PEO hot melt extrudates for controlled drug delivery: Importance of the type of drug and loading

Oriane Cantin, Florence Siepmann, Jean-François Willart, Florence Danede, Juergen Siepmann, Youness Karrout

Research article

PEO hot melt extrudates for controlled drug delivery: Importance of the type of drug and loading

O. Cantin,[1] F. Siepmann,[1] J.F. Willart,[2] F. Danede,[2] J. Siepmann,[1,*] Y. Karrout[1]

[1]*Univ. Lille, Inserm, CHU Lille, U1008, F-59000 Lille, France*

[2] *Univ. Lille, UMR CNRS 8207, UMET, F-59655, Villeneuve d'Ascq, France*

[*]corresponding author:

Prof. Juergen Siepmann

University of Lille, College of Pharmacy, Inserm U1008

3 rue du Professeur Laguesse, 59006 Lille, France

juergen.siepmann@univ-lille.fr

Abstract

A variety of poly(ethylene oxide) (PEO)-based matrix tablets loaded with theophylline, ibuprofen or metoprolol tartrate was prepared via hot melt extrusion. The initial drug loading was varied from 10 to 60 %, the PEO polymer molecular weight from 300 to 7,000 kDa. The extrudates were characterized before and after exposure to phosphate buffer pH 7.4 at 37 °C using optical and scanning electron microscopy, X-ray diffraction analysis and drug release measurements. In the case of *metoprolol tartrate*, the resulting drug release rates monotonically increased with increasing initial drug loading, irrespective of the PEO grade. This can be attributed to an "increased porosity effect" upon drug leaching, resulting in less hindrance for subsequent drug release. However, in the case of *theophylline and ibuprofen*, also "limited drug solubility effects" played a role and were even dominant in 7,000 kDa PEO-based extrudates: Upon water penetration into the system, not all of the drug was dissolved. Dissolved and non-dissolved drug co-existed. Importantly, only dissolved drug is available for diffusion. Thus, increasing the initial drug content did not increase the concentration gradients of dissolved drug (and the absolute drug release rates in the absence of porosity effects), but increased the 100 % reference values. Interestingly, in *300 kDa PEO*-based extrudates, "increased porosity effects" dominated for all drugs, and the relative release rates always increased with increasing drug loading. At *1,000 and 7,000 kDa*, the resulting released rate increased or decreased with increasing drug loading, depending of the type of drug.

Keywords: PEO; hot melt extrudate; controlled release; theophylline; metoprolol; ibuprofen

1. Introduction

Poly(ethylene glycol) (PEO) offers an interesting potential as matrix former in controlled release dosage forms [1,2,3,4], including drug abuse deterrent formulations [5]. A variety of PEO grades, differing in polymer molecular weight are commercially available. Drug loaded PEO matrices can be prepared by several processes, such as compression [6,7,8], injection molding [9,10], 3D printing [11] or hot melt extrusion [12,13,14].

Different types of mass transport mechanisms are involved in the control of drug release from PEO-based matrices [15,16,17,18]. Upon contact with aqueous body fluids, water penetrates into the system and dissolves the drug. Once dissolved, the drug molecules/ions diffuse out into the surrounding environment, due to concentration gradients. In addition, the PEO-based polymeric network swells and at the interface with the surrounding bulk fluid, polymer chain disentangle from the 3 dimensional network, followed by diffusion through the surrounding liquid unstirred layer into the often well-stirred liquid: The polymeric matrix dissolves. Depending on the type of drug and drug loading, PEO polymer molecular weight & content as well as manufacturing method (and potentially other factors such as eventual drug – polymer interactions), the underlying drug release mechanisms can be more or less complex. Different zones can often be distinguished during drug release, including a (solid) core, a swollen zone containing dissolved and non-dissolved drug, a swollen zone containing only dissolved drug and an erosion zone. Interesting mathematical models have been reported to quantitatively describe the different phenomena, which can be involved [19,20,21].

Drug abuse is an important health concern [22,23]. In particular, highly dosed controlled release opioid drug products can be fatal, when misused: The benefit of these dosage forms is to reduce the administration frequency for the patient and to allow for an improved pain treatment. For example, the daily dose of an opioid might be administered in the form of one single tablet and the incorporated drug is released slowly during the day. If a polymeric film coating controls drug release from such as system, drug abusers might crush the tablet to

immediately release the entire drug amount. The aim is to experience a “high”, but the risk is to attaint toxic and life-threatening concentrations. This is why a variety of abuse-deterrent formulation strategies have been proposed [24,25,26,27,28]. They are more or less efficient towards different types of abuse techniques, e.g. crushing & swallowing, crushing & snorting, dissolution & injection. PEO-based matrix tablets can be mechanically very stable and difficult to crush. Also, dissolution of PEO tablets in a variety of solvents generally takes a long time, deterring abuse (which is often spontaneous, so rapid methods are preferred).

To intimately blend a drug and a polymer, hot melt extrusion can be used [29,30,31]. This manufacturing process is getting more and more established in the pharmaceutical industry, also at the market scale. A blend of the drug and polymer (and optionally additional excipients, such as plasticizers) are intensively mixed using one or two screws in a cylindrical barrel [32,33,34,35]. The temperature of the latter is accurately controlled. The mechanical shear combined with the increased temperature very much favor an intense mixing of the compounds, potentially at the molecular level (depending for instance on the solubility of the drug in the polymer). The blend is extruded through a die, producing strains, which can for example be cut into tablets or granules, ground & compressed into tablets or shaped into films. In contrast to “drug and polymer powder blending followed by compression”, the degree of mixing is much higher, resulting in a different internal system structure. This can potentially lead to different key properties of the tablets, such as mechanical strength (and, thus, abuse deterrence) and drug release kinetics.

Despite the very interesting potential of PEO-based controlled release tablets prepared by hot melt extrusion, yet the effects of various formulation parameters, such as the importance of the initial drug loading and drug solubility, on system performance are not fully understood. Often, rather surprising or opposite effects are observed when varying one parameter with a specific type of drug or PEO grade compared to another type of drug or PEO grade. The aim of this study was to systematically investigate how the initial drug loading (10, 20, 40 and 60 %),

type of drug (theophylline, ibuprofen and metoprolol tartrate, with substantially different solubilities) and PEO polymer molecular weight (300, 1,000 and 7,000 kDa) affect the resulting drug release rates from hot melt extrudates.

2. Materials and methods

2.1. Materials

Theophylline monohydrate (theophylline; BASF, Ludwigshafen, Germany); ibuprofen (Merck, Darmstadt, Germany); metoprolol tartrate (Ipca, Mumbai, India); poly(ethylene oxide) (PEO): Polyox WSR N-750 (300 kDa), Polyox WSR N-12K (1,000 kDa) and Polyox WSR-303 (7,000 kDa) (Colorcon, Dartford, UK).

2.2. Preparation of hot melt extrudates

Drug and PEO powders were blended for 10 min at 98 rpm in a Turbula T2A mixer (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland). The drug contents and PEO polymer molecular weight were varied as indicated. The blends were hot melt extruded using a Leistritz "Nano 16" apparatus (Leistritz, Nuremberg, Germany), equipped with a co-rotating twin screw (diameter = 16 mm, 4 heating zones, Figure S1 shows the screw configuration, diameter of the die orifice = 4 mm). The screw speed and feed rate were kept constant at 30 rpm and 3 cm^3/min, respectively. The process temperatures were 100-97-95-90 °C (die - zone 3 - zone 2 - zone 1). The extrudates were air-cooled and manually cut into cylinders of 1 cm length.

