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Note

New method of preparing high-porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material

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Abstract

Compressed tablets of a water-soluble material, prepared using mannitol, did not rapidly dissolve in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using mannitol, we developed a novel method whereby camphor, a subliming material, is removed by sublimation from compressed tablets prepared using a mixture of mannitol and camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 s in saliva in the mouth. We developed a direct compression method for the preparation, using mannitol and camphor, of a meclizine (antidinic agent) tablet with high porosity which dissolves rapidly in saliva. © 1997 Elsevier Science B.V.

Keywords: Rapidly saliva soluble tablet; Subliming material; Mannitol; Camphor; Meclizine; High porosity; Direct compression

1. Introduction

We often experience inconvenience in swallowing conventional tablets when water is not available. Furthermore, patients who have problems

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swallowing encounter difficulties in taking tablets (Ito et al., 1994). Recently, we confirmed that a compressed tablet prepared with crystalline cellulose and low-substituted hydroxypropylcellulose (L-HPC) rapidly disintegrated (within 15 s) in saliva (or a small amount of water) in the mouth of humans (Watanabe et al., 1995). However, patients sometimes feel a rough texture in their mouth due to the incomplete solubilization of this type of tablet in saliva. To eliminate the rough texture in the mouth, we attempted to use a water-soluble material (mannitol) as an excipient instead of crystalline cellulose and L-HPC, in the preparation of this type of tablet. However, the compressed tablet prepared using mannitol did not rapidly dissolve in saliva since it is difficult for water to penetrate into the tablet due to its low porosity. We therefore investigated a new convenient method of preparing compressed tablets with high porosity, which dissolve rapidly in the mouth, using mannitol with a subliming material. We chose camphor as a subliming material since it can be used as a medicinal drug.

2. Materials and methods

d-Mannitol (Mannit™), (±)-camphor and meclizine (hydrochloride salt) were purchased from Towa Chemical Industry (Tokyo), Wako Pure Chemical Industries (Osaka), and Nihon Baruku Yakuhin (Osaka, Japan), respectively. Sieved camphor particles with diameters from 149 to 355 and from 355 to 500 μm were used. Mannitol and camphor with or without the model drug (meclizine) were mixed in various compounding ratios for 2 min in a plastic bottle. A schematic representation of tablet preparation is shown in Fig. 1. For compression of materials, a tablet-hitting pressure displacement measuring system (Sratt Press™, N-20E, Okada-Seiko, Tokyo, Japan) equipped with punches (flat-faced, 8 mm diameter) was employed. To prepare 200 mg tablets, mixtures of meclizine, mannitol and camphor in various ratios were compressed by approximately 1500 kgf. For elimination of camphor from the tablets, camphor was sublimed in vacuo at 80°C for 30 min. The crushing strength

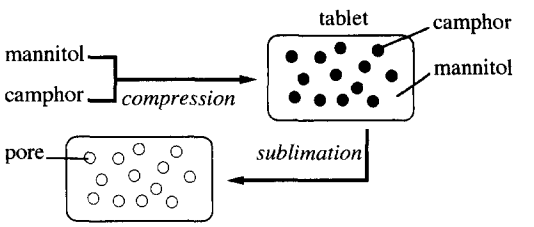

Fig. 1. Schematic illustration of the preparation of a high-porosity compressed tablet using mannitol and camphor.

(kg) of prepared tablets was measured using a tablet hardness tester (TS-50N, Okada-Seiko, Tokyo, Japan). The absolute density (ρ) of ten tablets was measured using a multi-volume pycnometer (Accupyc 1330, Shimadzu, Kyoto, Japan) and the mean for these ten tablets was calculated. The porosity (ε) of the tablets was determined using Eq. (1):

$$\varepsilon(\%) = (1 - \rho_{ap}/\rho) \times 100, \quad (1)$$

where ρ_{ap} is the apparent density calculated using the mean weight, diameter and thickness of ten tablets.

