ELSEVIER

International Journal of Pharmaceutics 203 (2000) 203–210

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

# Whisker growth of ℓ-menthol in coexistence with various excipients☆

Hiroshi Yuasa*, Michi Ooi, Yuki Takashima, Yoshio Kanaya

*Laboratory of Medical and Pharmaceutical Technology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

Received 16 March 2000; received in revised form 19 May 2000; accepted 23 May 2000

**Abstract**

The purpose of the present study was to clarify the mechanism for ℓ-menthol whisker growth. ℓ-Menthol was mixed with an excipient, and the interaction was examined by IR measurement, thermal analysis and powder X-ray diffraction. Then we examined the involvement of the capillary condensation using the pore size distribution measurement. By mixing ℓ-menthol with an excipient with whisker growth, the hydroxyl group stretching band of ℓ-menthol was shifted to the higher wavenumber in the IR spectrum, the melting point and heat of fusion of ℓ-menthol became lower in the thermal analysis, and the diffraction intensity of ℓ-menthol became lower in the powder X-ray diffraction. The excipients with whisker growth showed the tendency to have the *meso*-pore involved in the capillary condensation in the pore size distribution measurement. From the above results, the whisker growth mechanism is considered as follows. When ℓ-menthol was mixed with an excipient with whisker growth, the crystallinity of ℓ-menthol was lowered and the vapor pressure was increased by the interaction mainly consisting of the hydrogen bond. The generated ℓ-menthol vapor entered *meso*-pore, the saturated vapor pressure was lowered by the capillary condensation, and the nucleation occurred. The vapor was further supplied, generating the growth of whisker. © 2000 Elsevier Science B.V. All rights reserved.

*Keywords:* Whisker; ℓ-Menthol; Excipient; Hydrogen bond; Capillary condensation

## 1. Introduction

Usually the diameter of whiskers is about 0.1–tens of micrometer, the length is about tens–hundreds of micrometer, and the aspect ratio (the ratio of length to diameter) of most whiskers is about 10–200. The research on whisker is said to been started by Erker L., who reported about the whiskers that grew from sulphide ore stone in 1547 (Fujiki and Mitomo, 1993). After that, many studies on whisker have been carried out, but most of them have dealt with inorganic substance Compton et al., 1951; Hashiguchi, 1966a,b; Nakata, 1975; Okura, 1975; Tanaka et al., 1977, and so on.

0378-5173/00/$ - see front matter © 2000 Elsevier Science B.V. All rights reserved.
PII: S0378-5173(00)00458-0

Whisker is often observed when the medical supplies are preserved as solid preparations such as tablets and granules. The chemicals that grow whisker are polyoxymethylene (van der Heijde, 1963, 1965), triglyceride (Okada, 1970), the complex of caffeine and salicylamide (Murata et al., 1976), carbamazepine (Laine et al., 1984), the sodium valproate–synthetic aluminum silicate system (Kuriyama et al., 1985), and the lactose–mannitol system (Ando et al., 1985). We reported about the whisker growth in ethenzamide (Murayama et al., 1981; Yuasa et al., 1981a,b,c), caffeine (Yamada et al., 1976; Yamamoto and Yonemochi, 1992; Yuasa et al., 1981a,b,c), abaspirin (Yuasa et al., 1986, 1993), salicylic acid (Yuasa et al., 1986, 1993), and *l*-menthol (Yuasa et al., 1995). It is known that whisker causes the lowering of the mixing degree and fluidity in powder and granules, the lowering of the medicine quantity in tablets, mistaking them for mold, and the lowering of the commodity value due to the damaged aesthetic appearance.

The growth mechanism of whisker can't be explained easily. Comparatively well understood mechanisms are the Frank model (Frank, 1949), the VLS model (Wagner and Ellis, 1965) and the Kossel (1927) model. The environment of the high-saturated vapor pressure is necessary for all of these models. But the ℓ-menthol whisker reported in this paper grew in the sealed and preserved tablets at certain temperature at which the environment of the high-saturated vapor pressure does not appear.