2.3. In vitro drug release measurements

Drug release from hot melt extrudates was measured in phosphate buffer pH 7.4 (USP 42) using the USP 42 basket apparatus (AT7; Sotax, Aesch, Switzerland) (900 mL, 37 °C,

50 rpm). At pre-determined time points, 3 mL samples were withdrawn (not replaced) and analyzed for their drug content by UV-spectrophotometry (λ = 272, 221 and 220 nm for theophylline, ibuprofen and metoprolol, respectively) (UV-1650; Shimadzu, Kyoto, Japan). Each experiment was conducted in triplicate. Mean values +/- standard deviations are reported.

2.4. Swelling studies

Hot melt extrudates were treated as for the in vitro drug release measurements (*section 2.3.*). At predetermined time points, extrudates were withdrawn, surface water was carefully removed with absorbent tissue (Goma-Camps, La Riba, Spain), and the samples were weighted [*wet mass (t)*] and dried to constant weight in an oven at 60 °C [*dry mass (t)*]. The *dry mass (%)* and *water content (%)* at time *t* were calculated as follows:

$$dry\ mass\ (\%)(t) = \frac{dry\ mass(t)}{dry\ mass(t=0)}\ x\ 100\ \% \quad (1)$$

$$water\ content\ (\%)(t) = \frac{wet\ mass(t) - dry\ mass(t)}{wet\ mass(t)}\ x\ 100\ \% \quad (2)$$

where *dry mass (t = 0)* is the dry mass of the extrudates before exposure to the release medium.

Furthermore, macroscopic pictures were taken using an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with an Axiocam ICc1 camera (Axiovision software; Carl Zeiss MicroImaging, Jena, Germany). Up to three different zones could be distinguished: a transparent gel layer, a non-transparent gel layer and a (solid) core.

2.5. X-ray diffraction studies

X-ray powder diffraction patterns were recorded using a PANalytical X'Pert pro MPD powder diffractometer (PANalytical, Almelo, Netherlands), equipped with a Cu X-ray tube

(λCuKα = 1.54 Å) and the X'celerator detector. Powder samples were placed in a spinning flat sample holder; the measurements were performed in Bragg–Brentano θ-θ geometry. The angular range (2θ) varied from 5 to 60 °, at a speed of 100 s per step (1 step = 0.0167 °).

3. Results and discussion

3.1. Extrudate morphology, swelling and dissolution behavior

Figure 1 shows optical macroscopy pictures of the investigated hot melt extrudates based on different PEO grades, loaded with various amounts of theophylline, ibuprofen or metoprolol tartrate. The photos were taken before exposure to the release medium. As it can be seen, shark skinning was observed in the case of different types of extrudates based on PEO 300 kDa. Importantly, homogeneous systems were obtained in all cases.

The dynamic changes in the tablets' morphology and visual appearance upon exposure to phosphate buffer pH 7.4 are shown in Figures 2, 3 and 4 for extrudates based on PEO 300, 1,000 and 7,000 kDa, respectively. Again, the type of drug and initial drug loading were varied (as indicated). As it can be seen, the systems swelled and eroded at different rates and to different extents. During most parts of the observation period, transparent gels surrounded opaque/white zones. It has to be pointed out that these white/opaque zones consisted of swollen gels and of (solid) cores, at least initially. It has recently been reported how these different zones evolve with time in the case of extrudates based on a variety of PEO grades (100 to 7,000 kDa), which were loaded with 10 % theophylline [36]. The fact that also *swollen* PEO zones were white/opaque can at least in part be attributed to the fact that the drugs were dispersed as particles within these gels. It has recently been shown that in PEO (300, 1,000 and 7,000 kDa)-based hot melt extrudates loaded with 10 % theophylline, the drug was at least partially distributed in the form of drug crystals within the polymer matrices before exposure to the

release medium [36]. Thus, limited drug solubility effects might play a role for the control of drug release. The potential importance of limited drug solubility effects, even in the case of freely water-soluble drugs in highly swollen polymeric matrices and under sink conditions in the well-stirred surrounding bulk fluid, has recently been pointed out [37,38].

Comparing the various pictures in Figures 2 to 4, the following overall observations can be made: (i) With increasing polymer molecular weight, PEO swelling becomes more pronounced and matrix erosion is slowed down, irrespective of the type of drug and initial drug loading. This is expected, since longer polymer chains form more stable 3 dimensional networks and less rapidly disentangle from these systems. (ii) The type and amount of incorporated drug affects the erosion behavior of the matrices: Generally, metoprolol tartrate loaded systems eroded faster than ibuprofen and theophylline loaded extrudates. This can probably be explained by the much higher solubility of this drug in the release medium: 3560 mg/mL at 37 °C, compared to 7.5 and 12 mg/mL in the case of ibuprofen and theophylline, respectively [39,40,41]. Freely water-soluble drugs like metoprolol tartrate can be expected to be released faster from the extrudates, resulting in a more fragile remaining polymeric network and, thus, accelerated system erosion. Comparing the behavior of ibuprofen- and theophylline-loaded extrudates in Figures 2 to 4, it can be seen that there is only a limited/moderate difference: Ibuprofen containing matrices seem to erode somewhat more slowly than theophylline loaded systems. This is consistent with the only limited (absolute) difference in drug solubility in the release medium. For the same PEO grade and same type of drug, an increase in the initial drug loading generally led to a more rapid erosion of the swollen matrix, which can again be attributed to a more fragile remaining polymer network upon drug release.

The X-ray diffraction patterns of ibuprofen- and metoprolol tartrate-loaded 7,000 kDa PEO extrudates (10 and 60 % drug content) before exposure to the release medium are shown in Figures 5a and b. For reasons of comparison, also the diffraction patterns of the raw materials

are shown. Please note that the respective results for theophylline loaded matrices have previously been reported [36]. Importantly, all drug raw materials were crystalline and all hot melt extrudates showed the presence of crystalline drug particles at 60 % drug content. In contrast, no drug crystal peaks were observed in extrudates loaded with 10 % ibuprofen (e.g., at 2 Θ = 6.07, 16.60, 20.10 et 22.30°). Hence, all drug is either dissolved or in the form of amorphous particles in this system. In the case of extrudates loaded with 10 % metoprolol tartrate, drug crystal peaks were observed, but their intensity was lower than 1/6th of the intensity of the peaks in extrudates loaded with 60 % metoprolol tartrate. For theophylline-loaded extrudates, it has previously been reported that the drug was at least partially in the crystalline state at 10 % drug content [36]. The PEO reference powder (as received) showed diffraction peaks, due the semi-crystalline nature of this polymer [42].

3.2. Drug release

Figure 6 shows the resulting drug release kinetics from hot melt extrudates loaded with 10 to 60 % theophylline, ibuprofen or metoprolol tartrate in phosphate buffer pH 7.4. The polymer molecular weight was varied from 300 to 7,000 kDa, as indicated. Interestingly, the following tendencies were observed:

(i) With increasing **metoprolol tartrate** content, the relative release rate monotonically increased, irrespective of the PEO grade. This can be explained by an increased porosity effect, which is schematically illustrated at the top of Figure 7 (please note that accelerated matrix erosion, as discussed above, and potential limited drug solubility effects are neglected in this scheme for reasons of simplicity). Drug particles dissolve and the dissolved drug molecules diffuse out (due to concentration gradients) (non-dissolved drug particles cannot diffuse). The created pores are filled with water. With increasing initial drug loading, the porosity of the remaining swollen hydrogel increases and, thus, the mobility of the remaining drug molecules also increases: It is easier to

diffuse through a water-filled pore than through a polymeric network.