In the first experiments, we used camphor particles with diameters from 355 to 500 μm. Table 1 shows tablet weight before and after sublimation of camphor. For 10 tablets prepared using a mannitol/camphor compounding ratio of 9:1, the mean weight before camphor sublimation was 204 ± 2 mg and that after camphor sublimation was 184 ± 2 mg. The decrease in mean weight (approximately 20 mg) corresponded to the weight of the camphor added to the tablets. Similar results were obtained in the case of tablets

Table 1
Tablet weight (mg) before and after sublimation of camphor

Camphor (mg)	Sublimation	
	Before	After
0	198 ± 2	197 ± 1
20	204 ± 2	184 ± 2
40	200 ± 1	163 ± 2
60	198 ± 2	139 ± 1

Camphor particle diameter from 355 to 500 μm was used. Each value represents the mean ± S.D. for ten tablets.

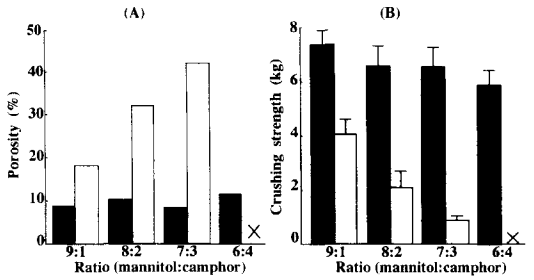

Fig. 2. Porosity (A) and crushing strength (B) of the tablets prepared using various ratios of mannitol and camphor (particle diameter 355–500 μm). ■, before sublimation of camphor; □, after sublimation of camphor; X, tablet was very fragile after sublimation of camphor.

prepared using mannitol/camphor compounding ratios of 8:2 and 7:3. In the case of a mannitol/camphor compounding ratio of 6:4, tablets did not have sufficient strength for what after the sublimation of camphor. We concluded that almost all of camphor had sublimated from the tablets, based on the agreement between the weight of camphor added and the weight decrease observed.

3. Results and discussion

As shown in Fig. 2, there were no pre-camphor sublimation differences in porosity (panel A) and crushing strength (panel B) among the tablets prepared using various mannitol/camphor compounding ratios. The pre-camphor sublimation porosity of the tablets was approximately 8–11%. Upon sublimation of camphor, the porosity increased significantly (unshaded columns in Fig. 2A). The maximum porosity (42%) after sublimation of camphor was obtained for tablets containing mannitol and camphor in a ratio of 7:3. The magnitude of the increase in porosity (by approximately 30%) indicates that camphor was completely replaced by pores in the tablet. The pre-camphor sublimation crushing strength of tablets prepared using various mannitol/camphor compounding ratios was about 7 kg (shaded columns in Fig. 2B). Unfortunately, the crushing strength of these tablets after sublimation of camphor decreased and consequently tablets with a ratio of mannitol to camphor of 6:4 did not remain compressed. However, tablets prepared using camphor concentrations of less than 30% remained compressed. The tablets prepared using a mannitol/camphor compounding ratio of 9:1 have sufficient strength for practical use.

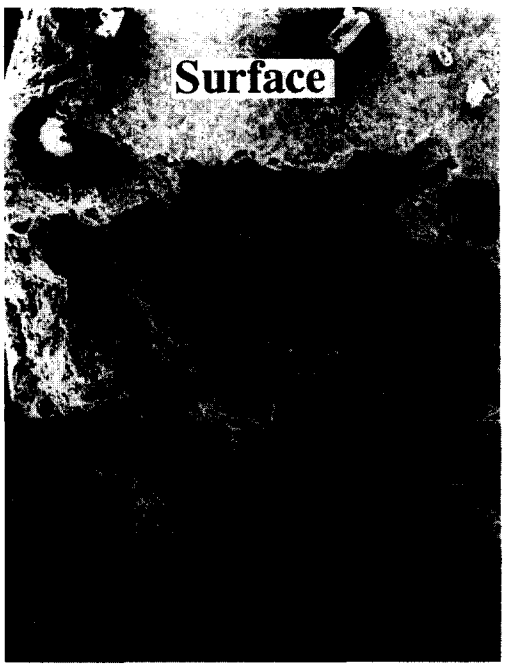

Fig. 3. SEM micrograph of the cross sectional view of a high-porosity rapidly saliva soluble tablet after sublimation of camphor from a compressed mixture of mannitol and camphor. Camphor of particle diameter from 355 to 500 μm was used.

