various grades of hypromellose was also reported (Missaghi, 2009). Alcohol resistance of HPMC were studied using the different viscosity grades of HPMC (Methocel K100LV CR, K4M CR, and K100M CR) and consistent swelling and gel formation were confirmed when exposed to hydroalcoholic media (Levina et al, 2007). To improve alcohol resistance of extended release tablets based on glyceryl behenate, a continuous twin screw melt granulation of glyceryl behenate was investigated using tramadol hydrochloride as model highly water soluble drug (Keen et al, 2015). It was found that continuous twin screw granulation results in a mixture of stable polymorphs of glyceryl behenate and resulting tablets exhibit a stable dissolution profile in hydroalcoholic medium (Keen et al, 2015).

Based on results of next studies it is clear that for development of alcohol-resistant dosage form, the physico-chemical properties (solubility, wettability, swellability) and mechanical

properties of the API and the excipients and the properties of the final dosage form (hardness, swelling and drug release characteristics) have to be analyzed (Jedinger et al, 2014).

The aim of this work is quantitative evaluation of the effect of alcohol (20 and 40% v/v) on the release mechanism and release rate of a highly water soluble drug (tramadol hydrochloride) and non-ionizing drug (pentoxifylline) from lipophilic, hydrophilic or hydrophilic-lipophilic matrix tablets with extended release.

2. Materials and methods

2.1. Materials

Hypromellose (MethocelTM K4M Premium CR, Colorcon GmbH Germany) and/or glyceryl behenate (Compritol[®] 888 ATO, Gattefossé France) were used as the controlled release agents forming matrix system. Prosolv[®] SMCC 90 (JRS PHARMA, GmbH & Co. KG, Germany) was used as a co-processed dry binder and magnesium stearate (Acros Organics, USA) was used as a lubricant. Tramadol hydrochloride and pentoxifylline (both European Pharmacopoeia Reference Standard, Sigma Aldrich Chemie GmbH, Germany) were chosen as the model highly water soluble drug and non-ionizing drug, respectively. Ethanol (96% v/v, 0.81 g/cm³) according to specification ph. eur. (Lach-Ner s.r.o., Neratovice, Czech Republic) was used to prepare the alcoholic dissolution medium (20 and 40% v/v).

For the preparation of dissolution media and standard solution of tramadol hydrochloride or pentoxifylline, redistilled water and chemicals of analytical grade (Lach-Ner s.r.o., Neratovice, Czech Republic) were used.

2.2. Methods

2.2.1. Preparation of tablets

Composition of studied formulations is described in Tab. 1. Tablets were prepared by the direct compression using a material testing equipment T1-FRO 50 TH.A1K Zwick/Roell (Zwick GmbH&Co, Germany) by means of a special die with a lower and an upper punch. The rate of compaction was 40 mm/min, pre-load was 2 N, and the rate of pre-load 2 mm/s. The tablets were of cylindrical shape without facets of a diameter of 13 mm and weight of 0.5 ± 0.0010 g. Preparation of tableting materials is described in detail in previous paper (Komersová et al., 2016).

For one dissolution test, 6 tablets with the active ingredient and 1 tablet without the active ingredient as the blank sample were compressed. In the blank samples, the amount of the retarding agents was replaced with the co-processed dry binder.

In the same way, samples for the photographic observation of the tablets swelling and erosion were prepared.

2.2.2. SEM

The compact scanning electron microscope VEGA3 SBU (Tescan, Brno, Czech Republic) was used to evaluate the homogeneity of compressed tablets. An acceleration voltage of 15 kV, backscattered electron (BSE) detector and low vacuum mode (10 Pa, N₂) were applied. The studied tablet was lightly fixated to a carbon double-side adhesive tape (Pelco Tabs™, 12mm OD, Ted Pella, Inc., CA, USA) placed on a circular aluminium disc. The disc with tablet was blown by compressed air and placed into a microscope chamber.

2.2.3. In vitro dissolution studies

The release of tramadol hydrochloride (TH) or pentoxifylline (PTX) from prepared drug formulations was studied by the dissolution test method according to the European Pharmacopoeia 9th (European Pharmacopoeia, 2017) using rotating basket apparatus (Sotax AT 7 Smart, Allschwil, Switzerland). All tests were carried for 10 hours at a stirring rate of 100 rpm. Temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Tablets were tested for only 2 hours in alcoholic medium (20 and 40 % of ethanol in acidic medium pH 1.2) and then were transferred together with the basket to the non-alcoholic acidic medium (acidic medium pH 1.2 prepared according to the European Pharmacopoeia 9th (European Pharmacopoeia, 2017)) and dissolution testing continued for an additional 8 hours as described above.

At predetermined times, 3 mL of the dissolution medium was automatically withdrawn, filtered and the TH or PTX concentration was determined using UV VIS spectrometry. The dissolution profiles obtained were compared to the drug release in non-alcoholic media (dissolution performed 10 hours in acidic medium).

Each experiment was performed once (with six tablets) and the mean values of the released amount of the drug with standard deviations (SD) were calculated.

2.2.4. Determination of TH and PTX using UV VIS spectrometry

UV VIS determination of TH or PTX concentration in samples from dissolution was performed using spectrophotometer HP Agilent 8453 at wavelength of 271 nm (TH) and 274 nm (PTX). Corresponding dissolution medium (automatically withdrawn from vessel containing blank tablet at the same times as the sample) was used as blank sample and three points background correction was applied. To transform absorbance values into concentrations and percentage, the calibration curve method was used. Validity of Lambert-Beer law in studied concentration range was verified and potential interference of some excipients of drug form was also tested.

2.2.5. Mathematical and statistical evaluation of the dissolution profiles

Similarity factor

To statistically evaluate the similarity of the dissolution profiles obtained, similarity factor f_2 as a logarithmic transformation of the sum-squared error of the differences between the test T_j and reference product R_j was determined according to equation:

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \sum_{j=1}^n |R_j - T_j|^2 \right) \right]^{-0.5} \times 100 \right\} \quad (1)$$

where j is the sample number, n is the number of dissolution sample times (Costa and Sousa Lobo, 2001). The dissolution profile obtained in the acidic medium pH of 1.2 was used as the reference (R_j). Similarity factor f_2 is 100 when the test and reference profiles are identical and decreases to 0 as the dissimilarity increases.

The dissolution efficiency

The dissolution efficiency (DE) was evaluated as model-independent parameter. The dissolution efficiency (DE) of a pharmaceutical dosage form (Khan, 1975; Costa and Sousa Lobo, 2001) expressed as the area under the dissolution curve up to a certain time t was calculated by the equation

$$DE = \frac{\int_0^t Y dt}{Y_{100} \times t} \times 100\% \quad (2)$$

where Y is the percentage of drug dissolved at time t . This parameter expresses a percentage of the area of the rectangle described by 100% dissolution in the same time.

All experimental data were mathematically processed and statistically evaluated by means of the computer programmes GraphPad Prism and Origin 9 Pro. Statistical significance was tested using Student's t test for unpaired samples, at a significance level of $P < 0.05$.

2.2.6. *Photographic observation*

In situ photographic observation of studied formulations during dissolution test was carried out using a digital camera Panasonic Lumix DMC-FZ18. To monitor the overall change the tablets, the recording was performed for 2 hrs but photographs were taken at 1 and 2 hrs from the beginning of the dissolution test.

3. Results and discussion

SEM

Representative SEM images of tablet surfaces are given in Fig. 1 a Fig. 2. It is clear from the images (see Fig. 1 and Fig. 2) that all components are evenly distributed in the tablets. Glyceryl behenate, consisting of a fine powder, was not changed by compression. The fine powder fills the space between the other tablet components very well (the darkest part of the tablets on the images), especially in tablets containing a higher content of glyceryl behenate. Similarly, the particles of HPMC are almost unchanged and have a dual form – on the one hand, round, oval to kidney sized 50 to 100 μm , while also often found as elongated „wormy“ formations of up to 200 μm in length and up to 20 μm in diameter. Due to the compression, these elongated formations are more or less parallel to the upper and lower tablet surface. Prosolv[®] SMCC 90 is made up of fine flakes, the size of which is usually about 20 μm , and are organized into larger disintegrating clusters. These clusters are likely to have disintegrated during blending of tableting material before the tablet compression. PTX is similar to Prosolv[®]

SMCC 90, consisting of platelets of approximately 40x20 μm , the surface of which is covered with smaller platelets sized a few μm to 10 μm . Larger plates in places form clusters of up to 200 μm , very rarely larger. These clusters likely disintegrated into individual platelets during compression. TH, which is evenly dispersed in the tablet, is made up of bulky elongated crystals most often 50 to 100 μm in size, and a large amount of fine pulp up to 10 μm in size. Based on Fig. 1 and Fig. 2 it is clear, that the visually biggest difference is between the tablets which contain and those that do not contain glyceryl behenate, because this substance is significantly darker in images than all other substances. "Wormy" and spherical particles of HPMC are also clearly visible in comparison to difficult to distinguish crystals of TH. Magnesium stearate, due to its low content in the tablets, small particle size and fine dispersion, is not visible in the images.