(ii) With increasing **ibuprofen and theophylline** loading the same tendency was observed in **300 kDa PEO** extrudates: The relative release rates monotonically increased with increasing initial drug content, for the same reason. However, the opposite trend was observed in the case of **7,000 kDa PEO**-based matrices: The relative drug release rates decreased with increasing initial drug loading. This can be explained by the dominance of another effect: the "limited drug solubility" effect, which is illustrated at the bottom of Figure 7: In these cases, the initial drug loading is so high that the quantities of water penetrating into the systems are not sufficient to dissolve the entire drug amounts: *Dissolved* and *non-dissolved* drug co-exist. The crosses in Figure 7 represent dissolved drug molecules/ions, the filled circles non-dissolved drug excess (in the form of crystalline or amorphous particles). Importantly, only dissolved drug is available for diffusion. Non-dissolved drug does not diffuse. Thus, increasing the initial drug content does not increase the concentration of *dissolved* drug and, hence, not the resulting *absolute* drug release rate (in the absence of any "increased porosity effect"). However, the 100 % reference value for the *relative* drug release rate increases. Hence, the *relative* release rate decreases. Please note that of course, in addition the above described "increased porosity effect" is involved, but this effect is less important than the "limited drug solubility effect" in these cases. The fact that the *relative* theophylline and ibuprofen release rates increased with increasing drug loading in 300 kDa PEO-based extrudates and decreased in the case of 7,000 kDa-based systems clearly reflects the importance of system erosion: In the case of shorter chain PEO, matrix erosion is dominant, whereas in the case of longer chain PEO, matrix erosion is slowed down and limited drug solubility effects are dominant.

(iii) In the case of extrudates based on **1,000 kDa** PEO, loaded with **ibuprofen or theophylline**, increasing initial drug contents led to very slightly decreasing relative

theophylline release rates and about constant ibuprofen release rates (except for the highest drug loading where an increase was observed). This indicates that these cases are somewhat at the "borderline": The "increased porosity effect" and the "limited drug solubility effect" are of relatively similar importance.

(iv) Comparing the top, middle and bottom rows of the diagrams in Figure 6 for the same type of drug, it can be seen that with increasing PEO polymer molecular weight, the drug release rates decreased, irrespective of the initial drug loading. This is expected, due to the increasing macromolecular entanglement and stability of the polymeric networks.

4. Conclusions

The relative importance of limited drug solubility, polymer swelling and matrix erosion in PEO matrix tablets prepared by hot melt extrusion for the control of drug release strongly depends on the system's composition. In particular, the PEO polymer molecular weight and drug solubility determine whether "increased porosity effects" or "increased limited drug solubility effects" dominate. The relative importance of matrix erosion and drug diffusion/limited drug solubility can be altered by varying the PEO polymer molecular weight and initial drug loading for a given drug.

Declaration of competing interest

One of the authors is the Editor-in-Chief of this journal. The manuscript has been subject to all of the journal's usual procedures, including peer review, which has been handled independently of the Editor-in-Chief.

Figure captions

Fig. 1: Macroscopic pictures of the investigated hot melt extrudates (before exposure to the release medium). The PEO polymer molecular weight, type of drug and loading were varied as indicated.

Fig. 2: Effects of the type of drug and loading on the swelling of theophylline, ibuprofen and metoprolol-containing hot melt extrudates based on **PEO 300 kDa**: Macroscopic pictures of samples after different exposure times to phosphate buffer pH 7.4.

Fig. 3: Effects of the type of drug and loading on the swelling of theophylline, ibuprofen and metoprolol-containing hot melt extrudates based on **PEO 1,000 kDa**: Macroscopic pictures of samples after different exposure times to phosphate buffer pH 7.4.

Fig. 4: Effects of the type of drug and loading on the swelling of theophylline, ibuprofen and metoprolol-containing hot melt extrudates based on **PEO 7,000 kDa**: Macroscopic pictures of samples after different exposure times to phosphate buffer pH 7.4.

Fig. 5: X-ray diffraction patterns of PEO 7,000 kDa-based hot melt extrudates loaded with 10 or 60 %: a) ibuprofen or b) metoprolol tartrate. For reasons of comparison, also the X-ray diffraction patterns of the drug and PEO powders (as received, solid curves) are illustrated.

Fig. 6: Impact of the PEO polymer molecular weight, type of drug and loading on theophylline, ibuprofen and metoprolol release from the investigated hot melt extrudates in phosphate buffer pH 7.4.

Fig. 7: Schematic presentations illustrating the “increased porosity effects” and “limited drug solubility effects” observed in the investigated PEO extrudates. Please note that the schemes are simplified, details are discussed in the text.

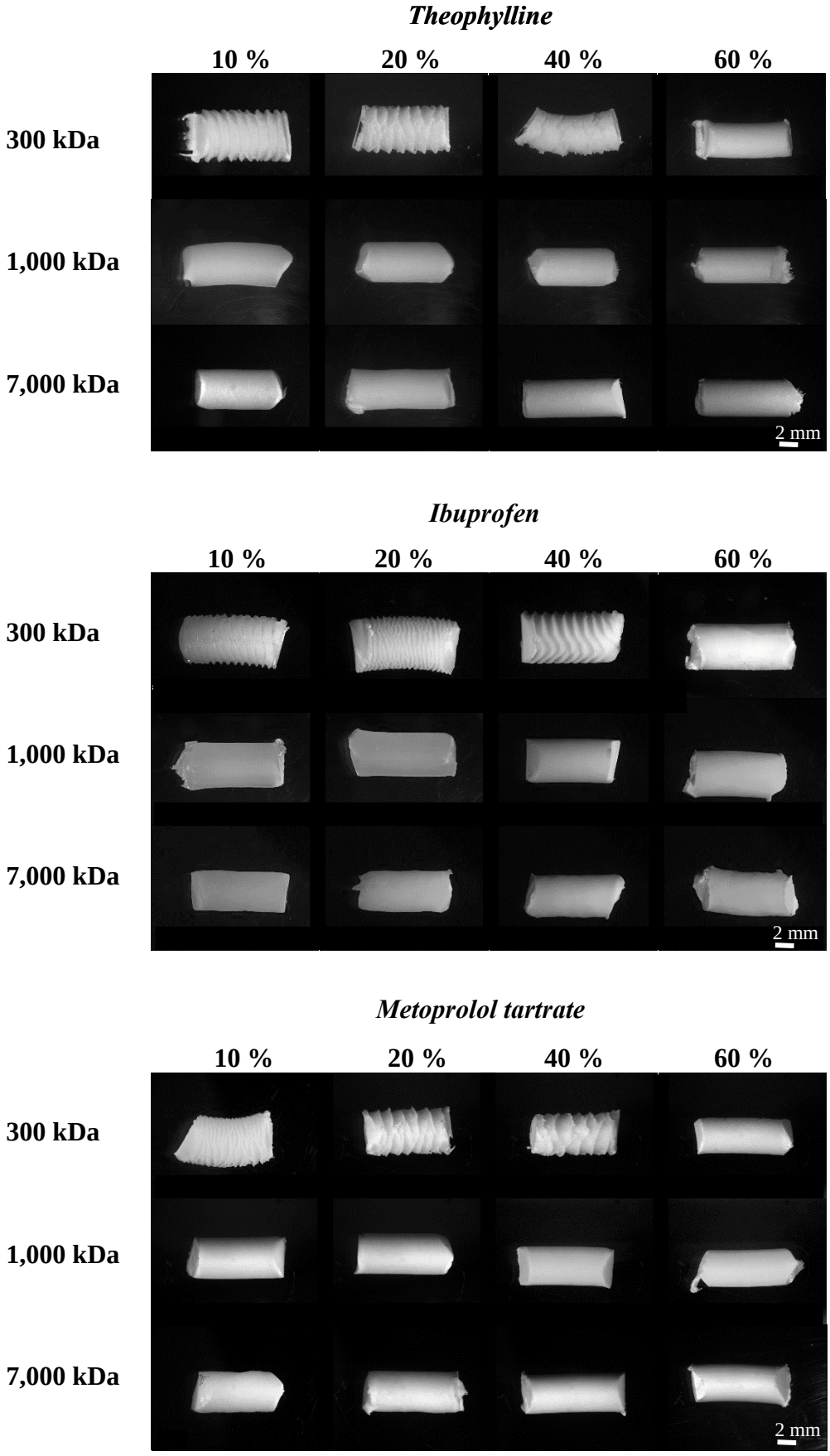
Theophylline
10 %
20 %
40 %
60 %
300 kDa
1,000 kDa
7,000 kDa
2 mm
Ibuprofen
10 %
20 %
40 %
60 %
300 kDa
1,000 kDa
7,000 kDa
2 mm
Metoprolol tartrate
10 %
20 %
40 %
60 %
300 kDa
1,000 kDa
7,000 kDa
2 mm