About this point, we examined the relationship between whisker growth and pore size distribution in tablets and reported that, in addition to the above-mentioned models, the capillary condensation phenomenon caused by the *meso*-pore is involved in whisker growth (Yuasa et al., 1981a,b,c, 1986, 1993, 1995; Yuasa, 1995).

In this paper, the physical and chemical effects of various excipients on the ℓ-menthol whisker growth when the excipient coexists with the ℓ-menthol crystal was studied in order to find a way to prevent whisker growth in medicinal preparations.

Table 1
Physical properties of excipients

| Excipients | Density[a] (g/cm$^3$) | Particle size[b] (μm) |
|---|---|---|
| DAHG | $2.35 \pm 0.010$ | $14.9 \pm 2.1$ |
| DCP | $2.24 \pm 0.001$ | $98.4 \pm 15.9$ |
| FLR | $2.07 \pm 0.019$ | $31.2 \pm 2.8$ |
| MA | $2.39 \pm 0.013$ | $141.3 \pm 17.0$ |
| LACT | $1.16 \pm 0.001$ | $27.7 \pm 2.4$ |
| LACT/CS | $1.16 \pm 0.001$ | $17.9 \pm 0.8$ |
| PH-301 | $1.49 \pm 0.002$ | $76.3 \pm 4.5$ |
| SH | $2.13 \pm 0.008$ | $62.0 \pm 9.6$ |
| XL | $1.26 \pm 0.003$ | $68.7 \pm 10.9$ |
| XL-10 | $1.28 \pm 0.002$ | $33.5 \pm 3.3$ |
| INF-10 | $1.28 \pm 0.000$ | $16.3 \pm 0.9$ |

[a] These data ware measured by using an air comparison pycnometer.
[b] The mean feret diameter $\pm$ S.D. ($n = 1000$).

## 2. Material and method

### 2.1. Materials

ℓ-Menthol (perfume and flavor, melting point 42.5°C Kanto Chemical, Japan) was crushed and used after sieving (125–300 μm) as the model drug. Eleven kinds of excipients were used: dried aluminum hydroxide gel (DAHG, Kyowa Chemical Industry Co., Ltd., Japan), dibasic calcium phosphate (DCP, Kyowa Chemical Industry Co., Ltd., Japan), porous calcium silicate (Florite™ RE, FLR, Eisai Co., Ltd., Japan), magnesium aluminometasilicate (MA, Fuji Kagaku Sangyo Co., Ltd., Japan), lactose (LACT, DMV Co., Ltd., Japan), the mixture of LACT and CS (7/3, LACT/CS), microcrystalline cellulose (Avicel™ PH301, Asahi Chemical Industry Co., Ltd., Japan), synthetic hydrotalcite (Alcamac™, SH, Kyowa Chemical Industry Co., Ltd., Japan), and crosspovidone (Polyplasdone™, XL, XL-10, INF-10, ISP Japan Co., Ltd., Japan.). The densities and mean particle diameters of these excipients are shown in Table 1.

### 2.2. Preparation of tablets that contain an excipient and ℓ-menthol

Tablets that contain an excipient and ℓ-menthol were prepared by physically mixing them in the composition ratios shown in Table 2. The powder

Table 2
Formulation of tablets

| | Percentage of *l*-menthol | | | | |
|---|---|---|---|---|---|
| | 10 | 30 | 50 | 70 | 90 |
| ℓ-Menthol (mg) | 30 | 90 | 150 | 210 | 270 |
| Excipients (mg) | 270 | 210 | 150 | 90 | 30 |
| Total (mg) | 300 | 300 | 300 | 300 | 300 |

Table 3
Tableting condition

| | |
|---|---|
| Punch diameter (mm) | 11 |
| Compression pressure (MPa) | 100 |
| Compression speed (mm/min) | 50 |

mixture was compressed into tablets at the pressure of 100 MPa by the direct compression method, using a universal testing machine (model TCM-5000C, Minebea Co., Ltd., Japan) with a single flat punch of 1 $cm^2$ cross section Table 3.