In vitro dissolution studies

The evaluation of changes of the dissolution profiles due to the presence of alcohol was used as a suitable method for testing of alcohol resistance of solid dosage forms. The dissolution behaviour of all studied formulations (containing 30% of retarding agent) was studied in acidic dissolution medium and obtained dissolution profiles were compared with profiles in the presence of alcohol (2 hrs in 20 and 40% alcohol, then 8 hrs in acidic medium). The dissolution profiles obtained are presented in Fig. 3-6 (4 profiles in 20% hydroalcoholic medium (F2, F4, F5 and F8) are not shown in the figures due to overlap already viewed profiles).

Hydrophilic and lipophilic formulations

As can be seen from Fig. 3, the effect of alcohol on TH release from hydrophilic and lipophilic formulations is completely different. The release of the drug from lipophilic formulation F1 is strongly influenced by the presence of alcohol. The released amount of TH after 2 hrs in the dissolution medium containing 40 % of alcohol is about 30% lower compared

to the acidic medium. But once the tablets are transferred into the acidic medium (pH 1.2), the released amount of drug rapidly increases and within about 120 min., the same amount of TH as after 4 hrs in acidic medium is reached. It means that the mechanism of TH release from formulations based on glyceryl behenate as retarding agent is strongly affected by the presence of alcohol in the dissolution medium. The decrease of the dissolution profile in the first 4 hrs is independent on alcohol concentration.

In contrast, the released amount of TH from hydrophilic formulation F2 based on hypromellose is only slightly lower in the presence of alcohol (20%, 40%) and the difference in the amount of TH released in the range of 5-10% is maintained for 10 hrs of dissolution.

It is clear that after 2 hrs in an alcoholic medium, the mechanism of drug release is partially disrupted and it is not completely restored even after insertion of tablets into an acidic medium. The f_2 values for TH dissolution profiles of lipophilic and hydrophilic tablets exposed for 2 hrs to 40% ethanol solution, as compared to the profiles in acidic medium, were found to be 46 and 63, respectively. Similar values of f_2 factor were determined also in 20% hydroalcoholic dissolution medium (Tab. 2). These values indicate similarity of the dissolution profiles of hydrophilic formulation F2. For the lipophilic formulation F1, higher DE , as compared to F2, was confirmed in all dissolution media (Tab. 2).

The results mentioned above showed that the addition of alcohol into the dissolution medium decreases the drug release rate for both formulations and for TH as a model highly water soluble drug, the hydrophilic formulation based on hypromellose is much more resistant to the presence of alcohol than lipophilic formulations based on glyceryl behenate. The different behavior of studied lipophilic and hydrophilic formulation in alcoholic medium can be affected by the important physico-chemical factors responsible for the tablet alcohol resistance – drug solubility, wetting (glyceryl behenate matrix) and swelling (HPMC matrix). Generally, the solubility of a drug molecule in a solvent depends on the formation of hydrogen bonds of drug

molecules with molecules of the solvent. Ethanol is a less polar solvent compared to water and this fact results in the differences in the dielectric constants (20 and 80 for ethanol and water at 20°C, (Akerlof, 1932). Therefore, the addition of ethanol to water (dissolution medium) causes the decrease of the dielectric constant (in relation to water) and thus, the solubility of water poorly soluble drugs increases (Jedinger, 2014). TH is an ionizing molecule which dissociates in aqueous solutions to poorly soluble tramadol ion. The solubility of TH in the alcoholic medium is significantly higher compared to water (DrugBank1) which can increase the TH release rate from matrix tablets. Apart from solubility, another factor affecting TH release rate from studied formulations is the possible change of matrix swelling (F2 formulation based on HPMC) and change of wetting (F1 formulation based on glyceryl behenate). It has been published, that no significant difference in relative swelling of HPMC compacts resulting in higher drug release rate was observed in alcoholic media (Levina, 2007). The changes of wettability of glyceryl behenate (Compritol[®] 888 ATO) compacts were reported by (Jedinger, 2015). Due to the hydrophobic nature of glyceryl behenate, the contact angle measured in water is above 90°. The value of contact angle strongly decreases with the increasing concentration of alcohol – in a solution containing 40% of alcohol, the contact angle is reduced almost to 50%, which indicates enhanced wetting in alcoholic media. The better wettability of the tablet surface results in a higher penetration rate and a higher drug release rate.

The increase of TH solubility and wetting of glyceryl behenate could result in an increase of TH release rate from studied matrix tablets but as it is clear from the dissolution profiles of F1 and F2 formulation (Fig. 3), the released amount of TH from both types of matrix tablets is lower due to the presence of alcohol. This phenomenon can be explained by the formation of a „protecting“ layer on the tablet surface (due to the presence of alcohol) which causes the glyceryl behenate and HPMC to reach thermodynamic equilibrium with the surrounding medium. Penetration of ethanol into the matrix and TH release are then inhibited.

The dissolution behavior of hydrophilic and lipophilic formulation with PTX is presented in Fig. 4. The PTX is a non-ionizing molecule and this fact influences its interactions with a solvent and subsequently, the drug release rate. For the formulation based on hypromellose (F4), the dissolution profile in acidic medium overlaps the profiles in the presence of alcohol (20 and 40%), which confirmed that the exposure to the alcoholic media for 2 hrs does not result in changes of the matrix system and PTX release rate and this formulation can be considered alcohol resistant.

Lipophilic formulation F3 in alcoholic medium exhibits a lower released amount of PTX for about 1 hr and then a significant alcohol induced dose dumping effect. The dose dumping effect increases with increasing concentration of alcohol in the dissolution medium (Fig. 4). As opposed to the acidic medium, in the alcoholic medium the whole dose of PTX from the formulation F3 is released in 4 hours due to the action of alcohol. The f_2 value for dissolution profiles of F4 formulation exposed for 2 hrs to 20% and 40% ethanol solution, respectively, as compared to the profiles in acidic medium, was found to be 83 (Tab. 2) which indicates similarity of the dissolution profiles. For lipophilic formulation F3, higher value of DE , as compared to hydrophilic formulation F4, was confirmed for all dissolution media (Tab. 2).

Because of the significantly lower PTX solubility in alcohol in comparison to water (DrugBank2) it is clear that a crucial factor responsible for the strong alcohol induced dose dumping effect of F3 formulation (based on glyceryl behenate) is wettability. The increase of wettability allows the penetration of solvent into a matrix system and subsequent increase of the drug release.

Hydrophilic-lipophilic matrix tablets

The effect of alcohol on the dissolution profiles of matrix tablets containing lipophilic and hydrophilic retarding agent is clear from Fig. 5 and Fig. 6. As can be seen from Fig. 5, both

hydrophilic-lipophilic formulations with TH show induced dose dumping effect in 40% hydroalcoholic medium but the influence of alcohol is more significant for formulation F6 containing a higher proportion of hypromellose. In case of the dissolution in 20% hydroalcoholic medium, the dose dumping effect was not confirmed for F5 and F6 formulations (Fig. 5).

The behavior of hydrophilic-lipophilic formulations with PTX in the presence of alcohol (40%) is different in comparison with the same formulations containing TH. The formulation with a more lipophilic character (F7) shows a significant increase in the amount of drug released after transfer from alcoholic into acidic medium, as can be seen from Fig. 6. It means that during 2 hrs in alcoholic medium (40%) the release mechanism was disrupted and therefore, similarly to the pure lipophilic formulation F3, after 2 hrs in alcoholic medium, a significant alcohol induced dose dumping effect can be observed. The hydrophilic-lipophilic formulation F8 with a more hydrophilic character (with a higher proportion of hypromellose) exhibits in alcoholic medium and, during the first 3 hrs in an acidic medium, a decrease in the amount of PTX released and from about 5hr (2 hrs in alcoholic and 3 hrs in acidic medium) the amount of PTX released is almost the same as in the acidic medium without exposure to alcohol. The behavior of hydrophilic-lipophilic formulations with PTX in the presence of alcohol (20%) is not different in comparison with the same formulations containing TH.

The f_2 values (see Tab. 2) for dissolution profiles of hydrophilic-lipophilic formulations exposed for 2 hrs to 20 or 40% ethanol solution, as compared to the profiles in acidic medium, indicate similarity of the dissolution profiles of both formulations with PTX. For F5 formulation with TH, the highest values of DE were found in all dissolution media (Tab. 2).

Results mentioned above show that the alcohol resistance of the hydrophilic-lipophilic formulations with TH and the hydrophilic-lipophilic formulations with PTX containing a higher amount of hypromellose does not reflect the alcohol resistance of the formulations with pure

HPMC or glyceryl behenate. On the other hand, the behavior of the hydrophilic-lipophilic formulations with PTX containing a higher proportion of glyceryl behenate is in accordance with the dissolution behavior of a pure lipophilic formulation.