Figure 1

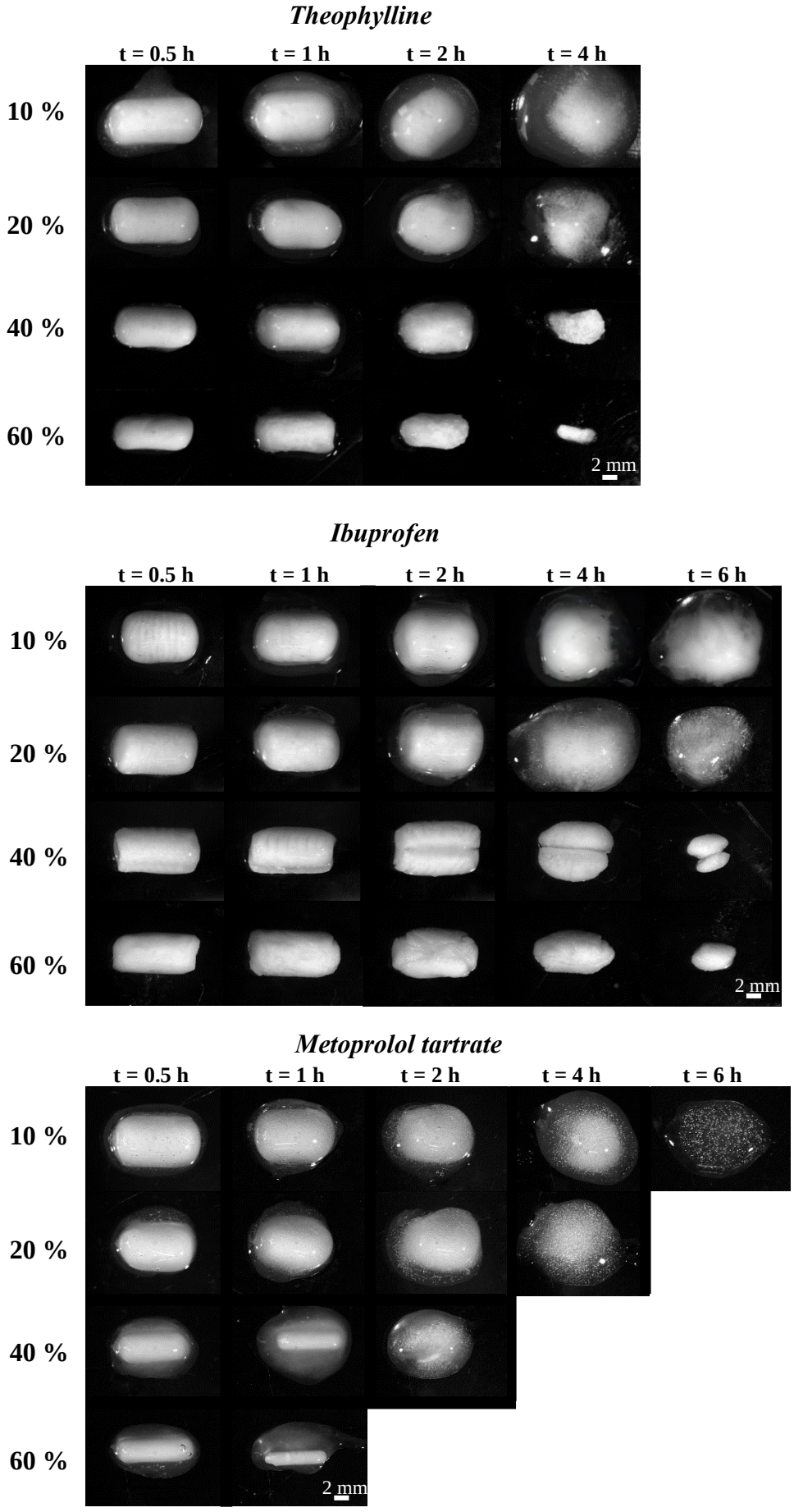
Theophylline
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
10 %
20 %
40 %
60 %
2 mm
Ibuprofen
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
10 %
20 %
40 %
60 %
2 mm
Metoprolol tartrate
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
10 %
20 %
40 %
60 %
2 mm

