Chem. Pharm. Bull.

Note

Investigation of physicochemical drug properties to prepare fine globular granules composed of only drug substance in fluidized bed rotor granulation

Ryohei Mise[a], Yasunori Iwao[a], Shin-ichiro Kimura[b], Yukiko Osugi[a], Shuji Noguchi[a], Shigeru Itai[a,*]

[a]*Department of Pharmaceutical Engineering, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan*

[b]*Pharmaceutical Research & Development, Kissei Pharmaceutical Co., Ltd. 19-48 Yoshino, Matsumoto, Nagano 399-8710, Japan*

*Address correspondence to:

Shigeru Itai, Ph.D. Professor

Department of Pharmaceutical Engineering, School of Pharmaceutical Sciences,

University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan.

Tel: +81 54 264 5614, Fax: +81 54 264 5615

E-mail: s-itai@u-shizuoka-ken.ac.jp (S. Itai).

Summary

The effect of some drug properties (wettability and particle size distribution) on the granule properties (mean particle size, particle size distribution, sphericity, and granule strength) were investigated in a high (>97%) drug-loading formulation using fluidized bed rotor granulation. Three drugs: acetaminophen (APAP); ibuprofen (IBU); and ethenzamide (ETZ) were used as model drugs based on their differences in wettability and particle size distribution. Granules with mean particle sizes of 100–200 μm and a narrow particle size distribution (PSD) could be prepared regardless of the drug used. IBU and ETZ granules showed a higher sphericity than APAP granules, while APAP and ETZ granules exhibited higher granule strength than IBU. The relationship between drug and granule properties suggested that the wettability and the PSD of the drugs were critical parameters affecting sphericity and granule strength, respectively. Furthermore, the dissolution profiles of granules prepared with poorly water-soluble drugs (IBU and ETZ) showed a rapid release (80% release in 20 min) because of the improved wettability with granulation. The present study demonstrated for the first time that fluidized bed rotor granulation can prepare high drug-loaded (>97%) globular granules with a mean particle size of less than 200 μm and the relationship between physicochemical drug properties and obtained granule properties was well determined, indicating the potential for further application of this methodology to various drugs.

Keywords: high drug-loading; globular fine granules; fluidized bed rotor granulation; wettability.

Abbreviations: APAP, acetaminophen; CMA, critical material attribute; CQA, critical quality attribute; ETZ, ethenzamide; IBU, ibuprofen; ICH, international conference on harmonization; GX, Granurex; PSD, particle size distribution; RW, relative width of particle size; SR-CT, cross sectional-computed tomography

1. Introduction

Wet granulation is a technique to enlarge particle size by the coalescence of primary particles with the binder liquid and contributes to improved powder flowability, compaction behavior, and uniformity of drug content. In particular, high drug-loading wet granulation has recently gathered special interest as it can enhance patient compliance through reduction of dosage size, save manufacturing costs, and simplify the granulation process. In addition, if the particle size is less than 200 μm, improvements in the taste and texture of the powders would also be expected. Alternatively, if the particle size is too small, especially if it is less than 100 μm, uniform coating is difficult because of the aggregation of smaller particles via static electrical charge. Therefore, manufacturing high drug-loaded granules with a narrow particle size distribution of approximately 100–200 μm is critically important. To date, there have been many reports of drug-loaded granules prepared using high shear mixing and surfactants [1]; however, the particle sizes of these granules were mostly over 200 μm, and it would be technically quite difficult to prepare high drug-loaded fine granules using just a basic granulation technique.

In the present study, we tried to investigate whether fluidized bed rotor granulation using the multi-functional rotor processor "Granurex® (GX)" can prepare fine granules of a high (> 97%) drug-loading formulation. In previous studies, we succeeded in preparing fine globular granules containing either only excipients or 50% drug, with a mean particle size of less than 200 μm [2-4]. Therefore, we believe that using our recently developed methodology, the preparation of high drug-loaded (>97%) fine globular granules with a narrow size distribution of less than 200 μm should also be possible.

In wet granulation to prepare the granules comprised of only drug substance, the physicochemical properties of the primary drug particles are considered to directly and sensitively affect the granule's properties because of the large amount of the drug in the formulation. In addition, from the International conference on harmonization (ICH) Q8 guideline, the critical

material attribute (CMA) (i.e. solubility, wettability, and intrinsic particle size) of the drugs should be investigated in wet granulation, as the critical quality attribute (CQA) (i.e. granule mean size, sphericity, and strength) are strongly influenced by the CMA of the drugs, indicating that the relationship between the physicochemical properties of the primary drug particles and the obtained granules should be carefully determined. Therefore, in the present study, three model drugs [acetaminophen (APAP), ibuprofen (IBU), and ethenzamide (ETZ)] with different physicochemical properties, including wettability and particle size distribution (PSD) (**Fig. 1A** and **Table 1**) were used to prepare high drug-loaded (>97%) granules with a particle size of less than 200 μm. After the physicochemical properties (mean particle size, PSD, sphericity, granule strength, and angle of repose) of the prepared granules were evaluated, the relationship between the CMA of these model drugs and the CQA was then investigated.