The dissolution behavior of hydrophilic-lipophilic formulations based on hypromellose and glyceryl behenate confirmed that the alcohol resistance of these formulations is influenced significantly by the type of incorporated drug (ionizing vs. non-ionizing). Probably, the interactions of dissociated TH with molecules of the solvent are the reason for the low resistance of hydrophilic-lipophilic formulations to alcohol. Unlike hydrophilic-lipophilic formulations with PTX (non-ionizing drug) where the dominant factor affecting their behavior in the presence of alcohol is the change of glyceryl behenate wettability.

Photographic observation

The changes of tablet shape during the dissolution test were observed photographically. The changes of tablet (swelling, cracks, erosion, etc.) influence the dissolution behavior of the studied formulation described above.

Formulations containing TH

It can be seen from Fig. 7 that even after an hour of dissolution in the 40% alcoholic solution, the tablet containing glyceryl behenate retained its original shape. Only after two hours are there slight cracks on the walls of the cylindrical tablet. After two hours of exposure to the acidic medium, changes in the surface of the tablets are evident. There was a significant cracking of the tablet surface. The tablets containing glyceryl behenate in the 40% alcoholic dissolution medium showed higher resistance than tablets of the same tablet composition in the acidic medium.

In the case of tablets containing HPMC, slight swelling occurs rapidly. As shown in Fig. 7, the shape of tablets containing HPMC differs only slightly after an hour of acidic dissolution medium with/without alcohol. However, after 2 hours, it is evident that erosion occurs more in the case of the acidic medium.

If the tablet contains both retarding agents but higher glyceryl behenate content, there is no significant difference in shape due to the dissolution medium with/without alcohol. Tablets with a higher content of HPMC show very marked changes in shape due to different dissolution media. However, as shown in Fig. 7, in both cases there is an increased release of TH.

Formulations containing PTX

As shown in Fig. 8, the presence of alcohol in the dissolution medium (40%) has no significant effect on the swelling of the tablet containing PTX and the various retarding components. Tablets containing glyceryl behenate in both dissolution media showed slight cracks on the walls of the cylinder and retained its original shape. On the other hand, there was a significant dose dumping effect in the case of dissolution in the 40% alcoholic medium. As seen in Fig. 8, the presence of HPMC prevents rapid swelling of the interior. No effect of alcohol on PTX release was registered in tablets containing HPMC.

In the case of tablets containing both retarding components, different behavior is observed depending on the ratio of these components in the tablet. If the tablet contains more glyceryl behenate than HPMC, its behavior differs with the use of different dissolution media, as shown in Fig. 8. Alcohol induced dose dumping effect becomes apparent only after two hours of dissolution. If the tablet contains more HPMC than glyceryl behenate, there is a massive swelling and subsequent disintegration of the tablet into small particles in both dissolution media.

4. Conclusions

Extended drug release formulations contain a larger unit dose than immediate release tablets, therefore their release mechanism must be robust to prevent any possibility of uncontrolled drug release leading to dose dumping. The effect of alcohol (20 and 40% v/v) on release mechanism and release rate of ionizing highly water soluble drug (TH) and non-ionizing drug (PTX) from lipophilic, hydrophilic or hydrophilic-lipophilic matrix tablets with extended release was studied. It was found that for the hydrophilic and lipophilic formulation containing TH, the addition of alcohol in the dissolution medium decreases the drug release rate for both formulations and the effect of alcohol is more significant for the lipophilic formulation based on glyceryl behenate. The released amount of PTX from the hydrophilic formulation based on HPMC due to alcohol action is only slightly lower in comparison with acidic medium but the lipophilic formulation based on glyceryl behenate shows a strong alcohol induced dose dumping effect. The alcohol resistance of the hydrophilic-lipophilic formulations with TH and the hydrophilic-lipophilic formulations with PTX containing a higher amount of hypromellose does not reflect the alcohol resistance of the formulations with pure HPMC or glyceryl behenate, only the PTX formulation containing a higher proportion of glyceryl behenate is in accordance with the dissolution behavior of pure lipophilic formulation. Both hydrophilic-lipophilic formulation with TH and more lipophilic formulation with PTX show a significant alcohol dose dumping effect.

Acknowledgement

This work was supported by the grant SGS_2019_004 of The Ministry of Education, Youth and Sports of The Czech Republic and by Colorcon GmbH, JRS PHARMA, GmbH & Co. KG, Acros Organics and Gattefossé, which supplied the samples of the excipients.

Reference

Aburahma M. H., S. M. Baldr-Eldin: Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals. *Expert Opin. Drug Deliv.* 2014, 11 (12), 1865–1883.

Akerlof G.: Dielectric constants of some organic solvent-water mixtures at various temperatures, *J. Am. Chem. Soc.* (1932), 54, 4125–4139.

Bettini, R., Colombo, P., Massimo, G., Gatellani, P.L., Vitali, T., 1994. Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. *Eur. J. Pharm. Sci.* 2, 213–219.

Colombo, P., Bettini, R., Santi, P., DeAscentiis, A., Peppas, N.A., 1996. Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. *J. Control. Release* 39, 231-237.

Costa, P., Sousa Lobo, J.M., 2001. Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.* 13, 123-133.

Dow Chemical Company: METHOCELL Cellulose Ethers. Technical Handbook.
http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_096d/0901b8038096d9ff.pdf?filepath=/pdfs/noreg/192-01062.pdf&fromPage=GetDoc

Driver, S.: Glyceryl Behenate. In Handbook of pharmaceutical excipients, 8th Ed., Sheskey P.J., Cook W. G., Cable C. G. Eds., p. 405-409, London: Pharmaceutical Press, 2017.

DrugBank1: <https://www.drugbank.ca/salts/DBSALT000181>

DrugBank2: <https://www.drugbank.ca/drugs/DB00806>

European Pharmacopoeia (Ph. Eur.), 9th Edition, Council of Europe, Strasbourg, 2017.

FDA (2005a). FDA asks Purdue Pharma to withdraw Palladone. FDA Consum., 39 (5), 2005.

FDA (2005b). Hydromorphone hydrochloride extended release capsules (marketed as Palladone™). FDA alert 07/2005.

Franke, A., Teyssen, S., Harder, H., Singer, M. V., 2004. Effect of ethanol and some ethanolic beverages on gastric emptying in humans. Scand. J. Gastroenterol. 39 (7), 638–644.

Gattefossé 1 : Compritol® 888 ATO A smart solution to sustain drug release. <https://www.gattefosse.com/back/files/Gattefosse%20Compritol%20888%20ATO%20A%20smart%20solution%20to%20sustain%20drug%20release.pdf>

Gattefossé 2. Developing sustained release tablets with Compritol® 888 ATO. Formulation Guidelines, Version 2, 2010.

- Jedinger, N., Khinast, J., Roblegg, E., 2014: The design of controlled-release formulations resistant to alcohol-induced dose dumping – A review. *Eur. J. Pharm. Biopharm.* 87, 217-226.
- Jedinger, N., Schrank, S., Mohr, S., Feichtinger, A., Khinast, J., Roblegg, E., 2015: Alcohol dose dumping: The influence of ethanol on hot-melt extruded pellets comprising solid lipids. *Eur. J. Pharm. Biopharm.* 92, 83-95.
- Keen, J.M., Foley, C.J., Hughey, J.R., Bennett, R.C., Jannin V., Rosiaux, Y., Marchaud, D., McGinity, J.W., 2015: Continuous twin screw melt granulation of glyceryl behenate: Development of controlled release tramadol hydrochloride tablets for improved safety. *Int. J. Pharm.* 487, 72-80.
- Khan, K.A., 1975. The concept of dissolution efficiency. *J. Pharm. Pharmacol.* 27, 48-49.
- Komersová, A., Lochař, V., Myslíková, K., Mužíková, J., Bartoš, M., 2016. Formulation and dissolution kinetics study of hydrophilic matrix tablets with tramadol hydrochloride and different co-processed dry binders. *Eur. J. Pharm. Sci.* 95, 36-45.
- Korsmeyer, R.W., Gurny, R., Doelker, E.M., Buri, P., Peppas, N.A., 1983. Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 15, 25-35.
- Levina, M., Vuong, H., Rajabi-Siahboomi, A.R., 2007: The influence of hydro-alcoholic media on hypromellose matrix systems. *Drug Dev. Ind. Pharm.* 33, 1125-1134.
- Li, C.L., Martini, L.G., Ford, J.L., & Roberts, M., 2005: The use of hypromellose in oral drug delivery. *J. Pharm. Pharmacol.*, 57(5), 533–546.