Figure 2

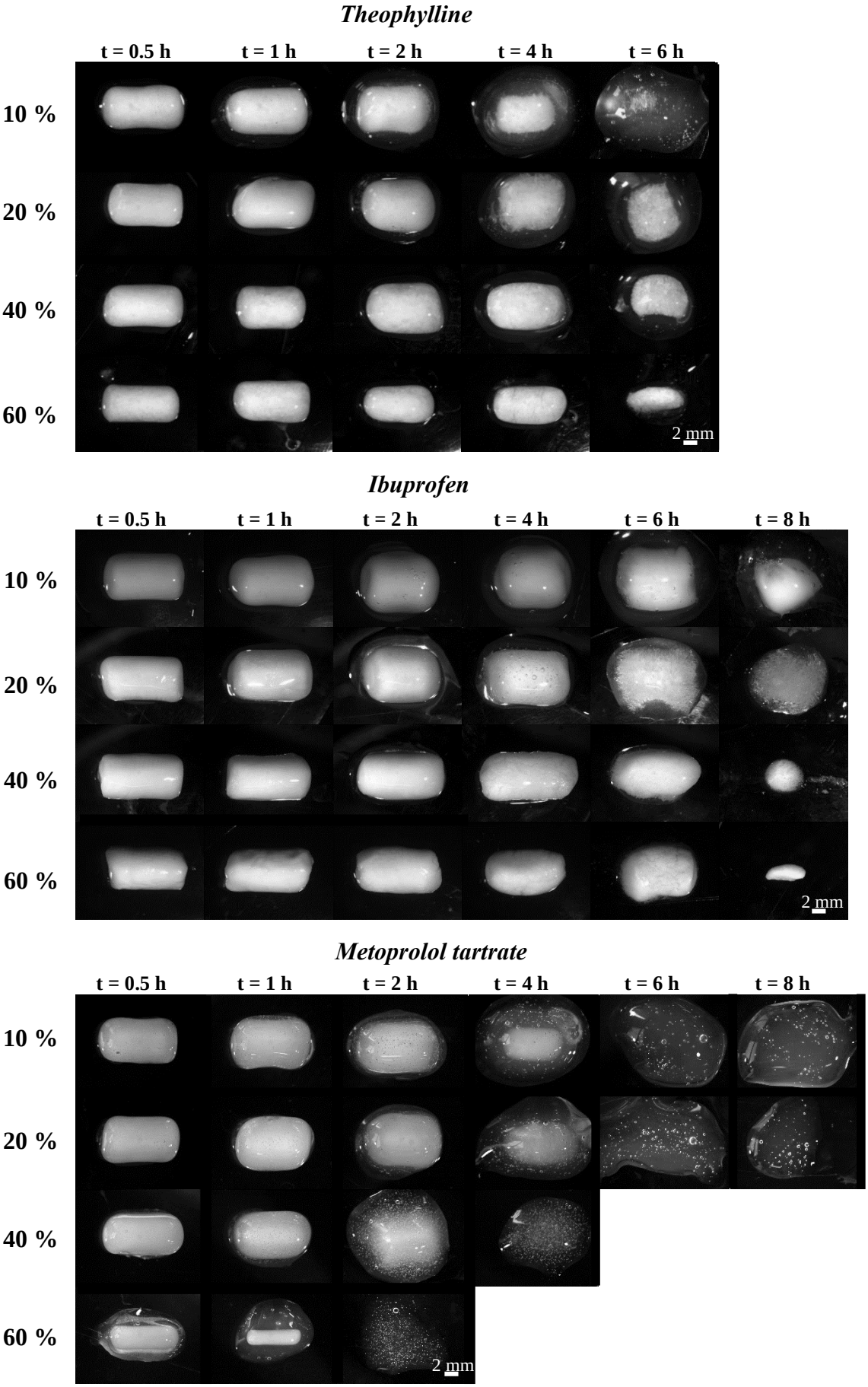
Theophylline
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
10 %
20 %
40 %
60 %
2 mm
Ibuprofen
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
t = 8 h
10 %
20 %
40 %
60 %
2 mm
Metoprolol tartrate
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
t = 8 h
10 %
20 %
40 %
60 %
2 mm

Figure 3

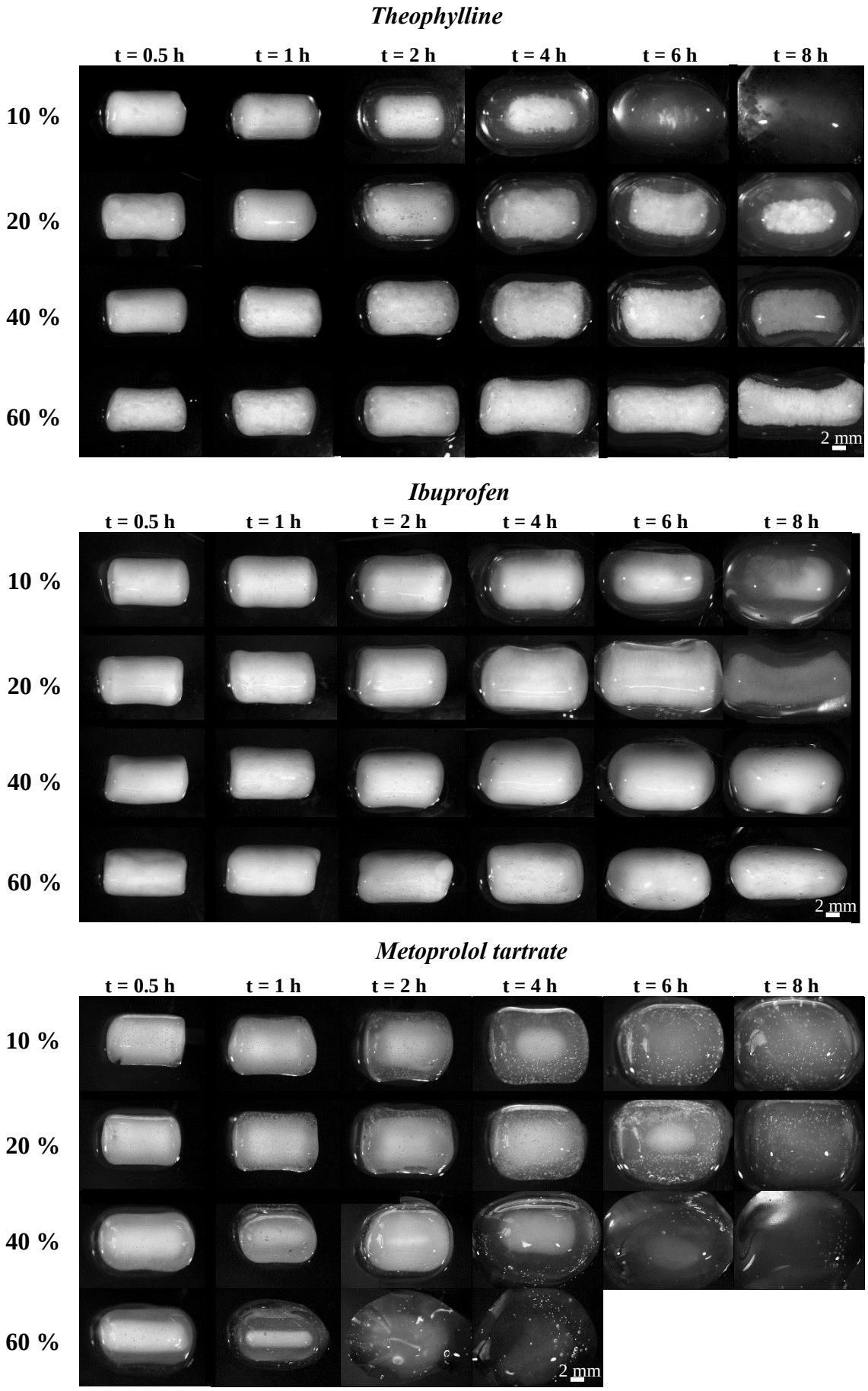
Theophylline
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
t = 8 h
10 %
20 %
40 %
60 %
2 mm
Ibuprofen
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
t = 8 h
10 %
20 %
40 %
60 %
2 mm
Metoprolol tartrate
t = 0.5 h
t = 1 h
t = 2 h
t = 4 h
t = 6 h
t = 8 h
10 %
20 %
40 %
60 %
2 mm