### 2.3. Storage of tablets

Three tablets were sealed in a 30-ml glass container immediately after tableting, so that they might not contact each other, and stored in a constant temperature oven at 30°C for 4 weeks.

### 2.4. Measurement of the amount of whisker

After being stored, the weight of these tablets was measured. After the whiskers that grew in the upper and side surfaces of the tablets were removed with brush, the weight of these tablets was measured again. The resultant weight difference was divided by the sum of the area of its upper and side surfaces of the tablets, and the answer considered on the amount of whisker per 1 $cm^2$. A similar operation was carried out with the tablets without whisker growth.

### 2.5. Measurement of pore size distribution

The pore size (0.002–100 μm) distribution was measured with a mercury porosimeter (Autoscan-33, Quantachrome Co.). The contact angle of mercury with the samples and the surface tension of mercury were regarded as 140° and 480 dyn/cm, respectively (Ritter and Drake, 1945). The sample was the excipient only, because the measurement by mercury intrusion porosimetry with the decompression condition was difficult for ℓ-menthol, which has sublimability and a high vapor pressure.

### 2.6. Fourier-transform infrared spectroscopy

The IR spectra of the samples were measured by the nujol method using a Fourier-transform infrared (FT-IR) spectrometer (type-620, Jas.Co., Tokyo). Excipients, ℓ-menthol and the melted mixture that was prepared by melting the mixture in the weight ratio of 3:1 ℓ-menthol and an excipient at 45°C for 3 h, and crushing it were used as samples. The samples were suspended in nujol, and were placed between two 5-mm thick boards for the measurement.

### 2.7. Measurement of melting point and heat of fusion of ℓ-menthol

Differential scanning calorimetry (DSC) curves were measured with a DSC instrument (SSC/560S, Seiko Instruments and Electronics, Tokyo). Excipients, ℓ-menthol and the melted mixture that was prepared by melting the mixture in the weight ratio of 3:1 ℓ-menthol and an excipient at 45°C for 3 h, and crushing it were used as samples. The heating rate was 4°C/min and nitrogen gas was flowed at the rate of 70 ml/min.

### 2.8. Measurement of crystallinity of ℓ-menthol

Powder X-ray diffraction patterns were measured with a diffractmeter (Geigerflex RAD-IB, Rigaku, Tokyo). Excipients, ℓ-menthol, the physical mixture in the weight ratio of 1:1 ℓ-menthol and an excipient and the melted mixture that was prepared by melting the physical mixture at 45°C for 3 h, and crushing it were used as samples. Based on the method of Iwai and Utagawa (1954), five points ($2\theta = 8$, 14, 17, 20, 21.5) that do not overlap with the peak of the excipient were chosen from the diffraction peaks of ℓ-menthol.