- Li, F.Q., Hu, J.H., Deng, J.X., Su, H., Xu, S., Liu, J.Y., 2006: In vitro controlled release of sodium ferulate from Compritol 888ATO based matrix tablets. *Int. J. Pharm.* 324, 152-157.
- Missaghi, S., Fegely, K.A. and Rajabi-Siahboomi, A.R., 2009: Investigation of the Effects of Hydroalcoholic Solutions on Textural and Rheological Properties of Various Controlled Release Grades of Hypromellose. *AAPS PharmSciTech* 10, 77-80.
- Rodriguez, C.F., Bruneua, N., Barra, J., Alfonso, D., & Doelker, E. Hydrophilic cellulose derivatives as drug delivery carriers: Influence of substitution type on the properties of compressed matrix tablets. In D. L. Wise (Ed.), *Handbook of pharmaceutical controlled release technology* (pp. 1–30). New York: Marcel Dekker, Inc., 2000.
- Walden, M., Nicholls, F.A., Smith, K.J., Tucker, G.T., 2007. The Effect of ethanol on the release of opioids from oral prolonged-release preparations. *Drug Dev. Ind. Pharm.* 33(10), 1101-1111.

Caption for Figures**Figure 1**

Representative SEM images of tablet surface: lipophilic and hydrophilic formulations F1 – F4 (A – D), width 1 mm.

Figure 2

Representative SEM images of tablet surface: hydrophilic-lipophilic formulations F5 – F8 (A – D), width 1 mm.

Figure 3

Dissolution profiles of lipophilic (F1) and hydrophilic (F2) formulation with TH in acidic (full triangles), 20% hydroalcoholic (half fill triangles) and 40% hydroalcoholic (empty triangles) dissolution medium.

Figure 4

Dissolution profiles of lipophilic (F3) and hydrophilic (F4) formulation with PTX in acidic (full triangles), 20% hydroalcoholic (half fill triangles) and 40% hydroalcoholic (empty triangles) dissolution medium.

Figure 5

Dissolution profiles of hydrophilic-lipophilic formulations with TH (F5, F6) in acidic (full triangles), 20% hydroalcoholic (half fill triangles) and 40% hydroalcoholic (empty triangles) dissolution medium.

Figure 6

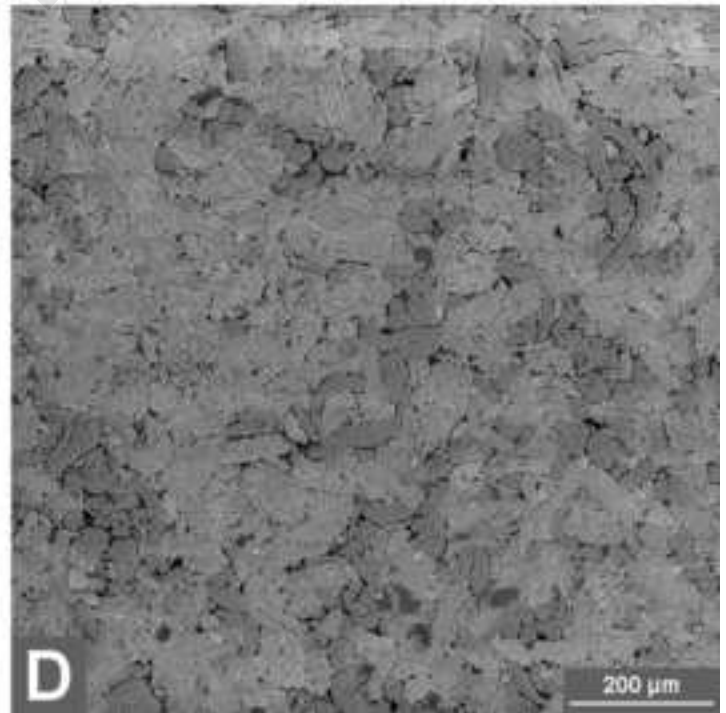
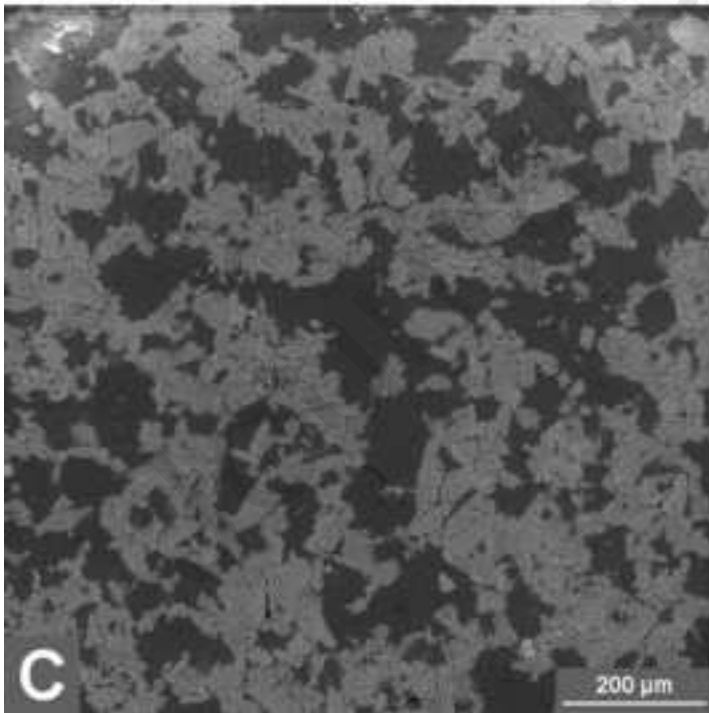
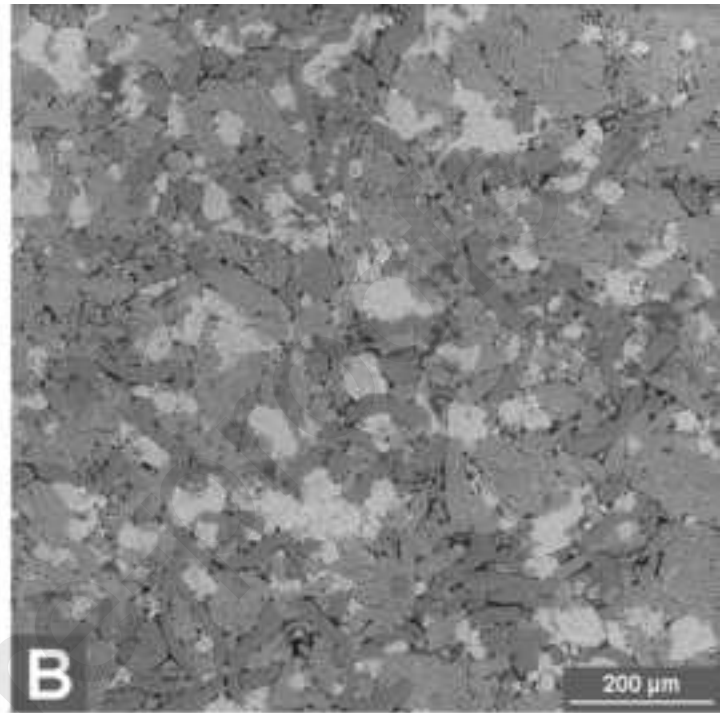
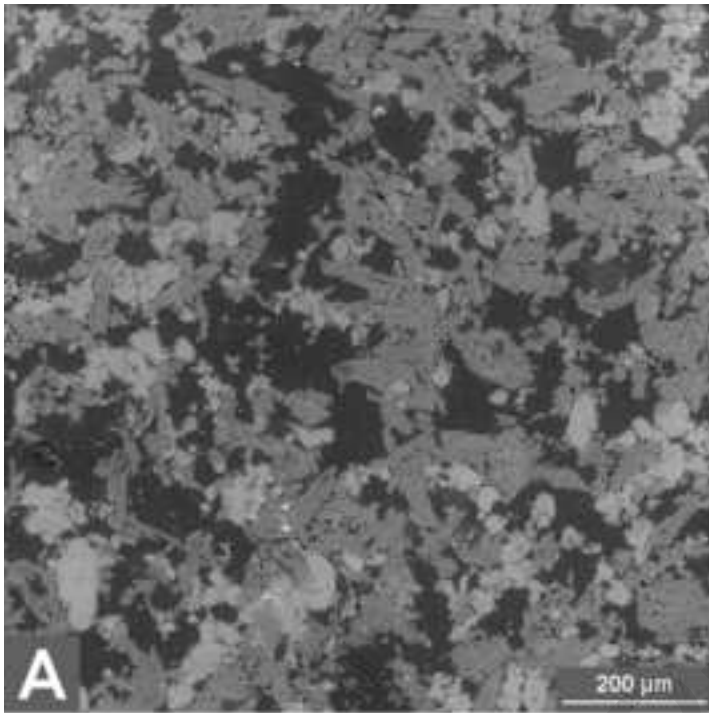
Dissolution profiles of hydrophilic-lipophilic formulations with PTX (F7, F8) in acidic (full triangles), 20% hydroalcoholic (half fill triangles) and 40% hydroalcoholic (empty triangles) dissolution medium.

