Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 347–354
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Stabilization of sodium guaiazulene sulfonate in granules for tableting prepared using a twin-screw extruder

Kouichi Nakamichi[a,*], Tomio Nakano[a], Hiroyuki Yasuura[a], Shogo Izumi[a], Yoshiaki Kawashima[b]

[a]*Pharmaceutics Research Laboratory, Nippon Shinyaku Co., Ltd., Kyoto, Japan*
[b]*Department of Pharmaceutical Engineering, Gifu Pharmaceutical University, Gifu, Japan*

Received 15 November 2002; accepted in revised form 5 May 2003

Abstract

Sodium guaiazulene sulfonate (GAS-Na), which has an anti-inflammatory effect, is an unstable compound, which is gradually decomposed in the solid state at room temperature. In fact, when heated (40 °C 6% RH), GAS-Na decomposes almost completely within 1 week. It was found that a kneaded mixture of GAS-Na and cornstarch (weight ratio; 1:250) for tableting with water is stable. So, during production, GAS-Na could be stabilized using water. Four kinds of tablet were prepared in different ways: direct tableting, tableting via screw granulation, tableting via fluidized bed granulation, and tableting via twin-screw extrusion. The stability of GAS-Na in these tablets was compared. The tablet prepared using screw granulation, during which 30% water was added to the material, was the most stable. It was, however, shown that reducing the water content to 12.5%, when screw granulation was conducted, made the GAS-Na less stable. Also, when a twin-screw extruder with kneading paddle elements in the screws was used even with lower water content of 12.5%, the stability of GAS-Na improved. In addition, when the kneading paddle elements were detached from the screws and only the feed screw elements were operated, GAS-Na lost its stability. These results show that the kneading paddle elements play a role in uniformly dispersing a small amount of water into the powder and stabilizing GAS-Na. It was found that the water presence was a very important factor with respect to the decomposition of GAS-Na, irrespective of the crystallinity. Furthermore, a twin-screw extruder with kneading paddle elements is useful for uniformly dispersing water to prepare stable formulations of GAS-Na.
© 2003 Elsevier B.V. All rights reserved.

Keywords: Sodium guaiazulene sulfonate; Stabilization; A twin-screw extruder; The kneading paddle elements; Water; Uniformly dispersing

1. Introduction

Sodium guaiazulene sulfonate (GAS-Na), which has excellent anti-inflammatory and wound-healing properties, is a hydrophilic derivative of guaiazulene (GA). GA is an active component of the plant, “Matricaria chamomilla L.”, which has been used as self-medication for gastritis or canker sores for many years. GAS-Na is a comparatively unstable compound, which gradually decomposes in the solid state at room temperature. Acid compounds and oxidizing agents accelerate the decomposition of GAS-Na, mainly causing a reaction, where the sulfonic acid group is removed and GA is formed, as illustrated in Fig. 1. Acid compounds arising from the sulfonic acid group and GA following decomposition, which is oily or in a paste state, promote the decomposition of GAS-Na. Some measures to combat this unwanted behavior have been tried. Anti-oxidants and weak basic metallic salts or alkaline-earth metals were employed as stabilizing agents by Kohlstaedt et al. [1] while, an amino acid was added by Ohara et al. [2]. Also, as shown by Kawamata et al. [3,4], spray-drying or freeze-drying aqueous solutions of GAS-Na containing a polymeric excipient such as polyvinyl pyrrolidone (PVP) stabilized GAS-Na as far as pharmaceutical processing was concerned.

A twin-screw extruder is a type of extrusion granulator with heating units, in which kneading paddle elements produce a marked shear effect on materials. Using this apparatus, we have prepared a number of pharmaceutically useful formulations, such as solid dispersions [5,6] and

* Corresponding author. Pharmaceutics Research Laboratory, Nippon Shinyaku Co., Ltd., 14, Nishinosyou-Monguti-cho, Kisshoin, Minami-ku, Kyoto 601-8550, Japan. Tel.: +81-75-321-9124; fax: +81-75-321-9038.
E-mail address: k.nakamichi@po.nippon-shinyaku.co.jp (K. Nakamichi).

0939-6411/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0939-6411(03)00100-0

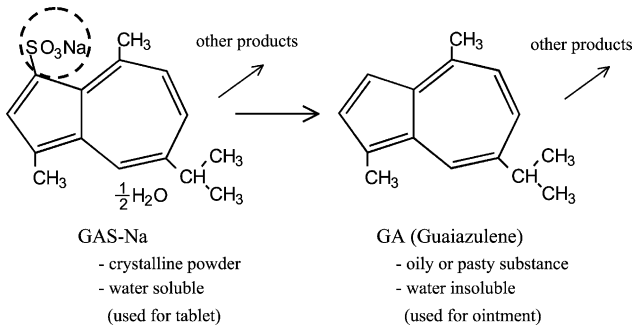

Fig. 1. Decomposition reaction of GAS-Na.

floating dosage forms [7]. Also, some sustained release systems have been prepared using this apparatus [8–11].