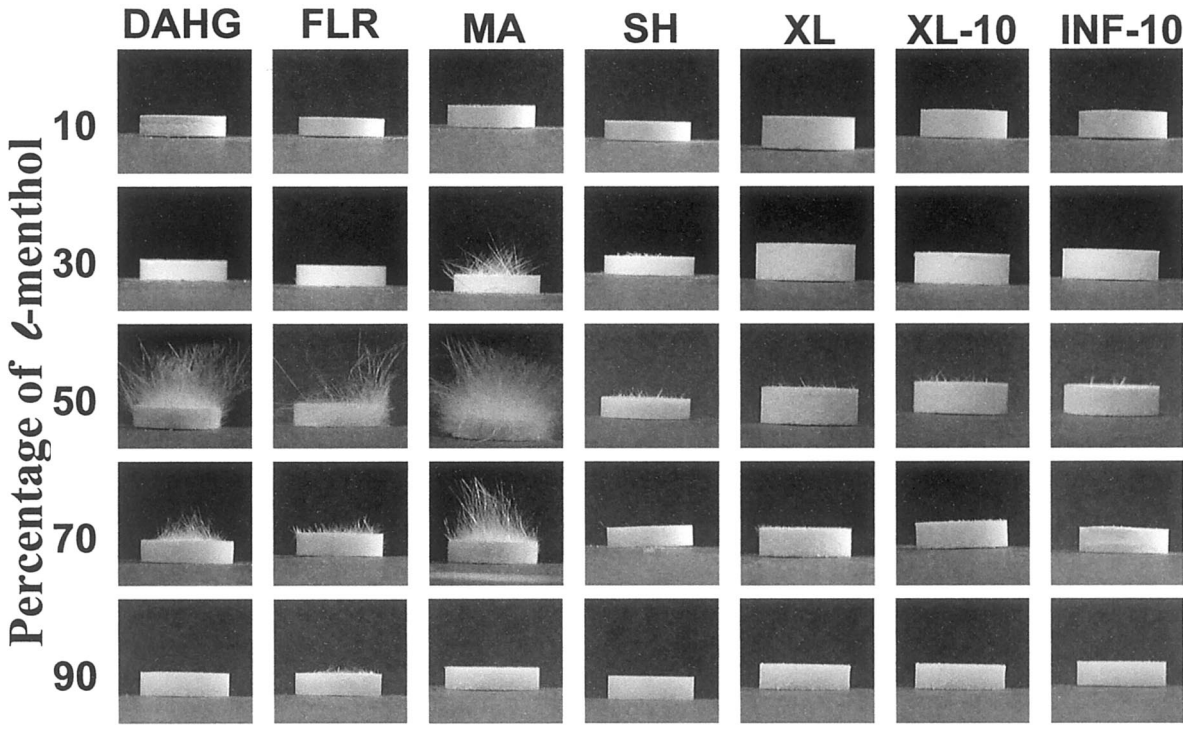


Fig. 1. Effect of the Percentage of ℓ-menthol on whisker growth.

The diffraction intensity of ℓ-menthol in each physical mixture was defined on 100%, and the diffraction intensity of each melted mixture was examined. The operating conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 20 mA and the scanning speed, $2\theta = 4°/\text{min}$.

## 3. Results and discussion

### *3.1. ℓ-Menthol whisker growth in coexistence with an excipient*

Whisker growth on the tablets containing an excipient and ℓ-menthol that were preserved at 30°C for 4 weeks is shown in Fig. 1. On the tablets with whisker growth, there was the largest amount of whiskers when ℓ-menthol was contained at 50%. This reason is not clear at the present.

Fig. 2 shows the amount of whisker on the tablets containing 50% ℓ-menthol. The amount of whisker was most remarkable on MA and DAHG. When ℓ-menthol only was compressed and preserved, whisker did not grow. It was guessed from this fact that whisker grew when