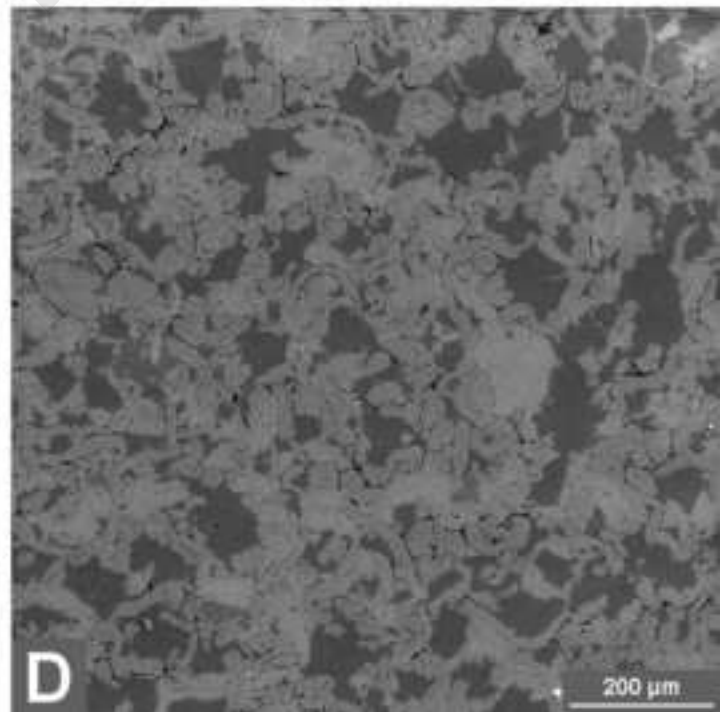
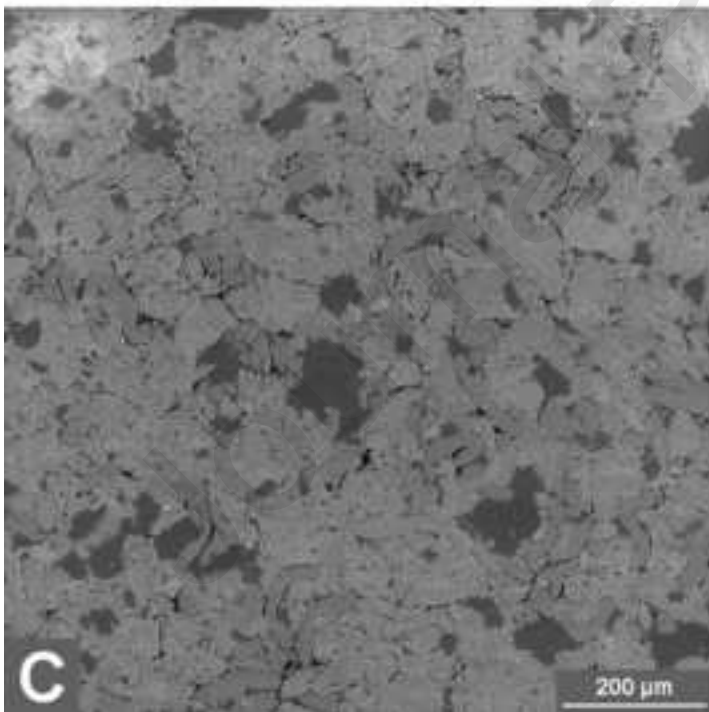
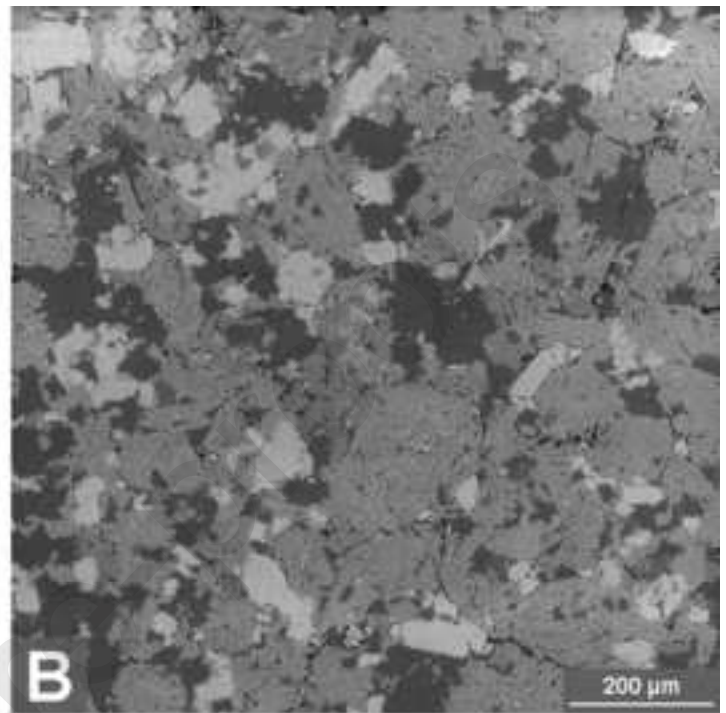
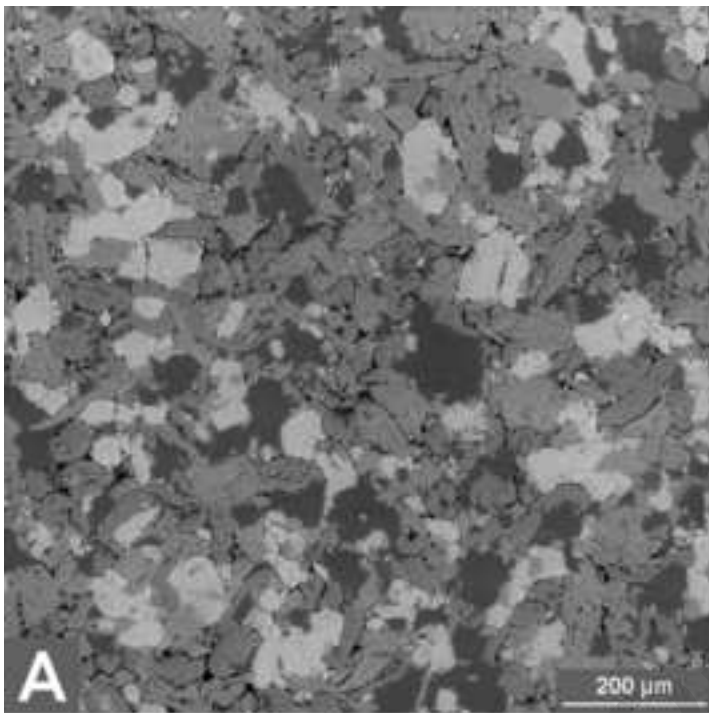
Figure 7