Figure 4

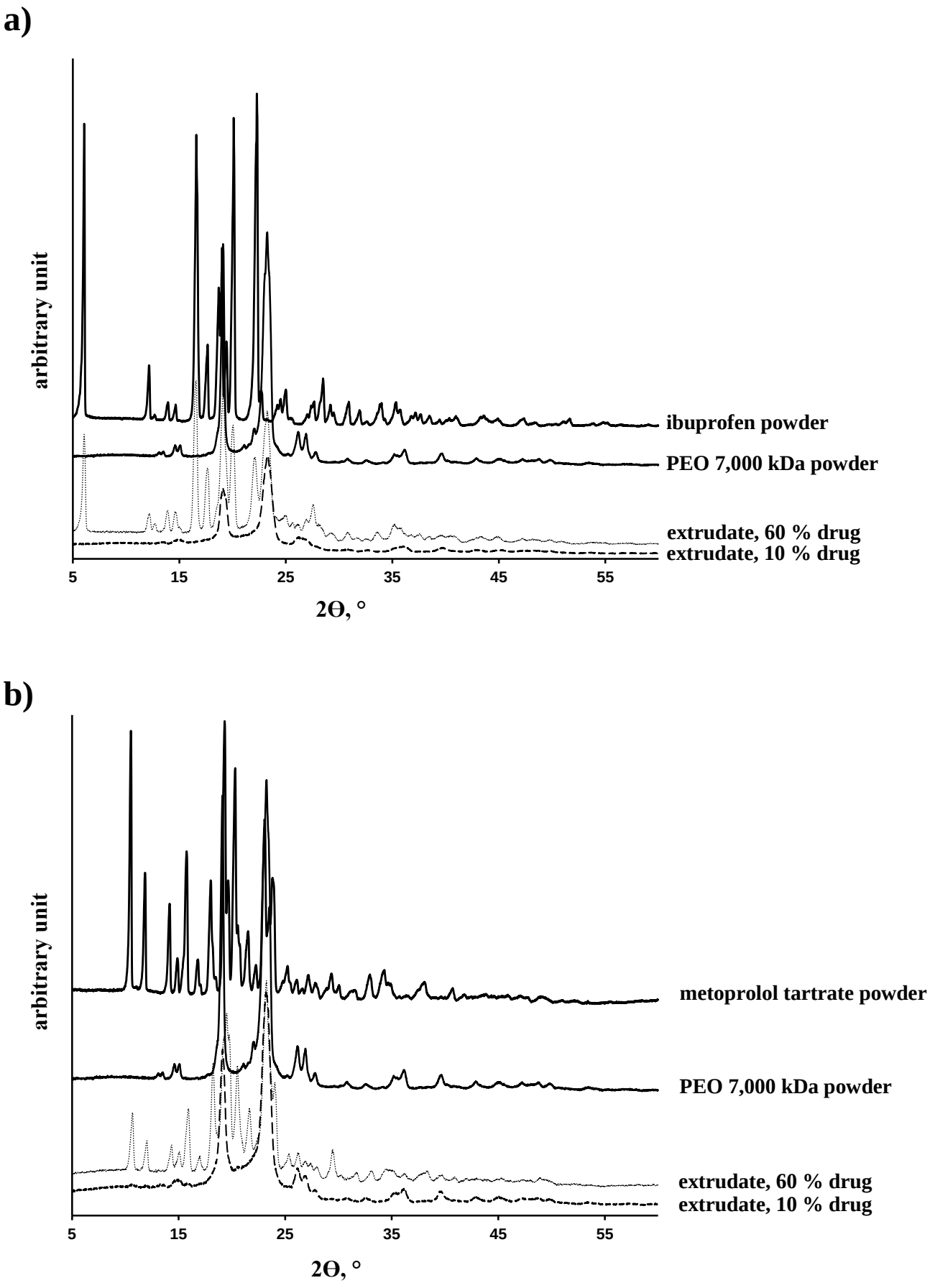
a)
arbitrary unit
ibuprofen powder
PEO 7,000 kDa powder
extrudate, 60 % drug
extrudate, 10 % drug
5
15
25
35
45
55
2Θ, °
b)
arbitrary unit
metoprolol tartrate powder
PEO 7,000 kDa powder
extrudate, 60 % drug
extrudate, 10 % drug
5
15
25
35
45
55
2Θ, °

Figure 5

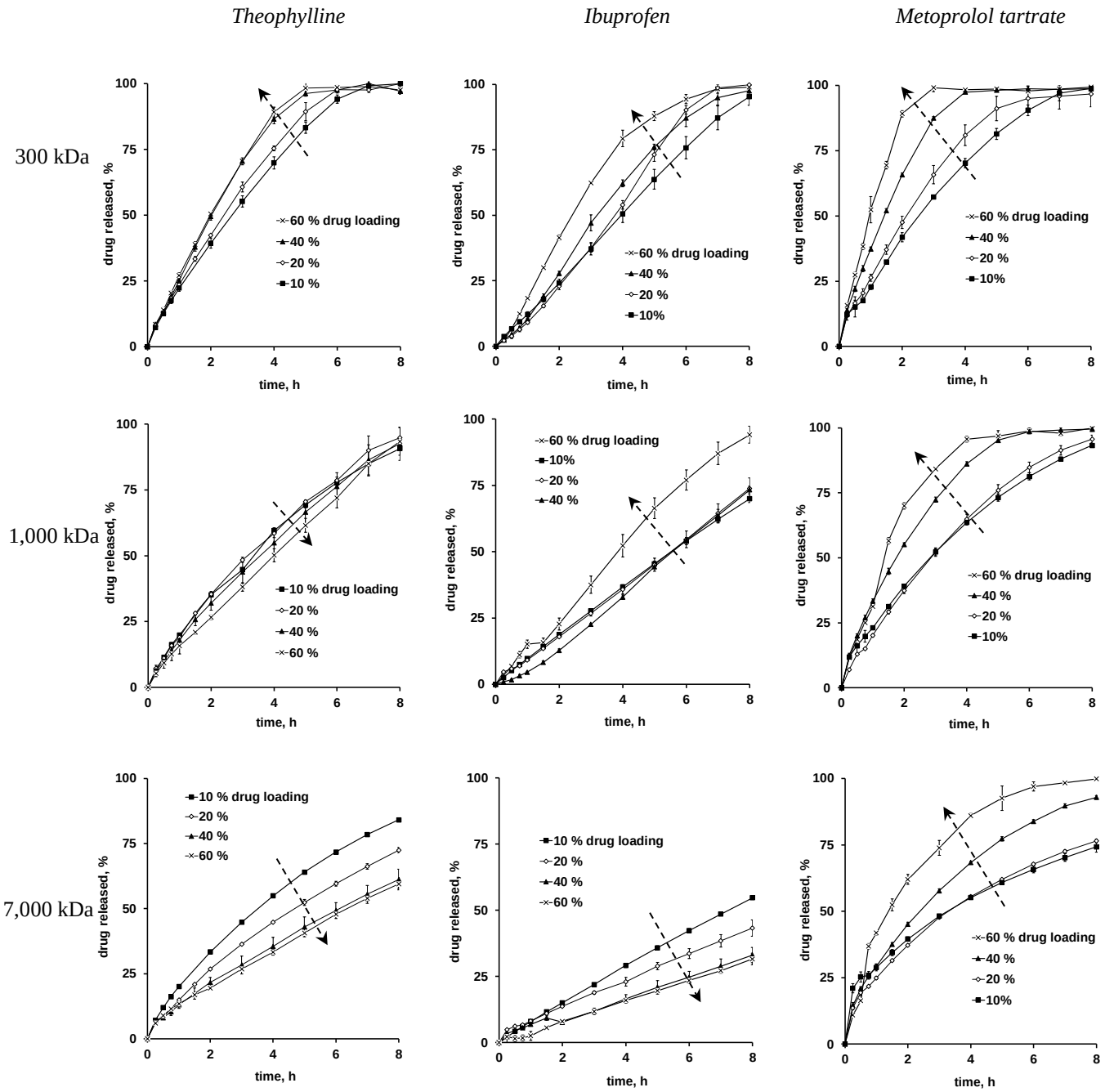
Theophylline
Ibuprofen
Metoprolol tartrate
300 kDa
1,000 kDa
7,000 kDa
drug released, %
time, h
60 % drug loading
40 %
20 %
10 %
10%