Results and Discussion

When we started granulation using the same methodology we previously reported [4], the primary drug powders essentially adhered to the wall of chamber because of strong intrinsic electrostatic force of drugs and the granulation could not be successfully performed. Therefore, in this study, the rotating speed was firstly set at 300 rpm until 5 min to allow the powders to be wetted enough and reduce the electrostatic force, and then increased to 400 rpm. As a result, using the three drugs, high drug-loaded (>97%) fine granules with a narrow PSD and a mean particle size of 100–200 μm were successfully prepared using a similar amount of binder liquid (**Fig. 1 B and C, Table 2**). From the angle of repose, the flowability of each drug was remarkably improved by granulation (**Table 2**). Furthermore, from the SEM images of the ETZ granules, well-granulated particles were observed in each sieved fraction, even in the fine particle fractions (45–105 μm) (**Fig. 2**), indicating that this methodology can prepare fine granules regardless of the drug properties (wettability and primary PSD). However, the yields of the granules were in the range of 68–78%,

indicating that raw drug materials would have flied and adhered more readily to the walls of upper part of the equipment at the early stage of granulation.

However, IBU and ETZ granules were found to show a higher sphericity (> 0.72) compared with APAP granules (**Fig. 3A-a**). Previously, Hamashita et al. [5] reported that granules containing 40% IBU with a sphericity of more than 0.72 could be successfully coated with ethylcellulose and hydroxypropyl methylcellulose in an agitation fluidized bed, indicating that IBU and ETZ granules can achieve a suitable sphericity and be subjected to a coating process. In addition, a positive relationship in which the sphericity of the granules increased with an increase in the contact angle of the drugs was observed (**Fig. 3A-b**), indicating that the wettability (contact angle) of drugs is a critical parameter affecting the sphericity. We hypothesized the following two spheronization mechanisms dependent on the wettability of drugs. In the case of APAP with a low contact angle, meaning high wettability, the droplets of binder liquid immediately spread and cover the surface of the drug particles and form solid bridges between the drug particles, resulting in granules with an unspherical shape. While, in the case of IBU and ETZ with a high contact angle (low wettability), the binder liquid is present as large droplets localized on the surface of the granules, the droplets can then agglomerate each primary particle together and the granules form into a spherical shape because of the shear force of the rotor or collisions with other agglomerates (**Fig. 3B**).

Furthermore, ETZ granules were found to show the highest granule strength of the three granules (**Fig. 3C-a**). Cross-sectional X-ray computed tomography (SR-CT) image measurement revealed that thick solid bridges (approximately 5 μm) between the primary particles were observed in IBU and ETZ granules indicated as solid arrows, while thin solid bridges (less than 1 μm) were observed in APAP granules indicated as dashed arrows (**Fig. 4**), indicating that the ETZ granules have a rigid internal structure in the central compared with the other drugs. In addition, a positive relationship in which granule strength became higher with increasing relative width of particle size (RW) of the drugs was observed (**Fig. 3C-b**). These results suggest that the sphericity and granule

strength of the granules can be controlled by modifying the surface wettability of the drugs or by changing the PSD of the materials.

The dissolution profiles of granules are shown in **Fig. 5**. APAP granules showed rapid release similar to un-granulated powder. However, as for the poorly water-soluble drugs IBU and ETZ, IBU and ETZ granules showed remarkably rapid release compared with un-granulated powder, reaching more than 80% drug release in 30 min. There are three possibilities to explain this result: reduction of aggregation due to improved powder flow; improved powder wettability because of spreading of the aqueous binder liquid on the surface of primary particle; and increased contact area with the solution because of a large amount of void space formed in the granules and of crushed primary drug particles.

In conclusion, high drug-loaded (>97%) globular granules with a mean particle size of less than 200 μm were successfully prepared and the relationship between CMA (wettability, primary PSD and intrinsic particle size) and CQA (sphericity and granule strength) was well defined, indicating the potential for further application of this methodology to various drugs.

Experimental

Materials

APAP and ETZ were given by the Iwaki Seiyaku Co., Ltd. (Shizuoka, Japan). IBU was given by the BASF Co., Ltd. (Tokyo, Japan). Fumed silica (Aerosil 200®, Nippon Aerosil Co., Ltd., Tokyo, Japan) was used as a glidant. Hydroxypropyl cellulose (HPC-L®, Nippon Soda Co., Ltd., Tokyo, Japan), which is also listed in Japanese Pharmacopoeia 16th Edition (JP 16th), was used as a binder.

Equipment

The granulation experiments were performed in a centrifugal rotating disc processor

(Granurex® GX-20, Freund, Tokyo, Japan), which has been described in detail in our previous paper [3].