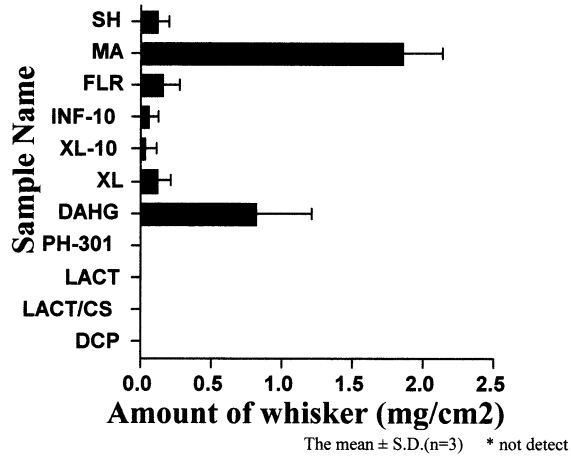


Fig. 2. Amount of whisker on tablets containing 50% ℓ-menthol

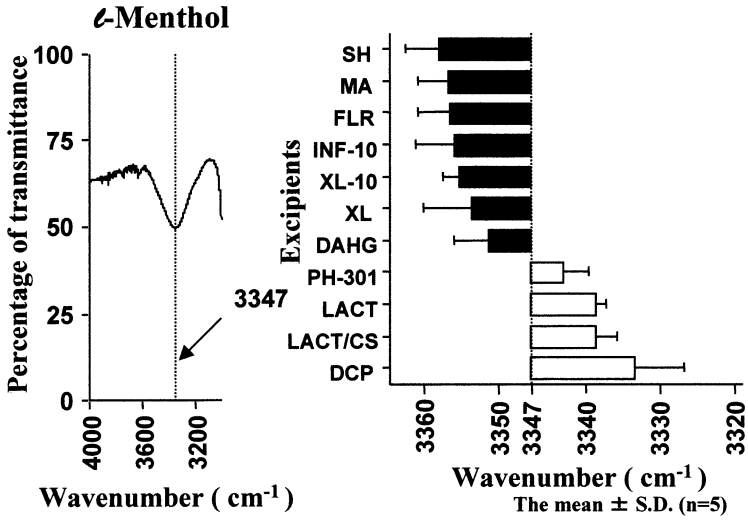


Fig. 3. Shift of the wave number of stretching vibration of ℓ-menthol hydroxyl group (3347 $cm^{-1}$) in IR spectrum in melted mixture of ℓ-menthol/excipient (3/1). ■, Whisker growth; □, non-whisker growth.

some physiochemical interaction caused between both by mixing ℓ-menthol and an excipient. Then, the physicochemical interaction was studied in the following experiments by using the melted mixture of ℓ-menthol and an excipient in which the contact area of the both and the interaction would be large.

### *3.2. The change in the IR spectrum of ℓ-menthol when mixed with an excipient*

Fig. 3 shows the change in the IR spectrum of the melted mixture. Fig. 3a shows the peak of the ℓ-menthol hydroxyl group stretching vibration in measuring ℓ-menthol only. Fig. 3b shows that the peak was shifted to the higher or the lower wavenumber by mixing ℓ-menthol with the excipient. Still, in the physical mixture in this ratio, the IR spectra of ℓ-menthol and any excipient did not change. When ℓ-menthol was mixed with the excipient with whisker growth, the peak of the hydroxyl group-stretching band of ℓ-menthol was shifted to the higher wavenumber. When it was mixed with the excipient without whisker growth, it was shifted to the lower wavenumber.

The peak of the hydroxyl group stretching vibration of ℓ-menthol that was in the crystal state showed that the ℓ-menthol condition was dimer and polymer due to the hydrogen bond of the hydroxyl groups (Cross and Jones, 1971). Generally, when a hydrogen bond is formed, the peak of the carbonyl group or the hydroxyl group tends to shift to the lower wavenumber, stabilize the energy state (Badger, 1940; Cross and Jones, 1971; Rath et al., 1998). But in our case, the hydroxyl group stretching vibration of ℓ-menthol containing the excipient with whisker growth was shifted to the higher wavenumber. The reason is considered that the monomer of ℓ-menthol increased, enhancing the energy state of ℓ-menthol. In this study, the hydroxyl group of ℓ-menthol and the hydroxyl and ketone groups of the excipient that have a high possibility of producing a hydrogen bond were also examined, but the analysis was impossible, since the peak of the hydroxyl group and the finger print region of ℓ-menthol were overlapped

### *3.3. The change in the melting point and the heat of fusion of ℓ-menthol when mixed with an excipient*

The melting point and the heat of fusion of ℓ-menthol measured with a DSC are shown in Fig. 4a and b, respectively. In Fig. 4a, the melting point of the ℓ-menthol crystal only showed