Figure 6

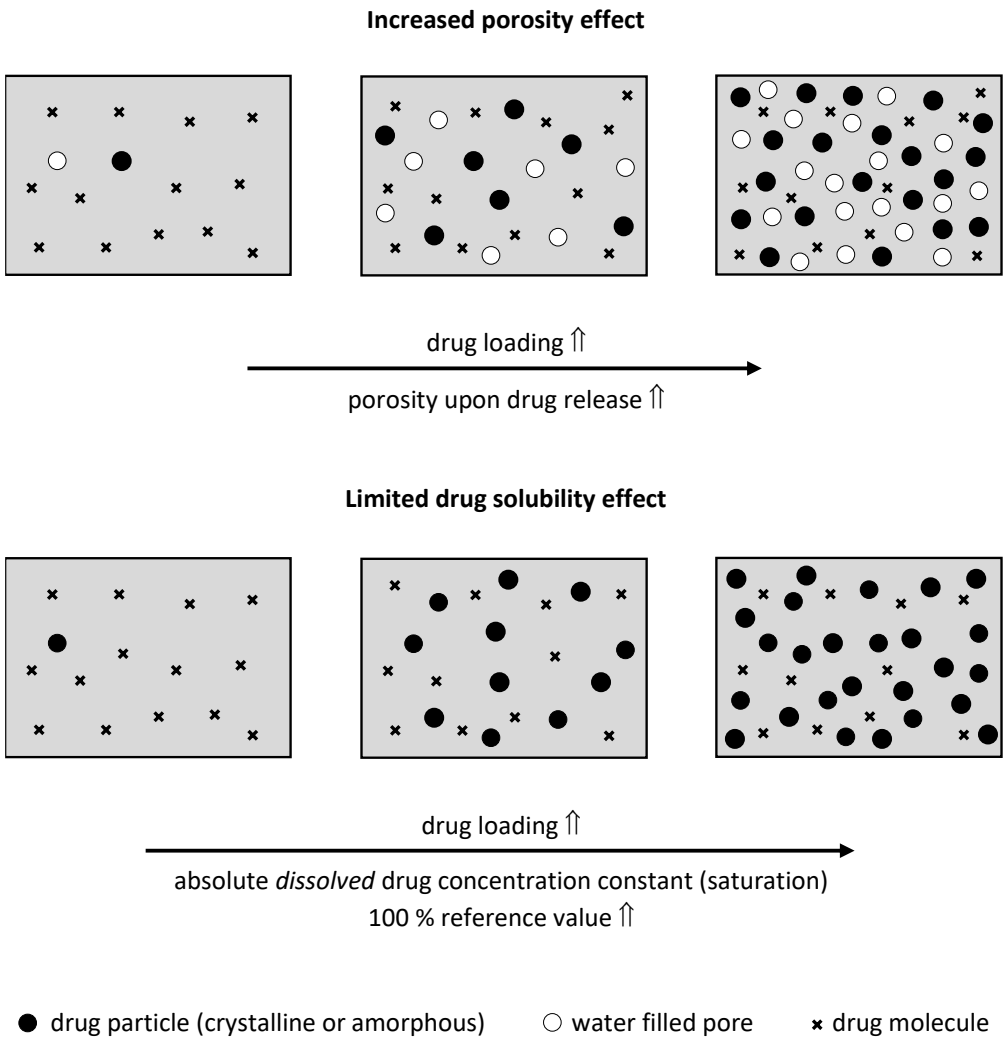
Increased porosity effect
drug loading ⇑
porosity upon drug release ⇑
Limited drug solubility effect
drug loading ⇑
absolute *dissolved* drug concentration constant (saturation)
100 % reference value ⇑
drug particle (crystalline or amorphous)
water filled pore
drug molecule

Figure 7

References

[1] L. Maggi, R. Bruni, U. Conte, High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms, Int. J. Pharmaceut. 195 (2000) 229-238.

[2] L. Maggi, L. Segale, M.L. Torre, E. Ochoa Machiste, U. Conte, Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study, Biomaterials 23 (2002) 1113-1119.

[3] L. Ma, L. Deng, J. Chen, Applications of poly(ethylene oxide) in controlled release tablet systems: a review, Drug Dev. Ind. Pharm. 9045 (2013) 1-7.

[4] F. Zhang, F. Meng, J. Lubach, J. Koleng, N. A. Watson, Properties and mechanisms of drug release from matrix tablets containing poly(ethylene oxide) and poly(acrylic acid) as release retardants, Eur. J. Pharm. Biopharm. 105 (2016) 97-105.

[5] Z. Rahman, Y. Yang, M. Korang-Yeboah, A. Siddiqui, M.A. Khan, Assessing impact of formulation and process variables on in-vitro performance of directly compressed abuse deterrent formulations, Int. J. Pharmaceut. 502 (2016) 138-150.

[6] C.J. Kim, Drug release from compressed hydrophilic Polyox-WSR tablets, J. Pharm. Sci. 84 (1995) 303-306.

[7] L. Yang, G. Venkatesh, R. Fassihi, Characterization of compressibility and compactibility of poly(ethylene oxide) polymers for modified release application by compaction simulator, J. Pharm. Sci. 85 (1996) 1085-1090.

[8] L. Casettari, G. Bonacucina, M. Cespi, D.R. Perinelli, M. Micheli, I. Cacciatore, A. Di Stefano, G.F. Palmieri, Effect of manufacturing temperature and molecular weights on compression, mechanical and dissolution properties of PEO matrix tablets, J. Drug Deliv. Sci. Technol. 32 (2016) 236-240.

[9] S. Deshmukh, A. Paradkar, S. Abrahmsén-Alami, R. Govender, A. Kelly, Injection moulded controlled release amorphous solid dispersions: Synchronized drug and polymer release for robust performance, Int. J. Pharmaceut. 575 (2020) e118908. https://doi.org/10.1016/j.ijpharm.2019.118908.

[10] J. Van Renterghem, H. Dhondt, G. Verstraete, M. De Bruyne, T. De Beer, The impact of the injection mold temperature upon polymer crystallization and resulting drug release from immediate and sustained release tablets, Int. J. Pharmaceut. 541 (2018) 108-116.

[11] A. Isreb, K. Baj, M. Wojsz, M. Isreb, M. A. Alhnan, 3D printed oral theophylline doses with innovative ‘radiator-like’ design: Impact of polyethylene oxide (PEO) molecular weight Int. J. Pharmaceut. 564 (2019) 98-105.