Granulation

Each drug was dried for 12 h at 50 °C in an oven, and sieved through a 297 μm sieve. The powders (500 g) and fumed silica (2.5 g) were mixed by hand for 5 min. The powder mixtures (502.5 g) were loaded into the chamber of the processor. The airflow rates at the inlet and the slit were adjusted to 200 L/min. Then, binder liquid containing 5% (w/w) of HPC-L was sprayed in the chamber of the processor, with a total solution mass of 195–250 g being sprayed. The rotational speed was changed from 300 to 400 rpm after 5 min binder spraying. The slit airflow rate was increased manually to 280 L/min in a stepwise manner to coincide with the increase in the bed weight that occurred because of the binder liquid being sprayed into the chamber. Following the complete addition of the binder liquid to the chamber of the processer, a drying process was performed until the particles reached a specified end product temperature (Te), which was defined as being equal to the sum of the product temperature and a ΔT of 10 °C. Details of the operational conditions are given in **Table 3**. Theoretical API content (% *w/w*) was calculated by dividing the mass of the API by that of API, fumed silica and dry binder liquid substance. Yield of granules (% *w/w*) was calculated by dividing the mass of the obtained granules by that of API, fumed silica and dry binder liquid substance.

Particle size distribution

The appropriate granule size distribution was obtained by sieve analysis of approximately 10 g of the granules using testing sieves (Tokyo Screen Co., Ltd., Tokyo, Japan) ranging in size from 45 to 1000 μm. The mean particle size of the granules was obtained from these data. Relative width of particle size (RW) was calculated by $(d_{90}- d_{10}) / d_{50,}$ where d_{10}, d_{50}, and d_{90} are 10%, 50%, and

90% of the accumulated particle size under a screen, respectively. The mean particle size and RW of the drugs were analyzed by laser light scattering at an atomizing air pressure of 0.3 MPa (laser micron sizer, LMS-2000e, SEISHIN Co., Ltd., Tokyo, Japan).

Contact angle of the water droplet

The wettability of each drug was determined by measurement of the contact angle of the water droplet. A sample (200 mg) of each drug was compressed using a hydraulic single punch tableting machine at 100 MPa. A 10 µL water droplet was dropped on the tablet and the contact angle was measured by the $\theta/2$ method.

Angle of repose

The angle of repose was measured with a protractor. The heap of drug powder or granules was formed by passing the sample through a funnel.

Sphericity

Sphericity was determined by image analysis of size fractions from 75–212 µm using WinROOF image analysis software (Version: 5.5, MITANI Co., Ltd., Tokyo, Japan). Three-hundred granules were chosen from each formulation randomly for this analysis. The sphericity of the granules was defined by their roundness (Pt/Pr), where Pt is the theoretical perimeter of a perfectly spherical granule of the same area as the real particle, and Pr is the real granule perimeter.

Granule strength

Granule strength was determined using a particle hardness tester (GRANO, Okada Seiko Co., Ltd., Tokyo, Japan). Thirty granules were chosen from each formulation randomly for this measurement. The descent speed of tip to break a granule was 50 µm/s. The granule strength was

199 defined by the Hiramatsu equation ($2.8P/\pi D_p^2$), where P is the pressed force to break a granule (N),
200 and D_p is the granule size (μm).
201
202 **Scanning electron microscopy**
203 The surface structures of the powders and granules were morphologically assessed using a
204 scanning electron microscope (SEM) (JSM-5310LV, JEOL, Tokyo, Japan). The samples were placed
205 on double-sided adhesive tape, which had been previously applied to an aluminum stub. The excess
206 samples were removed, and the samples were sputter coated with platinum/palladium under argon
207 gas prior to imaging.
208
209 **Synchrotron X-ray CT (SR-CT) measurement**
210 The internal structures of granules with each drug were measured by SR-CT. SR-CT
211 measurements were performed using a micro-CT instrument [6, 7] installed at the undulator beam
212 line BL37XU of SPring-8 (Hyogo, Japan), which has been described in detail in our previous paper
213 [8]. X-ray linear attenuation coefficient (LAC) values between 0 and 70 cm^{-1} are shown in 8-bit
214 grayscale in the images of granules, and LAC values higher than 70 cm^{-1} are in white.
215
216 **Drug release test**
217 The release behavior of API from granules with a diameter of 105–150 μm for each
218 formulation was examined in accordance with the paddle method listed in the JP 16th. The test
219 medium was 900 mL of distilled water. The medium temperature was set to 37.0 ± 0.5 °C and the
220 paddle speed was 50 rpm. At each time point, a 5 mL aliquot of the test solution was withdrawn and
221 replaced with an equal volume of buffer solution, and the aliquot was passed through a membrane
222 filter (pore size: 0.45 mm; Toyo Roshi Kaisha Ltd., Tokyo, Japan). The amount of API released into
223 the medium was quantitatively determined by UV absorptiometry (UV-mini, Shimadzu, Kyoto,

Japan) at 220 and 290 nm for IBU and ETZ, respectively.

Statistics

Statistical analyses were performed using the Student t-test. A probability value of $p < 0.05$ was considered to indicate statistical significance.

Acknowledgements

We are extremely grateful to Freund Corporation to lend us the Granurex® for this study, and would also like to thank Dr. Takeru Iwamura at the Department of Chemistry and Energy Engineering, Faculty of Engineering, Tokyo City University for SEM analysis. The synchrotron radiation experiments at BL37XU were performed with the approval of the Japan Synchrotron Radiation Research Institute (JASRI; proposal no. 2014A1205, 2012A1670, and 2012B1807).