Table 2
Dissolution time in saliva in the mouth

Compounding ratio (mannitol:camphor)	Meclizine	Dissolution time (s)
10:0	—	>120
9:1	—	40 ± 5
8:2	—	16 ± 5
8:2	10%	18 ± 3
7:3	—	5 ± 1

Camphor particle diameter from 355 to 500 μm was used. Each value represents the mean ± S.D. for six experiments.

Table 3
Effect of particle diameter of camphor on crushing strength, porosity and dissolution time

Particle diameter of camphor (μm)	Meclidine content (%)	Crushing strength[a] (kg)	Porosity (%)	Dissolution time[b] (s)
149–355	—	1.7 ± 0.3	28	8 ± 3
149–355	10	2.4 ± 1.4	32	11 ± 4
355–500	—	2.0 ± 0.6	32	16 ± 5
355–500	10	3.5 ± 1.3	32	18 ± 3

[a] Mean $\pm$ S.D. for ten tablets.
[b] Mean $\pm$ S.D. for six experiments.

For determination of dissolution time in saliva, the sensory test in human subjects described by Kimura et al. (1992) was applied with a slight modification. Six healthy volunteers, from whom informed consent was obtained, each took one tablet at random times. Each volunteer licked, without biting, the tablet without drinking water and the time (in s) required for complete dissolution of the tablet was evaluated. The mannitol tablets prepared without camphor did not dissolve rapidly in saliva. For complete dissolution, more than 120 s in the mouth were required (Table 2). However, the tablets prepared with camphor followed by sublimation were rapidly dissolved in saliva. The tablets prepared from mannitol and camphor in a ratio of 7:3 were dissolved completely in saliva in a few seconds. Rapid disintegration of the prepared tablets in saliva may be related to an improvement in the ability of water to penetrate into the tablets due to the high porosity obtained by the increase in the number of pores after sublimation of camphor. Fig. 3 shows a micrograph of the cross section of a high-porosity rapidly saliva soluble tablet taken by a scanning electron microscope (SEM, model S-2500, Hitachi Seisakusho, Tokyo, Japan). It was found that many porous cavities in the tablets were formed due to the sublimation of camphor. Since they are prepared from water-soluble materials these tablets have the advantage of not causing a feeling of roughness in the mouth.

When meclizine powder (10%) was added to a mixture of mannitol and camphor (in a ratio of 8:2), no difference in porosity was observed compared with a mixture of mannitol and camphor (8:2) without meclizine. However, the crushing strength (3.5 ± 1.3 kg) of tablets containing meclizine was higher than that of those (2.0 ± 0.6 kg) not containing meclizine. In addition, tablets containing meclizine (10%) rapidly dissolved in saliva (within 18 ± 3 s), and no difference in dissolution time was observed between tablets containing and ones not containing meclizine. The increase in crushing strength of the tablets prepared may be related to a decrease in the particle diameter of camphor. We therefore studied how the particle diameter of camphor effected crushing strength, porosity and dissolution time of tablets (Table 3). Tablets prepared with or without meclizine (10%) using a combination of mannitol and camphor (camphor particle diameter from 149 to 355 μm) rapidly dissolved in saliva, compared with the tablets prepared using camphor of particle diameter from 355 to 500 μm. However, no difference in porosity or dissolution time was observed between these two types of tablet. Tablets prepared with smaller camphor particle diameters from 105 to 149 μm were fragile after sublimation of camphor. Consequently, camphor with particle diameter from 355 to 500 μm is suitable for use in the preparation of rapidly saliva soluble compressed tablets.

Recently, a new formulation of a rapidly soluble tablet prepared using a water-soluble materials by means of a new freeze drying method was reporeted (Virley and Yarwood, 1990). This tablet rapidly dissolves in saliva. However, the introduction of a new freeze drying method is inconvenient in the tablet manufacturing process. We developed a new direct compression method for preparing water-soluble tablets with high porosity. These tablets rapidly dissolved (within 10–20

s) in saliva and were of sufficient strength for practical use.

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