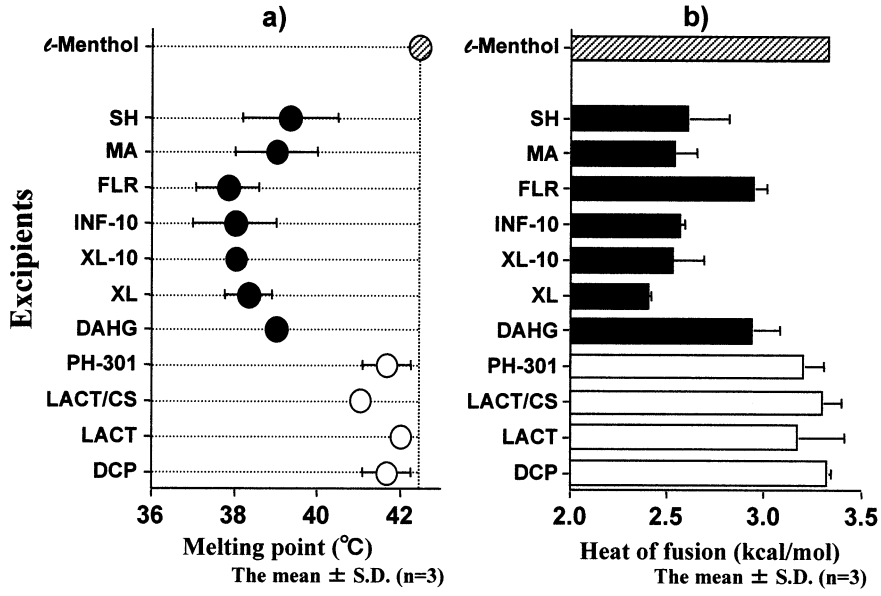


Fig. 4. Melting point and heat of fusion of ℓ-menthol in the melted mixture of ℓ-menthol/excipient (3/1). ■, Whisker growth; □, non-whisker growth.

42.5°C. When ℓ-menthol was mixed with an excipient with whisker growth, the lowering of ℓ-menthol melting point was large in comparison with an excipient without whisker growth. In Fig. 4b, the decrease in the heat of fusion of an excipient without whisker growth was slighter than that of the ℓ-menthol crystal. But, the decrease in the heat of fusion was larger in an excipient with whisker growth. The lowering of melting point and the decrease in the heat of fusion were thought to be caused because the crystal lattice of ℓ-menthol became unstable (Kim and Haren, 1995). These are presumed to have occurred because the crystallinity was lowered by mixing the ℓ-menthol with the excipient with whisker growth. So, the crystallinity of ℓ-menthol was examined using the powder X-ray diffraction.

### 3.4. The crystallinity in the melted mixture

The percentages of the peak intensity of the melted mixtures for that of physical mixtures of ℓ-menthol and an excipient in powder X-ray diffraction are shown in Fig. 5. The lowering of the diffraction intensity was not observed for the

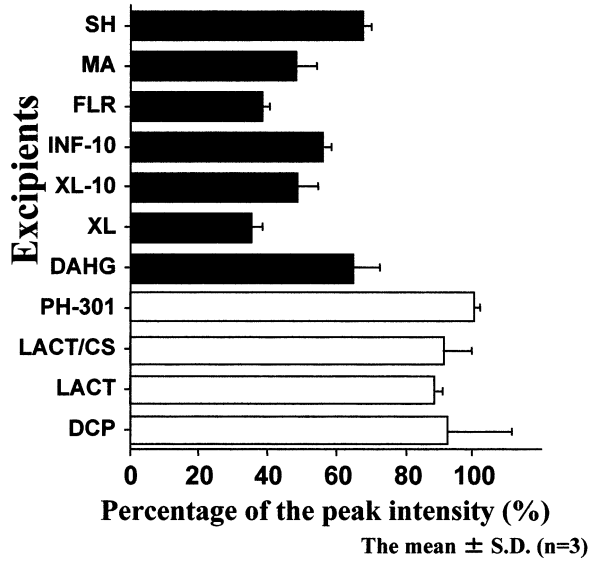


Fig. 5. Percentage of the peak intensity of the melted mixture for that of physical mixture of ℓ-menthol/excipient (1/1) in powder X-ray diffraction. ■, Whisker growth; □, non-whisker growth.