Conflict of Interest

The authors declare no conflict of interest

References

[1] Cai, L., Farber, L., Zhang, D., Li, F., Farabaugh, J., 2013. Int. J. Pharm. 441, 790–800.

[2] Kimura, S., Iwao, Y., Ishida, M., Uchimoto, T., Miyagishima, A., Sonobe, T., Itai, S., 2010. Int. J. Pharm. 399, 244–247.

[3] Kimura, S., Iwao, Y., Ishida, M., Noguchi, S., Itai, S., Uchida, S., Yamada, M., Namiki, N., 2014. Chem. Pharm. Bull. 62, 309–315.

[4] Iwao, Y., Kimura, S., Ishida, M., Mise, R., Noguchi, S., Itai, S., Uchida, S., Yamada, M., Namiki, N., 2015. Chem. Pharm. Bull. 63, 1–7.

[5] Hamashita, T., Nakagawa, Y., Aketo, T., Watano, S., 2007. Chem. Pharm. Bull. 55, 1169–1174.

[6] Uesugi, K., Hoshino, M., Takeuchi, A., Suzuki, Y., Yagi, N., 2012. Proc. SPIE 8506, 850601.

[7] Suzuki, Y., Takeuchi, A., Uesugi, K., 2011. J. Vac. Soc. Jpn. 54, 47–55.

[8] Noguchi, S., Kajihara, R., Iwao, Y., Fujinami, Y., Suzuki, Y., Terada, Y., Uesugi, K., Miura, K., Itai, S., 2013. Int. J. Pharm. 445, 93–98.

[9] Shiino, K., Iwao, Y., Miyagishima, A., Itai, S., 2010. Int. J. Pharm. 395, 71–77.

[10] Xu, L., Li, S.M., Sunada, H., 2007. Chem. Pharm. Bull. 55, 1545–1550.

257 **Table 1. Physicochemical properties of drugs used in this study.**

	APAP powder	IBU powder	ETZ powder
Solubility in water (µg/mL)	20 x 10^3*	30**	< 100
Mean particle size (µm)	39.9	40.6	24.7
Relative width of particle size (RW) (-)	4.5	1.8	6.2
Contact angle (°)	43.7±7.1	57.3±4.2	63.0±1.7
Angle of repose (°)	57.0±1.2	61.0±1.5	56.0±1.2

258 * Shiino et al. [9]. ** Xu et al. [10].

259

260

261 **Table 2.** Physicochemical properties of granules.

	APAP granules	IBU granules	ETZ granules
Amount of binder liquid (g)	213±32	217±7	210±3
Theoretical API content (%)	97.4±0.3	97.4±0.1	97.3±0.0
Mean granule size (µm)	123.7±3.8	113.7±8.5	140.7±15.3
RW (-)	1.1±0.1	1.4±0.1	1.4±0.2
Angle of repose (°)	33.0±1.5	33.0±0.6	31.0±0.6
Yield of granules (%)	75.5±7.5	68.0±5.0	76.3±12.4

262

263

264

265

266

267

268 **Table 3.** Granulation conditions.

Operational condition	Granulation		Drying
Operational time	0–5 (min)	≥5 (min)	
Rotor speed (rpm)	300	400	200
Inlet air temperature (˚C)	60	60	60–80
Slit air volume (L/min)	200	200–280	240
Atomizing air pressure (MPa)	0.3	0.3	0.1
Binder flow rate (g/min)	7	7	-

269

270

Figure captions

Figure 1. Granule growth behavior (A: SEM images of each drug, B: SEM images of each granule ranging from 105 to 150 μm, C: PSD of drugs and granules).