[12] F. Zhang, J.W. McGinity, Properties of sustained-release tablets prepared by hot-melt extrusion, Pharm. Dev. Technol. 4 (1999) 241-250.

[13] M.M. Crowley, F. Zhang, J.J. Koleng, J.W. McGinity, Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion, Biomaterials. 23 (2002) 4241-4248.

[14] T. Monteyne, P. Adriaensens, D. Brouckaert, J.P. Remon, C. Vervaet, T. De Beer, Stearic acid and high molecular weight PEO as matrix for the highly water soluble metoprolol tartrate in continuous twin-screw melt granulation, Int. J. Pharmaceut. 512 (2016) 158-167.

[15] A. Koerner, A. Larsson, A. Andersson, L. Piculell, Swelling and polymer erosion for poly(ethylene oxide) tablets of different molecular weights polydispersities, J. Pharm. Sci. 99 (2010) 1225-1238.

[16] J. Siepmann, F. Siepmann, Mathematical modeling of drug dissolution, Int. J. Pharmaceut. 453 (2013) 12-24.

[17] J. Siepmann, F. Siepmann, Modeling of diffusion controlled drug delivery, J. Control. Release. 161 (2012) 351-362.

[18] J. Siepmann, F. Siepmann, Mathematical modeling of drug delivery, Int. J. Pharmaceut. 364 (2008) 328–343.

[19] P. Borgquist, A. Koerner, L. Piculell, A. Larsson, A. Axelsson, A model for the drug release from a polymer matrix tablet-effects of swelling and dissolution, J. Control. Release 113 (2006) 216-225.

[20] E. Kaunisto, S. Abrahmsen-Alami, P. Borgquist, A. Larsson, B. Nilsson, A. Axelsson, A mechanistic modelling approach to polymer dissolution using magnetic resonance microimaging, J. Control. Release. 147 (2010) 232-241.

[21] E. Kaunisto, M. Marucci, P. Borgquist, A. Axelsson, Mechanistic modelling of drug release from polymer-coated and swelling and dissolving polymer matrix systems, Int. J. Pharmaceut. 418 (2011) 54-77.

[22] D. Pon, K. Awuah, D. Curi, E. Okyere, C.S. Stern, Combating an epidemic of prescription opioid abuse, J. Calif. Dent. Assoc. 43 (2015) 673-678.

[23] Results from the 2018 National Survey on Drug Use and Health (accessed 28 February 2020). U.S. Department of Health and Human Services, https://www.google.com/search?client=firefox-b-d&q=nsduhnationalfindingsreport2018.pdf).

[24] C. Herry, A. Monti, F. Vauzelle-Kervroedan, P. Oury, L. Michel, Reducing abuse of orally administered prescription opioids using formulation technologies, J. Drug Deliv. Sci. Technol. 23 (2013) 103-110.

[25] J. Maincent, F. Zhang, Recent advances in abuse-deterrent technologies for the delivery of opioids, Int. J. Pharmaceut. 510 (2016) 57-72.

[26] Z. Rahman, Y. Yang, M. Korang-Yeboah, A. Siddiqui, X. Xu, M. Ashraf, M. Khan, Assessing impact of formulation and process variables on in-vitro performance of directly compressed abuse deterrent formulations, Int. J. Pharm, 502 (2016) 138-150.

[27] R. Ahmad, H. Omidian, Development and in vitro evaluation of an abuse-deterrent formulation based on a crosslinked starch derivative Int. J. Pharmaceut. 569 (2019) e118602. https://doi.org/10.1016/j.ijpharm.2019.118602.

[28] J.J. Ong, A. Awad, A. Martorana, S. Gaisford, E. Stoyanov, A.W. Basit, A. Goyanes, 3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties, Int. J. Pharmaceut. 579 (2020) e119169. https://doi.org/10.1016/j.ijpharm.2020.119169.

[29] Z. Yang, Y. Hu, G. Tang, M. Dong, X. Lin, Development of ibuprofen dry suspensions by hot melt extrusion: Characterization, physical stability and pharmacokinetic studies, J. Drug Deliv. Sci. Technol. 54 (2019) e101313. https://doi.org/10.1016/j.jddst.2019.101313.

[30] M. Karimi-Jafari, A. Ziaee, J. Iqbal, E. O'Reilly, G. Walker, Impact of polymeric excipient on cocrystal formation via hot-melt extrusion and subsequent downstream processing Int. J. Pharmaceut. 566 (2019) 745-755.

[31] R. Thakkar, R. Thakkar, A. Pillai, E.A. Ashour, M.A. Repka, Systematic screening of pharmaceutical polymers for hot melt extrusion processing: a comprehensive review, Int. J. Pharmaceut. 576 (2020) e118989. https://doi.org/10.1016/j.ijpharm.2019.118989.

32 G. Loreti, A. Maroni, M.D. Del Curto, A. Melocchi, A. Gazzaniga, L. Zema, Evaluation of hot-melt extrusion technique in the preparation of HPC matrices for prolonged release, Eur. J. Pharm. Sci. 52 (2014) 77-85.

33 B. Claeys, A. Vervaeck, X.K.D. Hillewaere, S. Possemiers, L. Hansen, T. De Beer, J.P. Remon, C. Vervaet, Thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding, Eur. J. Pharm. Biopharm. 90 (2015) 44-52.

34 T. Kipping and H. Rein, Continuous production of controlled release dosage forms based on hot-melt extruded gum arabic: Formulation development, in vitro characterization and evaluation of potential application fields, Int. J. Pharmaceut. 497 (2016) 36-53.

35 X.M. Xu, A. Siddiqui, C. Srinivasan, A. Mohammad, Z. Rahman, M. Korang-Yeboah, X. Feng, M. Khan, M. Kshraf, Evaluation of Abuse-Deterrent Characteristics of Tablets Prepared via Hot-Melt Extrusion, AAPS PharmSciTech 20 (2019) # 230.

[36] O. Cantin, F. Siepmann, F. Danede, J.F. Willart, Y. Karrout, J. Siepmann, PEO hot melt extrudates for controlled drug delivery: Importance of the molecular weight, J. Drug Deliv. Sci. Technol. 36 (2016) 130-140.

[37] F. Siepmann, Y. Karrout, M. Gehrke, F. Penz, J.Siepmann. Limited drug solubility can be decisive even for freely soluble drugs in highly swollen matrix tablets. Int. J. Pharmaceut. 526, 280-290, 2017.

[38] J. Siepmann, F. Siepmann. Sink conditions do not guarantee the absence of saturation effects. Int. J. Pharmaceut. 577, 119009, 1-11, 2020.

[39] B. Glaessl, F. Siepmann, I. Tucker, T. Rades, J. Siepmann, Deeper insight into the drug release mechanisms in Eudragit RL-based delivery systems, Int. J. Pharmaceut. 389 (2010) 139-146.

[40] D. Klose, F. Siepmann, J.F. Willart, M. Descamps, J. Siepmann, Drug release from PLGA-based microparticles: effects of the "microparticle:bulk fluid" ratio, Int. J. Pharmaceut. 383 (2010) 123-131.

[41] R. Bodmeier, H.G. Chen, Evaluation of biodegradable poly(lactide) pellets prepared by direct compression, J. Pharm. Sci. 78 (1989) 819-822.

[42] N. Wu, L.S. Wang, D.C.W. Tan, S.M. Moochhala, Y.Y. Yang, Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights, J. Control. Release 102 (2005) 569-581.