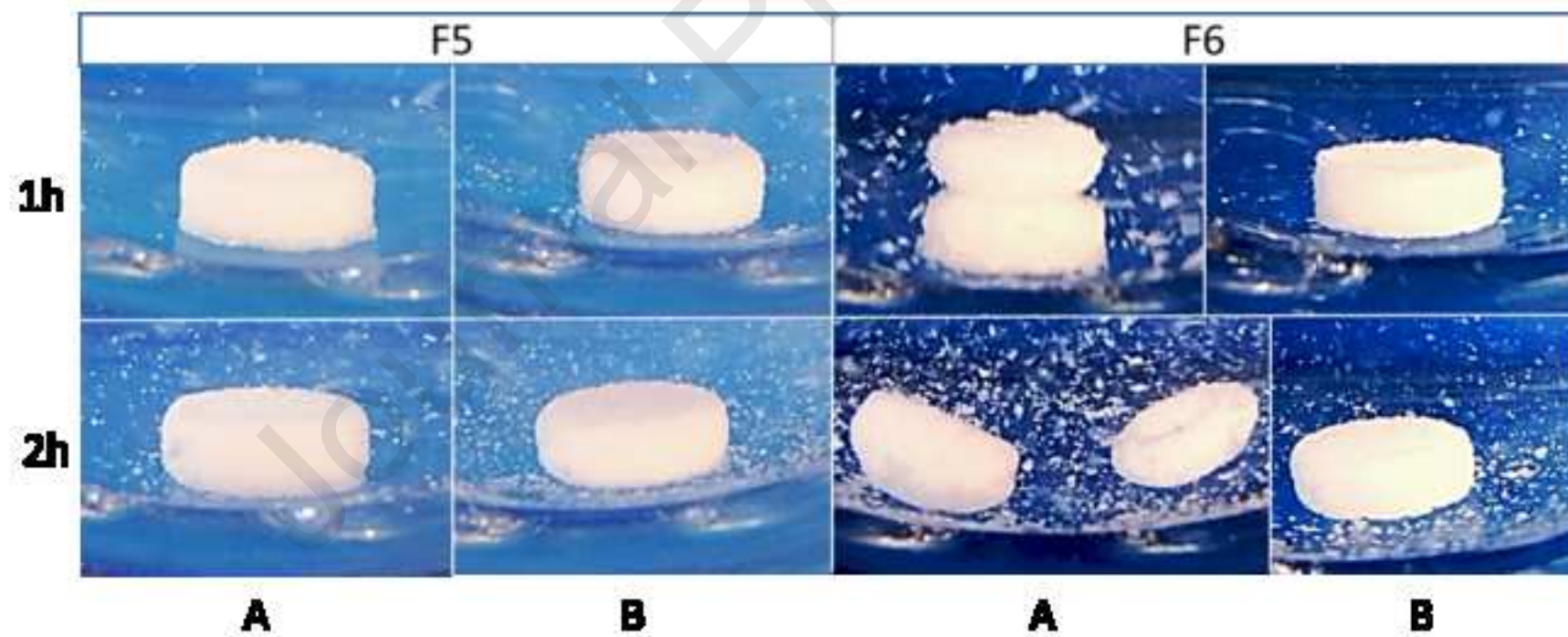
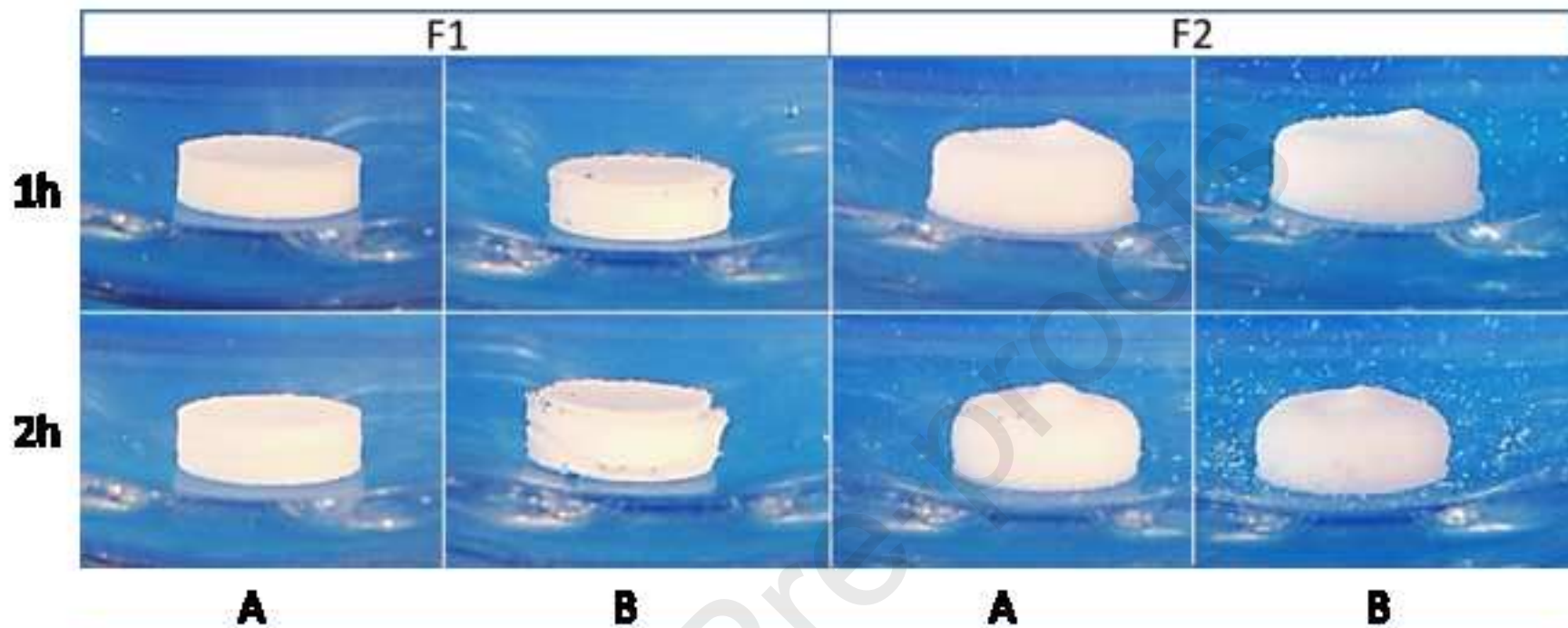
In situ photographic observation of formulations with TH during the dissolution test in alcoholic (A) and acidic medium (B).

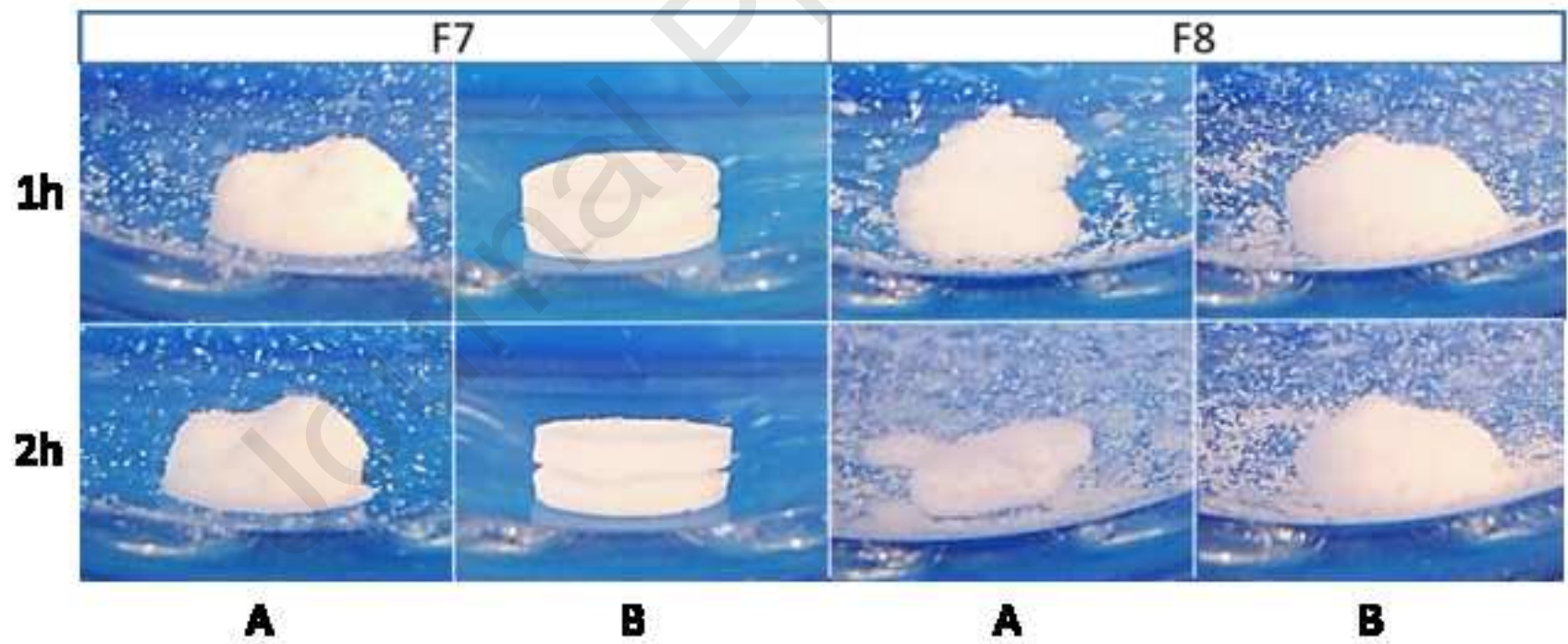
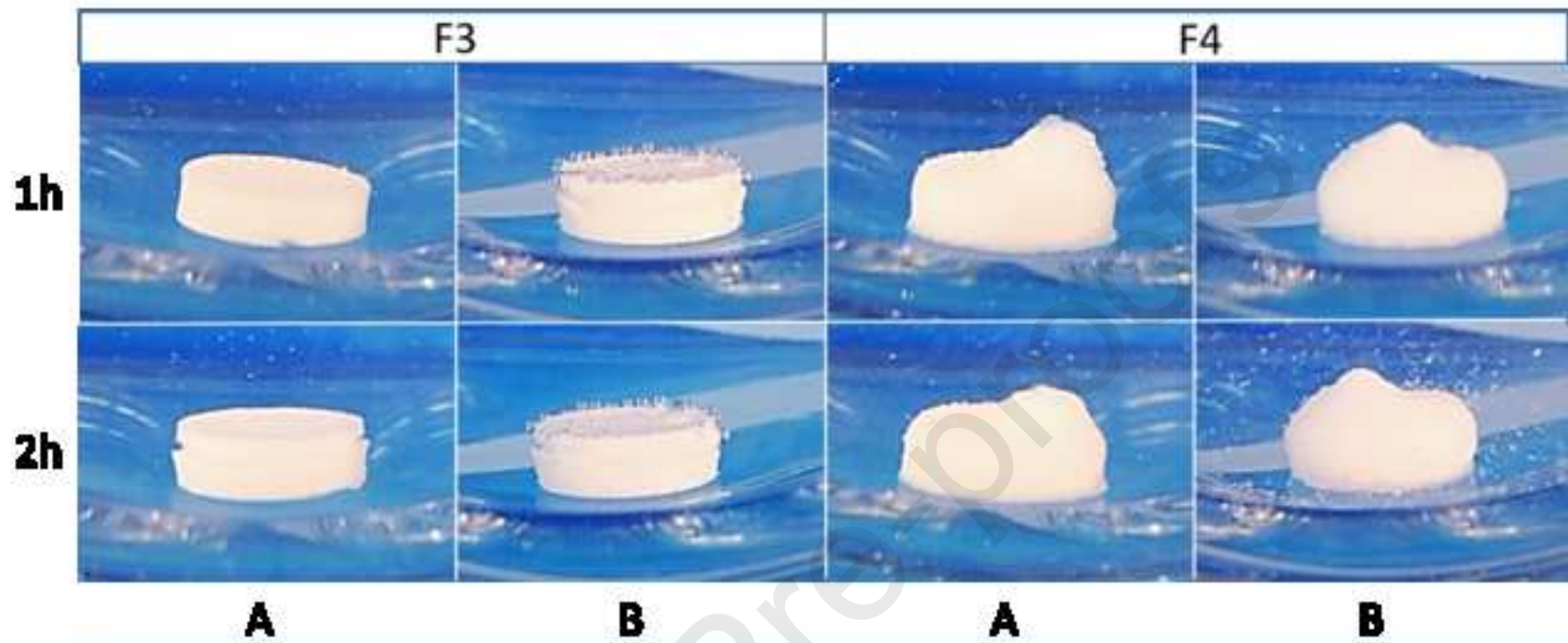
Figure 8