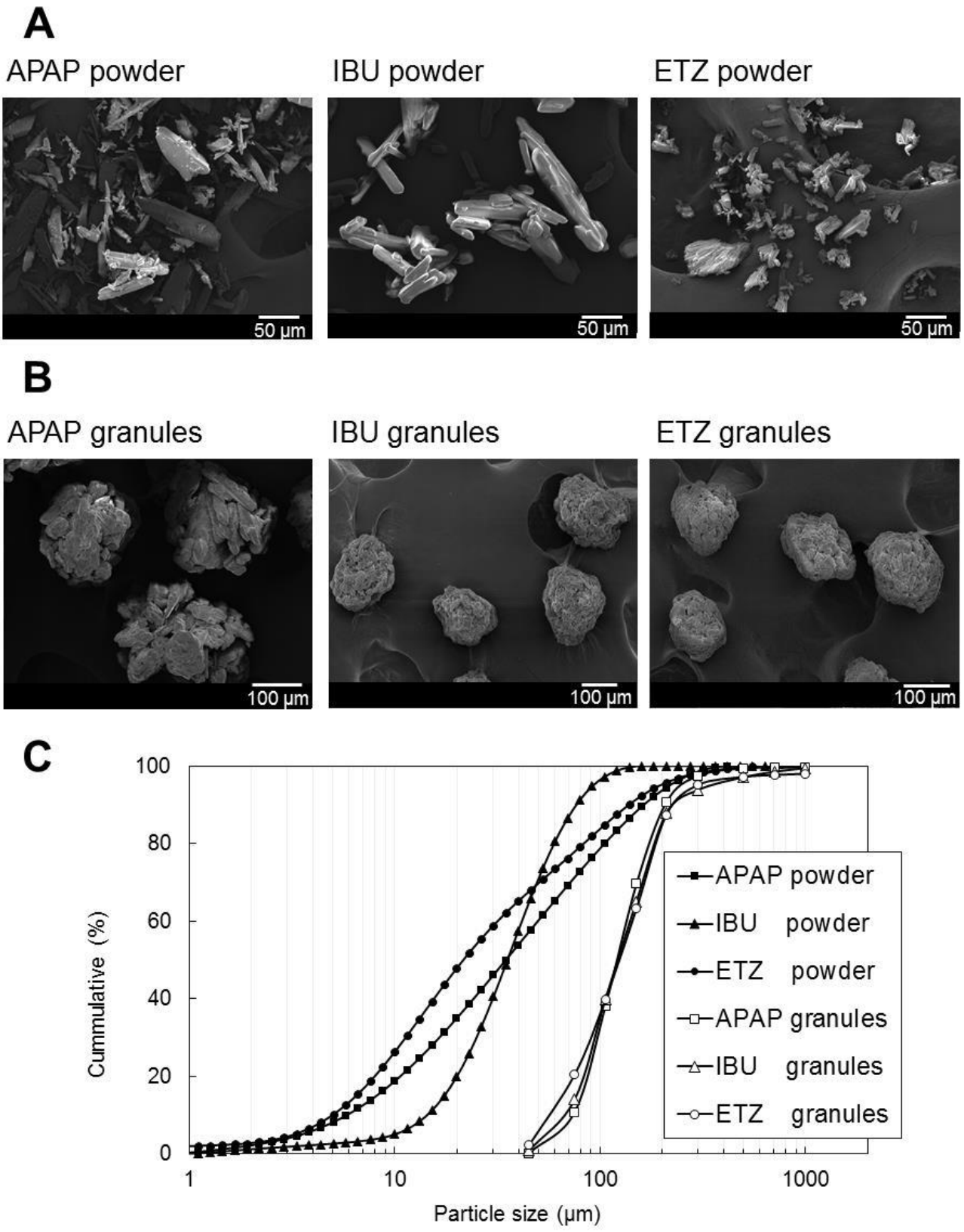
Figure 2. SEM images of ETZ powder and granules in each sieving fraction: A) ETZ powder and ETZ granules with a particle size ranging from B) 45 μm to 75 μm; C) 75 μm to 105 μm; D) 105 μm to 150 μm; E) 150 μm to 210 μm; F) 210 μm to 300 μm.

Figure 3. Relationship between the physicochemical properties of the drugs and the granules (A: a) sphericity of granules and b) relationship between wettability and sphericity, B: hypothesis of granulation mechanisms in drugs with different wettabilities, C: a) granule strength and b) relationship between RW and granule strength).

Figure 4. Cross-sectional X-ray CT images of the granules with a particle size ranging from 105 to 210 μm: A) APAP granule; B) IBU granule; C) ETZ granule and D-F) magnified images of each granule. Solid and dashed arrows indicated the solid bridges of the granules.

Figure 5. Dissolution profiles of the drugs (powder and granules); A) APAP, B) IBU and C) ETZ.

Fig. 1


A
APAP powder
IBU powder
ETZ powder
50 µm
50 µm
50 µm
B
APAP granules
IBU granules
ETZ granules
100 µm
100 µm
100 µm
C
Cummulative (%)
Particle size (µm)
0
20
40
60
80
100
1
10
100
1000
APAP powder
IBU powder
ETZ powder
APAP granules
IBU granules
ETZ granules