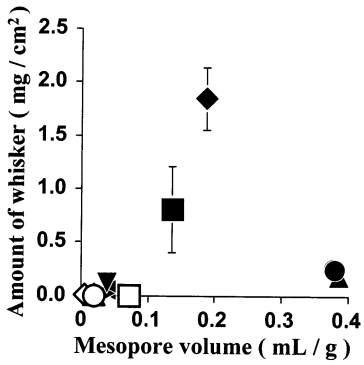


Fig. 6. Relationship between the amount of whisker and *meso*-pore volume. ▲, SH; ◆, MA; ●, FLR; ▼, XL; ◄, INF-10; ►, XL-10; ■, DAHG; □, PH-301; ○, LACT; △, LACT/CS; ◇, DCP

excipient on which whisker could not be recognized. The diffraction intensity of the excipient with whisker growth was remarkably lowered. It is indicated that these lowering of diffraction intensity occurred as follows. The monomer ℓ-menthol was increased in the melted mixture because ℓ-menthol that had intermolecular hydrogen bond made the hydrogen bond with the excipient. As a result, the crystal lattice of ℓ-menthol was disturbed lowering the crystallinity.

### *3.5. The effect of the pore volume for whisker growth*

Fig. 6 shows the relationship between the amount of whisker when 50% ℓ-menthol was mixed and the *meso*-pore volume in the tablets that were made by compressing the excipient only. The excipients without whisker growth showed the tendency to have slight *meso*-pore than the excipient whose whisker growth is remarkable. From these results, it is presumed that not only the hydrogen bond but also the capillary condensation, about which we have reported before (Yuasa et al., 1981a,b,c, 1993, 1995), is also involved in the whisker growth.

## 4. Conclusion

An excipient in which ℓ-menthol whisker grew raised the energy state of ℓ-menthol by being mixed with ℓ-menthol and the crystallinity of ℓ-menthol was lowered. In addition, it tended to have a lot of pore volume in the *meso*-pore range.

From the above result, the mechanism for whisker growth is considered as follows. By the interaction based on the hydrogen bond with the excipient, the energy state of ℓ-menthol is raised. The crystallinity of ℓ-menthol is lowered, and the vapor pressure is increased. The generated vapor enters the *meso*-pore, in which the saturated vapor pressure is lowered by the capillary condensation, causing nucleation. Vapor is further supplied, growing whisker.

Whisker growth is a very important problem in the medicine preparation and quality control for medical supplies. The more studies of the whisker with other medical supplies, which involve examining the mechanism and the prevention method for the whisker growth, are necessary.

## References

Ando, H., Watanabe, S., Ohwaki, T., Miyake, Y., 1985. Crystallization of excipients in tablets. J. Pharm. Sci. 74, 128–131.

Badger, R.M., 1940. J. Chem. Phys. 8, 288.

Compton, K.G., Mendizza, A., Arnold, S.M., 1951. Filamentary growths on methal surfaces — whiskers, corrosion. Natl. Assoc. Corrosion Eng. 7, 327–334.

Cross, A.D., Jones, R.A., 1971. An Introduction to Practical Infra-Red Spectroscopy. Kagaku Doujin, Tokyo, Japan.

Frank, F.C., 1949. Discuss. Faraday Soc. 5, 67.

Fujiki, Y., Mitomo, M., 1993. Whisker. Sangyotosyo, Japan.

Hashiguchi, R., 1966. Metal named whisker I. Solid State Phys. 1–1, 11–16.

Hashiguchi, R., 1966. Metal named whisker II. Solid State Phys. 1–2, 3–9.

Iwai, S., Utagawa, S., 1954. Youkyousi 62, 747.