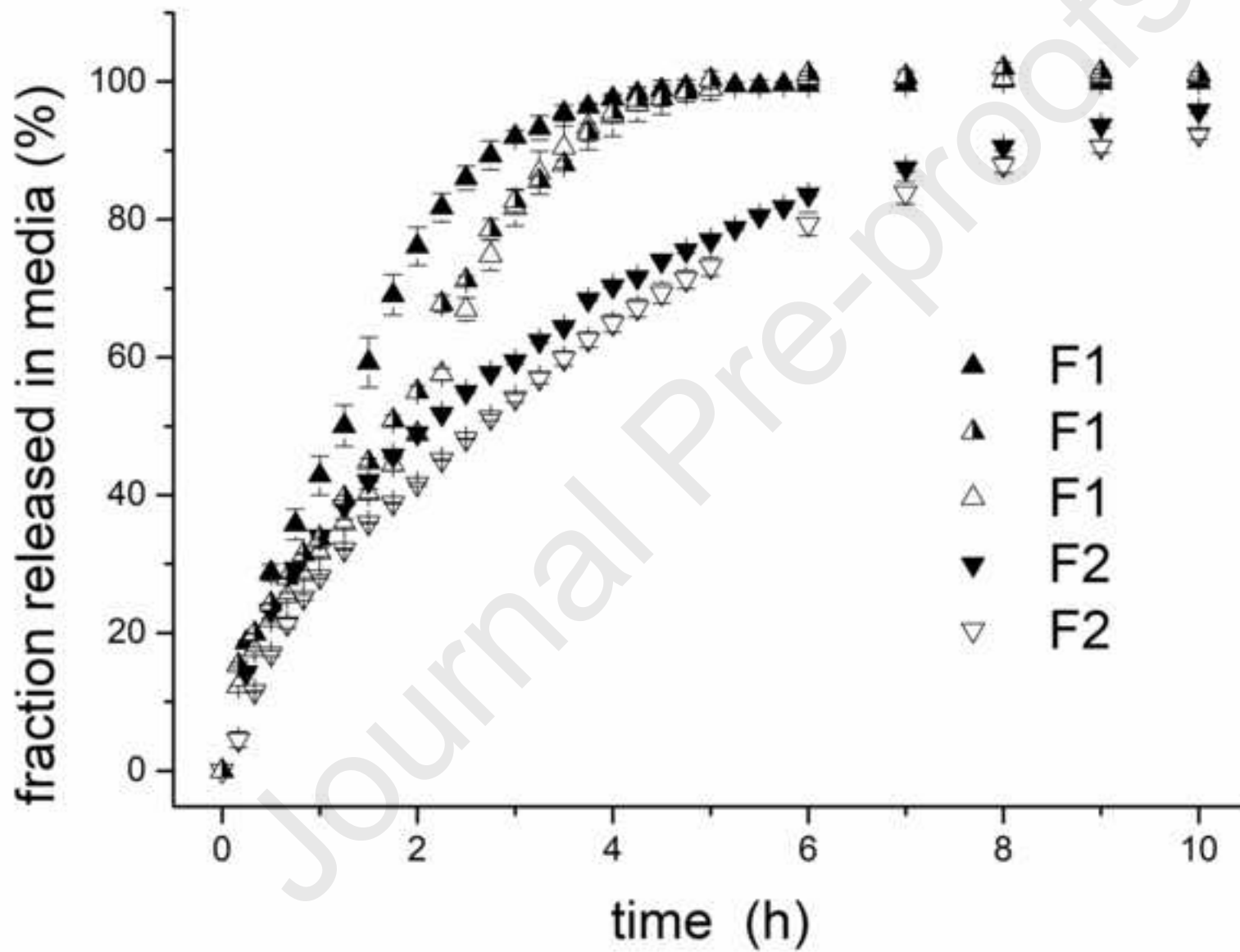
In situ photographic observation of formulations with PTX during the dissolution test in alcoholic (A) and acidic medium (B).