294

295

Fig. 2

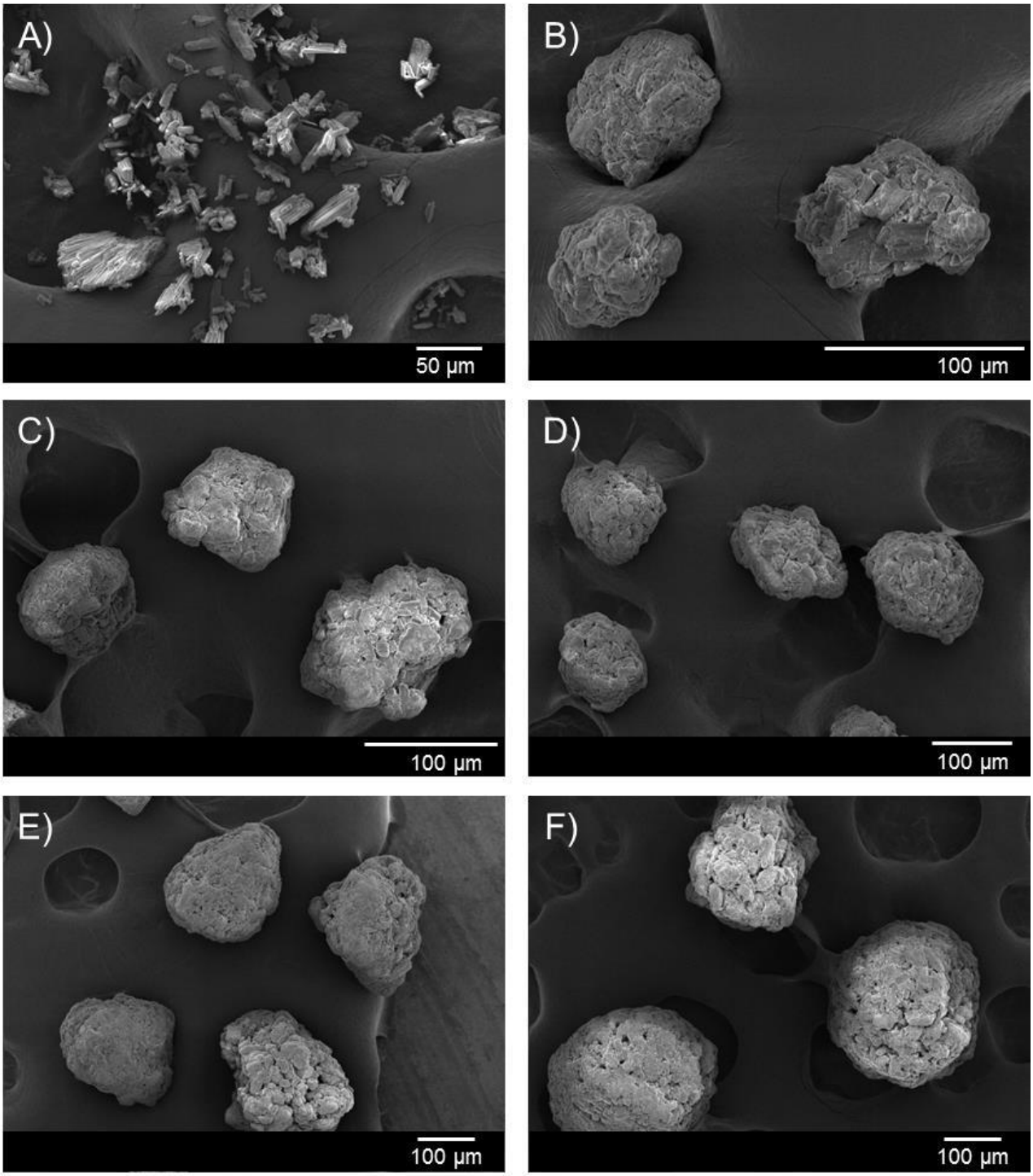


Fig. 3

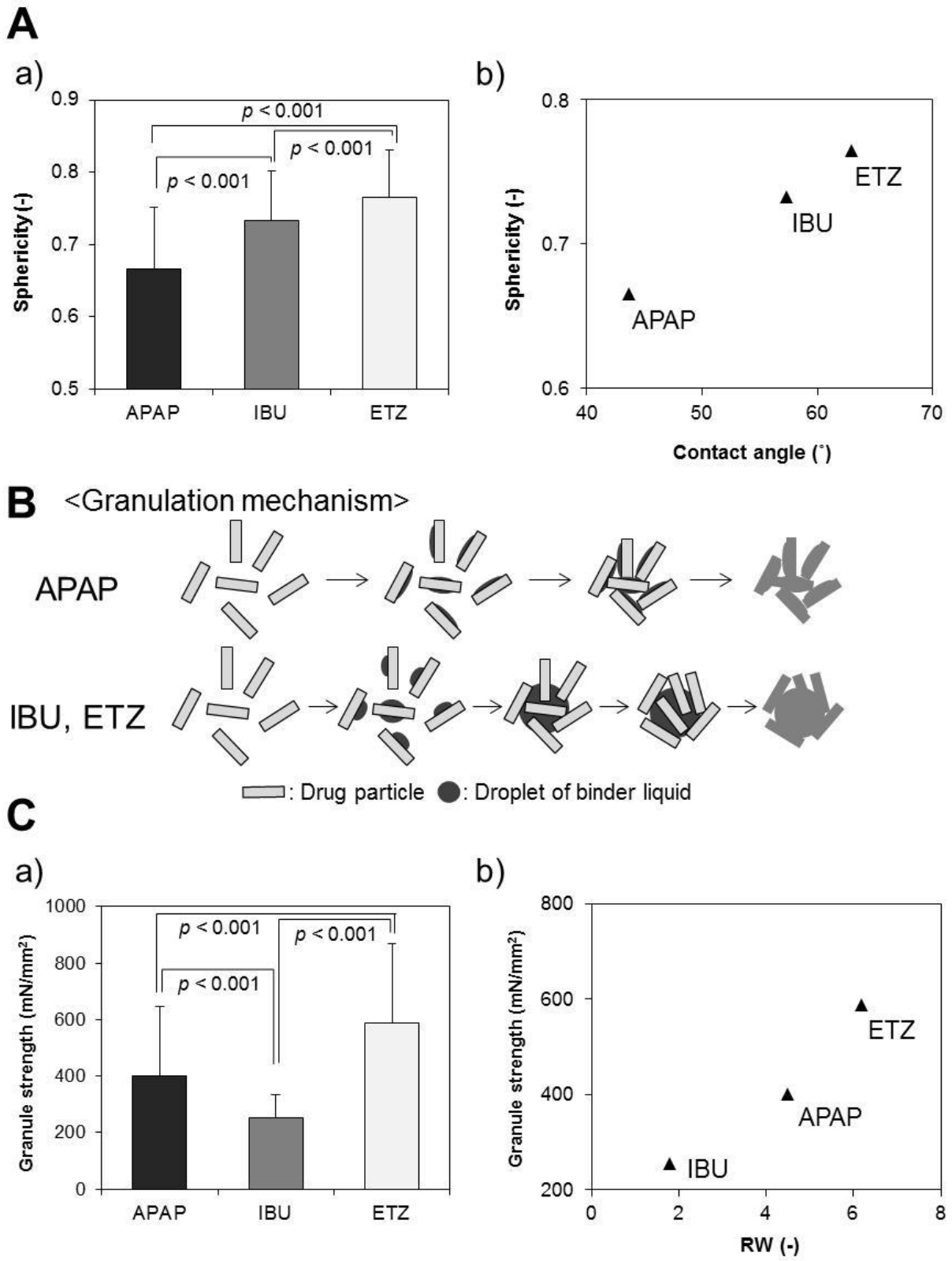
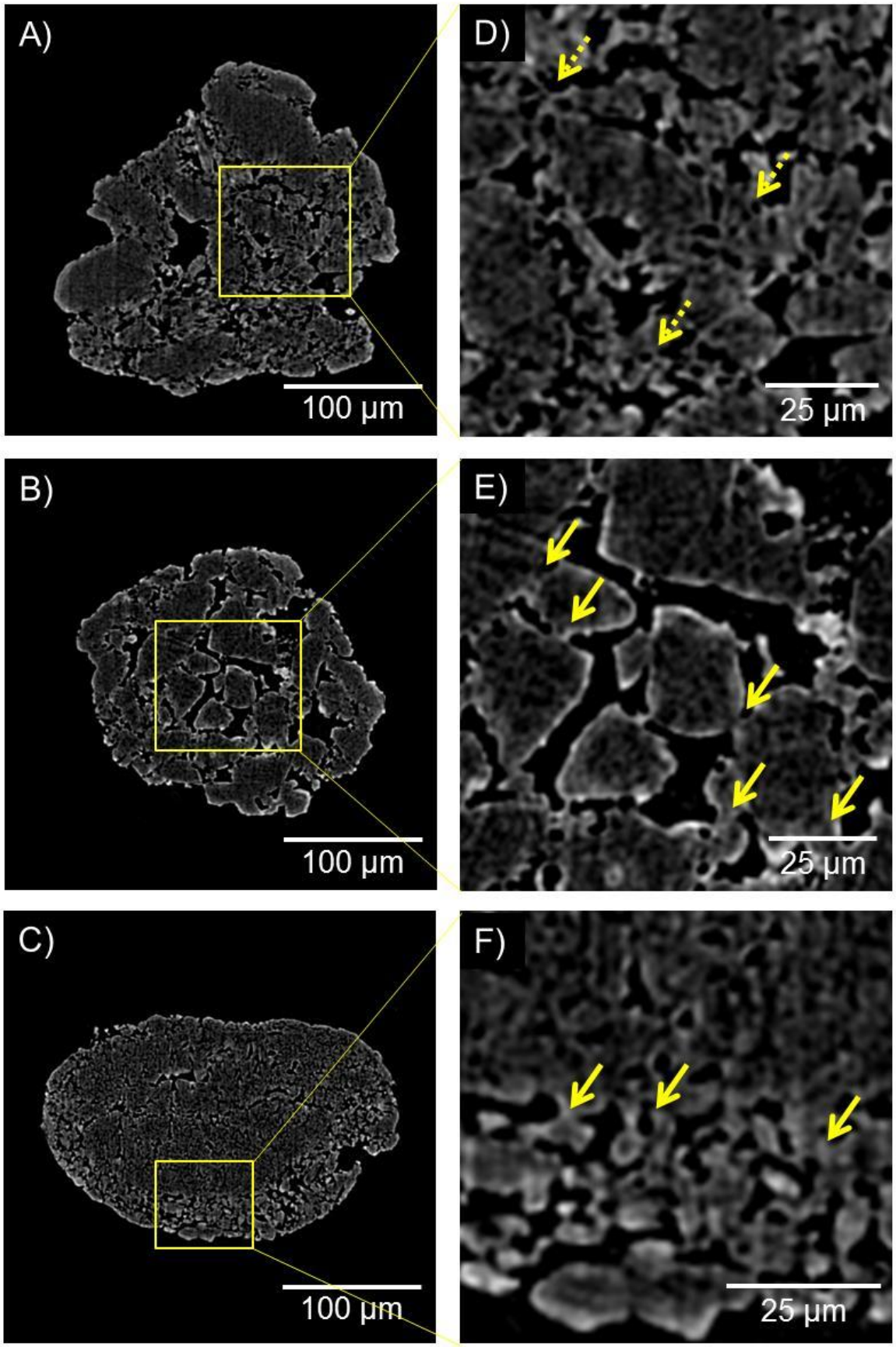
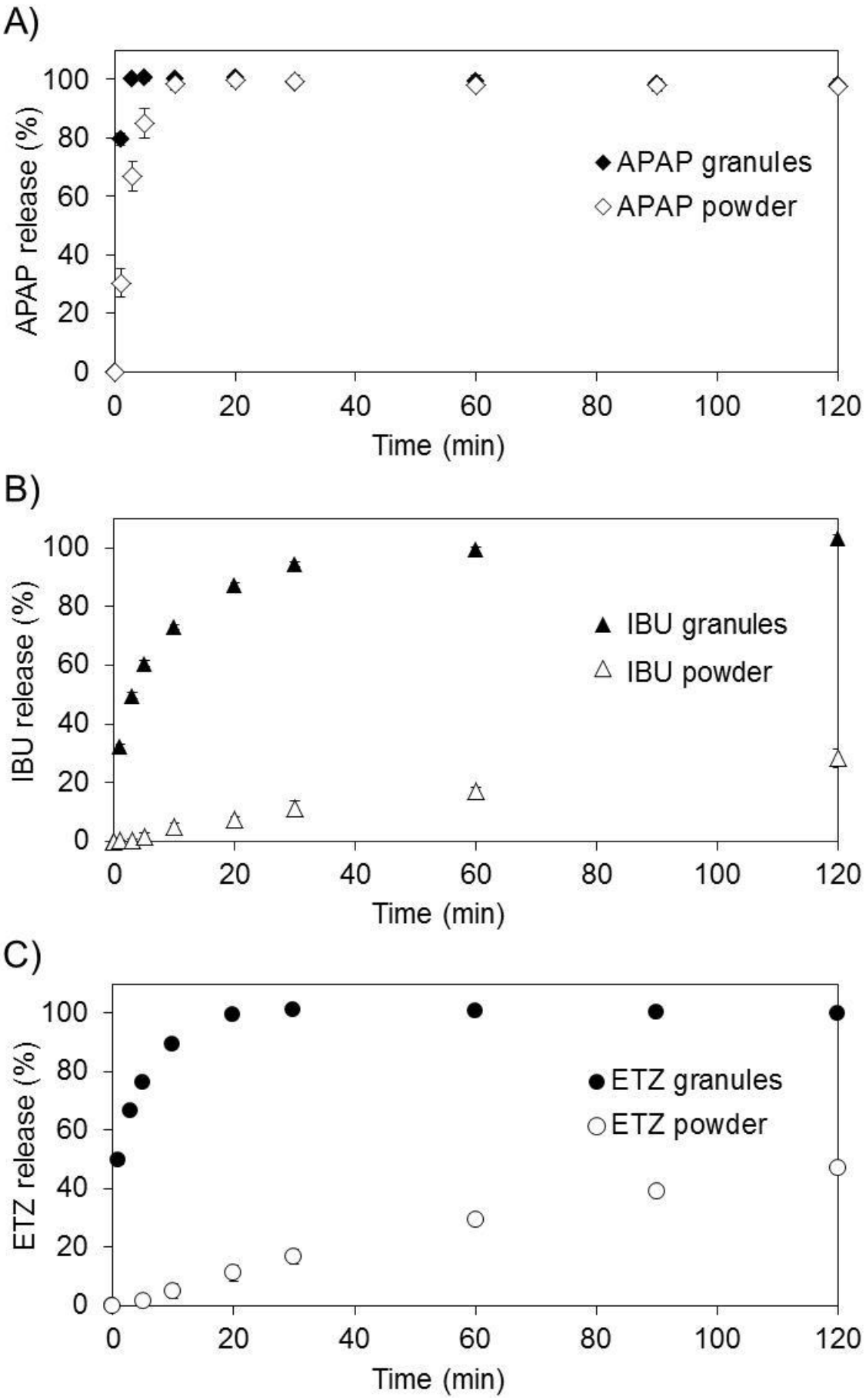

A
a)
Sphericity (-)
0.9
0.8
0.7
0.6
0.5
p < 0.001
p < 0.001
p < 0.001
APAP
IBU
ETZ
b)
Sphericity (-)
0.8
0.7
0.6
ETZ
IBU
APAP
40
50
60
70
Contact angle (˚)
B
<Granulation mechanism>
APAP
IBU, ETZ
: Drug particle
: Droplet of binder liquid
C
a)
Granule strength (mN/mm²)
1000
800
600
400
200
0
p < 0.001
p < 0.001
p < 0.001
APAP
IBU
ETZ
b)
Granule strength (mN/mm²)
800
600
400
200
ETZ
APAP
IBU
0
2
4
6
8
RW (-)

Fig. 4



301

Fig. 5


A)
APAP release (%)
Time (min)
APAP granules
APAP powder
B)
IBU release (%)
Time (min)
IBU granules
IBU powder
C)
ETZ release (%)
Time (min)
ETZ granules
ETZ powder

302