Kim, Y., Haren, A.M., 1995. The application of crystal soaking technique to insulinotropin crystals grown from a saline solution. Pharmaceut. Res. 12, 1664–1670.

Kossel, W., 1927. Nachr. Wiss, Gottingen, p. 135.

Kuriyama, T., Kobiki, M., Tanaka, T., Imazato, Y., 1985. Abstracts of Papers, 105th The Pharmaceutical Society of Japan, Kanazawa, p. 740.

Laine, E., Tuominen, V., Ilvessalo, P., Kahela, P., 1984. Formation of dihydrate from carbamazepine anhydrate in aqueous consitions. Int. J. Pharmaceut. 20, 307–314.

Murata, T., Sato, T., Tamiya, S., Taura, T., Yasubuchi, H., Minami, H., 1976. Abstracts of Papers, 96th The Pharmaceutical Society of Japan, Aichi, p. 221.

Murayama, H., Takahashi, M., Asano, M., Washitake, M., Yuasa, H., Asahina, K., 1981. Growth behaviors of whisker on ethenzamide tablet. Yakuzaigaku 41, 113–118.

Nakata, E., 1975. Whisker-ni-tuite. Hyomen 13, 195–207.

Okada, M., 1970. J. Crystal Growth 7, 371.

Okura, A., 1975. Hyomen 13, 524–531.

Rath, P., Delang, F., Degrip, W.J., Rothschild, K.L., 1998. Hydrogen bonding changes of internal water molecules in rhodopsin during metarhodopsin I and metarhodopsin II formation. Biochem. J. 329, 713–717.

Ritter, H.L., Drake, L.C., 1945. Ind. Eng. Chem. Anal. Ed. 17, 782.

Tanaka, M., Hashizume, G., Matsui, H., 1977. Zairyo 26, 309.

van der Heijde, H.B., 1963. Whisker-like growth of polyoxymethylene from solution. Nature 199, 786–799.

van der Heijde, H.B., 1965. Note on polyoxymethylene whisker, hesrites, axialites. Phil. Mag. 12, 1071–1077.

Wagner, R.S., Ellis, W.C., 1965. Trans. Met. Soc. AIME. 233, 1053.

Yamada, M., Nishimura, Y., Matsuzaki, T., 1976. Growth behaviors and mechanism of caffein whisker on the granules. Yakugaku Zasshi 96–10, 1223–1228.

Yamamoto, K., Yonemochi, E., 1992. Anomalous properties of drug molecules in micro porous matrices. Pharm. Tech. Jpn. 8, 431–439.

Yuasa, H., Miyata, K., Ando, T., Kanaya, Y., Asahina, K., Murayama, H., 1981. Effect of compression force on growth of whisker. Yakuzaigaku 41, 155–160.

Yuasa, H., Miyata, K., Ando, T., Kanaya, Y., Asahina, K., Murayama, H., 1981. Quantitative measurement and mechanism of whisker growth. Yakuzaigaku 41, 161–171.

Yuasa, H., Asahina, K., Murayama, H., Takahashi, M., Asano, M., Washitake, M., 1981. Effect of some constituents on the generation and growth of ethenzamide whisker. Yakuzaigaku 41, 237–244.

Yuasa, H., Kanaya, Y., Asahina, K., 1986. Studies on whisker growth on the tablet surface III. Mechanism of whisker growth on aspirin tablet and its effect on the mechanical strength of tablet. Chem. Pharm. Bull. 34, 850–857.

Yuasa, H., Yamashita, J., Kanaya, Y., 1993. Studies on whisker growth in solid preparations IV. Whisker growth in mixture composed of aspirin and porous glass powder. Chem. Pharm. Bull. 41, 731–736.

Yuasa, H., Yamashita, J., Kanaya, Y., 1995. Abstracts of Papers, 115th The Pharmaceutical Society of Japan, Sendai, vol. 4, p. 14.

Yuasa, H., 1995. Whisker growth in medicinal preparations. Pharm. Tech. Jpn. 11, 679–686.