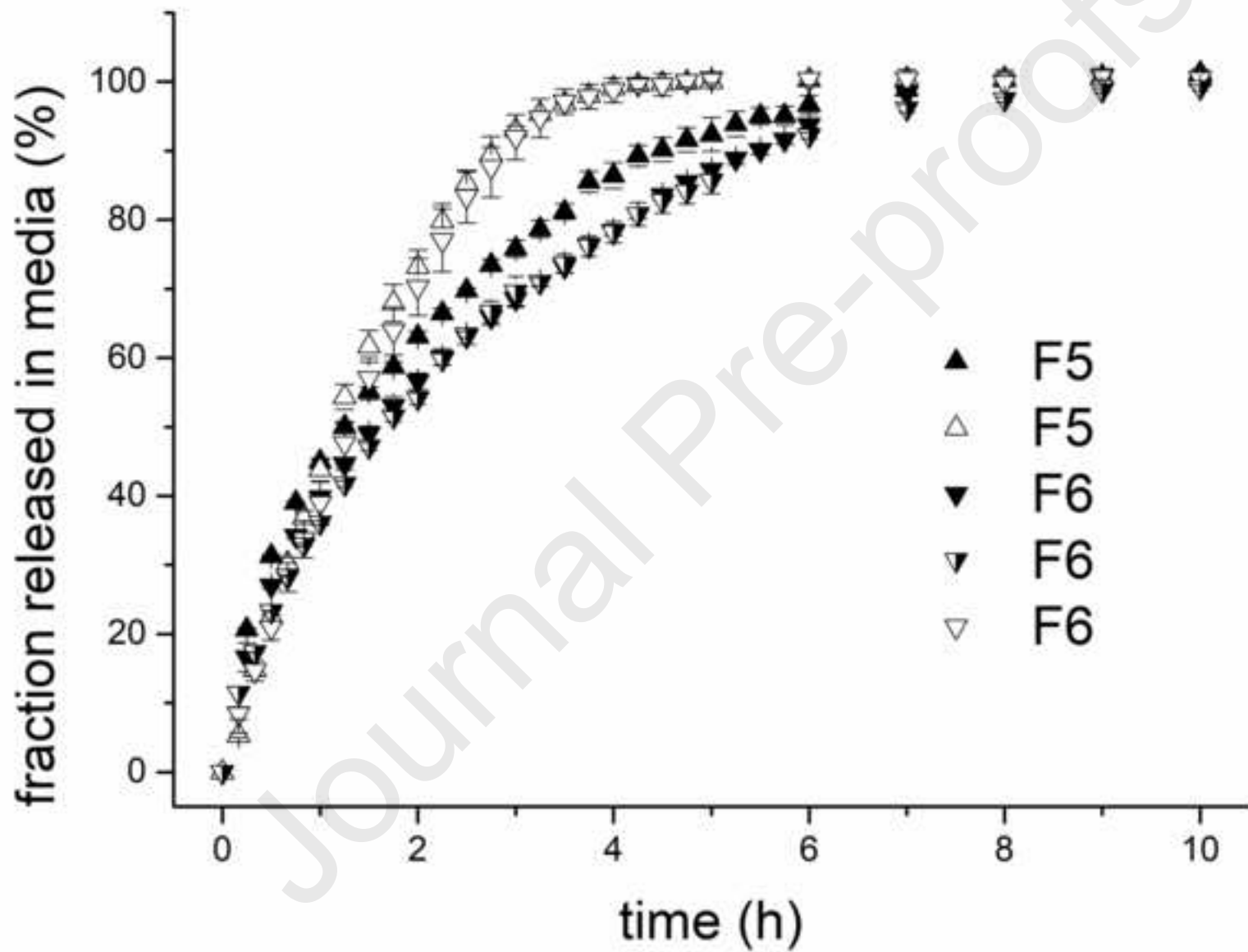


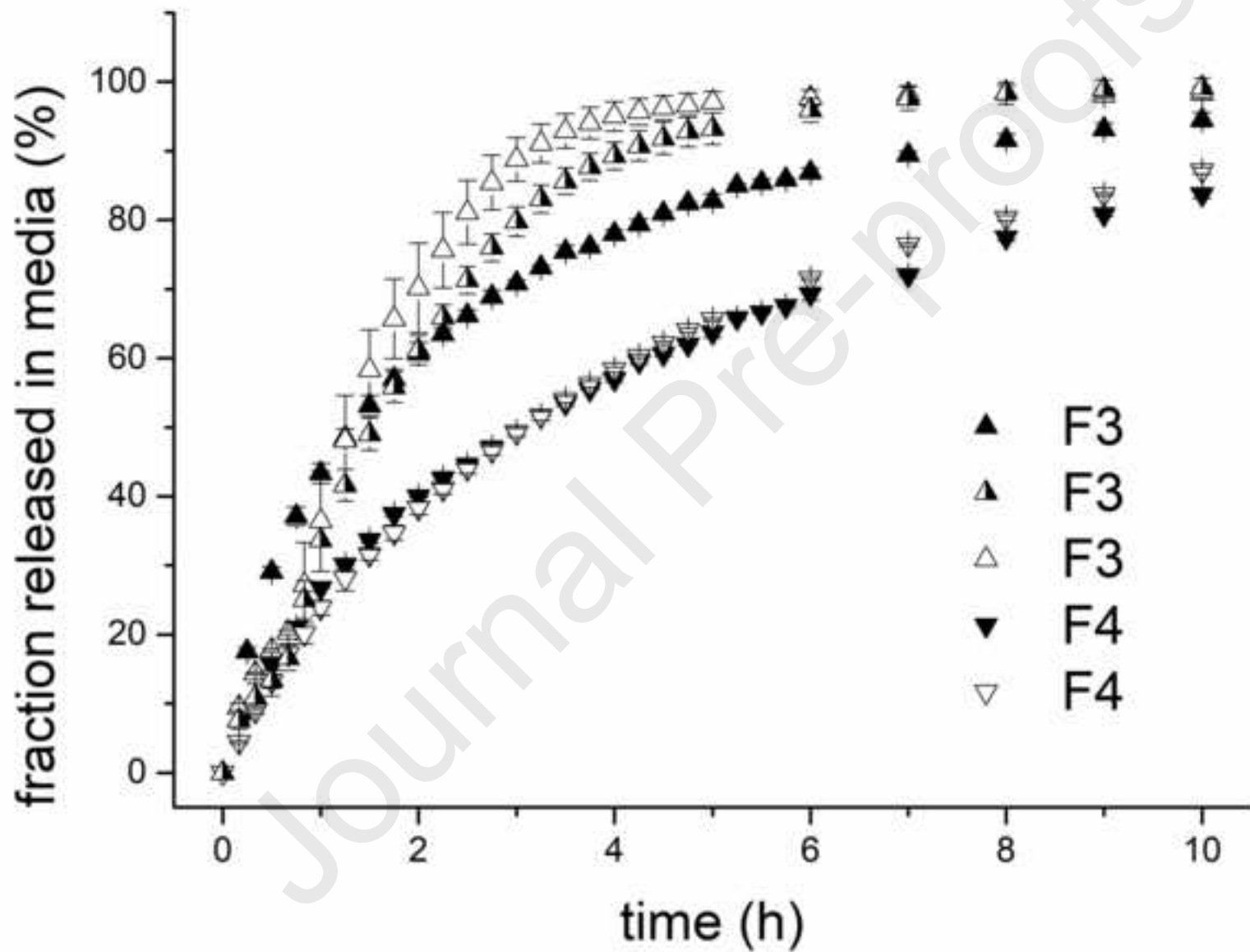


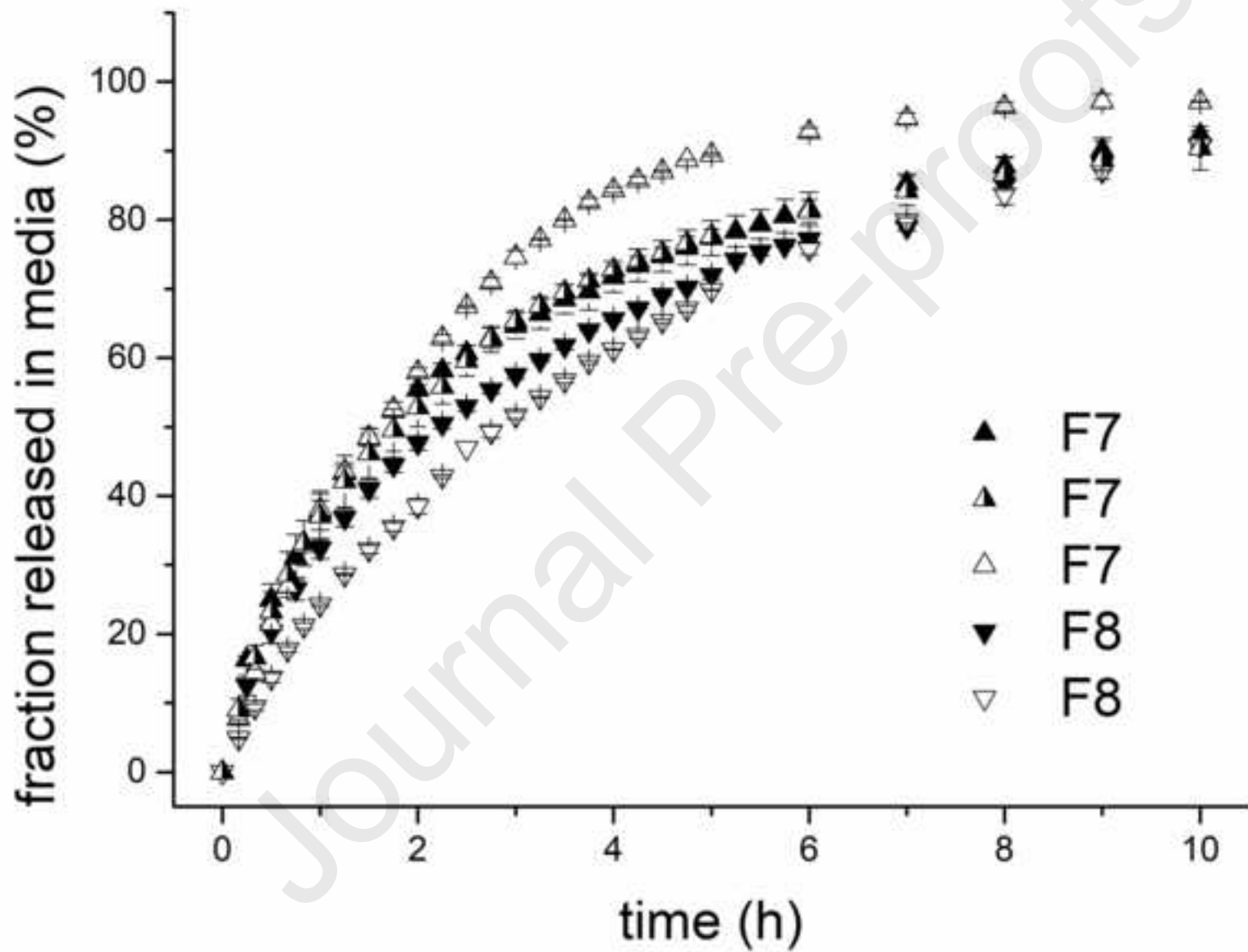












Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Pentoxifylline	-	-	20	20	-	-	20	20
Tramadol hydrochloride	20	20	-	-	20	20	-	-
Methocel™ K4M	-	30	-	30	10	20	10	20
Compritol® 888 ATO	30	-	30	-	20	10	20	10
Magnesium stearate	1	1	1	1	1	1	1	1
Prosolv® SMCC 90	49	49	49	49	49	49	49	49

Table 1

	F1	F2	F3	F4	F5	F6	F7	F8
<i>DE</i> (pH 1.2)	86.16	74.34	81.05	69.30	80.82	76.42	72.03	78.98
<i>DE</i> (20% EtOH)	82.16	72.11	80.54	68.03	82.53	76.75	77.01	70.35
<i>DE</i> (40% EtOH)	80.96	70.65	84.76	67.96	86.07	84.88	79.91	68.76
f_2 (20% EtOH)	47	65	55	83	57	66	62	71
f_2 (40% EtOH)	46	63	45	83	49	41	53	63

Table 2

Caption for Tables

Table 1 Composition of tableting materials (%).

Table 2 The dissolution efficiency (*DE*) and similarity factor f_2 .

Journal Pre-proofs