In the present study, we studied the physicochemical properties of GAS-Na relevant to its stability and tried to find appropriate methods to prepare a stable tablet formulated with conventionally used excipients, such as lactose, cornstarch, polyvinyl alcohol (PVA) and PVP. The effect of water on the stability of GAS-Na was discussed, and the usefulness of kneading paddle elements equipped with a twin-screw extruder was investigated to improve the stability of GAS-Na in the formulation for tableting.

2. Materials and methods

2.1. Materials

GAS-Na, which is a dark blue crystal or crystalline powder with a melting point of 108–110 °C, was synthesized at Nippon-Shinyaku Co., Ltd. GA, which is an oil or a paste at room temperature, was supplied by Alps Pharmaceutical Ind. Co., Ltd., Gifu, Japan. PVA (GOHSENOL EG-05, The Nippon Synthetic Chemical Industry Co., Ltd. (NIPPON GOHSEI)) and PVP (PLASDONE K-90, Gokyo Industrial Co., Ltd.) were used as polymeric excipients. All other excipients like lactose and cornstarch were of Japanese Pharmacopoeia grade or Japanese Pharmaceutical Excipients grade.

2.2. Preparation of four kinds of tablets containing GAS-Na

The formulation is given in Table 1 and a flowchart of the preparation is shown in Fig. 2.

Table 1
Formulation for extruding and granulating

GAS-Na	2 (g)
Lactose	300 (g)
Cornstarch	175 (g)
L-HPC (LH-11)	25 (g)
PVA	10 (g)
Total	512 (g)

(+H_2O~).

Screw granulating, fluidized bed granulating, and twin-screw extruding shown below were used to obtain powder or granules for tableting. Screw and fluidized bed granulatings were employed to prepare conventionally the tablets as a reference for twin-screw extruding granulation. Granules (each weighing 335 mg) were compressed using a press (autograph AG-5000A, Shimadzu; compression speed, 50 mm/min; load weight, 1000 kgf/cm^2) to form a flat-faced tablet of 10 mm in diameter.

Four types of tablet were prepared:

(A) Direct compression tablet prepared without water (named tablet A).
(B) Tablet prepared through screw granulation with water (named tablet B).
(C) Tablet prepared through fluidized bed granulation (named tablet C).
(D) Tablet prepared through twin-screw extrusion (named tablet D).

2.2.1. The granulation process using a screw granulator

The mixture containing GAS-Na shown in Table 1 was mixed with water for 10 min using a kneader (KDH-3, Fuji Paudal Co., Ltd.) and extruded at a speed of 30 rpm using a screw granulator (EXK-1, Fuji Paudal Co., Ltd.) with a screen having a 1 mm∅ aperture. When kneading the mixture, the weight ratio of water added to the material was 12.5 or 30%, based on the weight of dry powder. After drying in a hot-air circulating oven (Model GT-100; ALP Co., Ltd.) for 3 h at 45 °C, the extruded material was crushed using a sample mill (AP-S, Hosokawa Micron) with a screen having a 2 mm∅ aperture to obtain the powder for tableting.

2.2.2. The fluidized bed granulation process

The mixture containing GAS-Na (Table 1) was granulated with PVA aqueous solution (8% w/v, 125 mL) using a fluidized bed granulator (Multiplex MP-01, Powrex Corporation) to obtain the granules for tableting. The operating conditions were as follows: inlet temperature, 70 °C; spray rate, 5 mL/min.

2.2.3. The extrusion process using a twin-screw extruder (KEX-30, Kurimoto Co., Ltd.)

As is the case of the screw granulator, the mixture was mixed with 12.5% water, based on the weight of dry powder. The wet mixture containing GAS-Na was extruded using a twin-screw extruder in Fig. 3. After drying in a hot-air circulating oven, the material was crushed using a sample mill to obtain the powder for tableting as described above. The operating conditions were as follows: die diameter, 1 mm∅ × 5 holes; powder feed, 30 g/min; barrel temperature, 50 °C; revolution speed, 50 rpm. The kneading paddle elements, with twist angles of 30° and 60°, were positioned at the fourth barrel as employed in a previous study for the preparation of a solid dispersion [5,6]. Also, the experiment was conducted to demonstrate the role

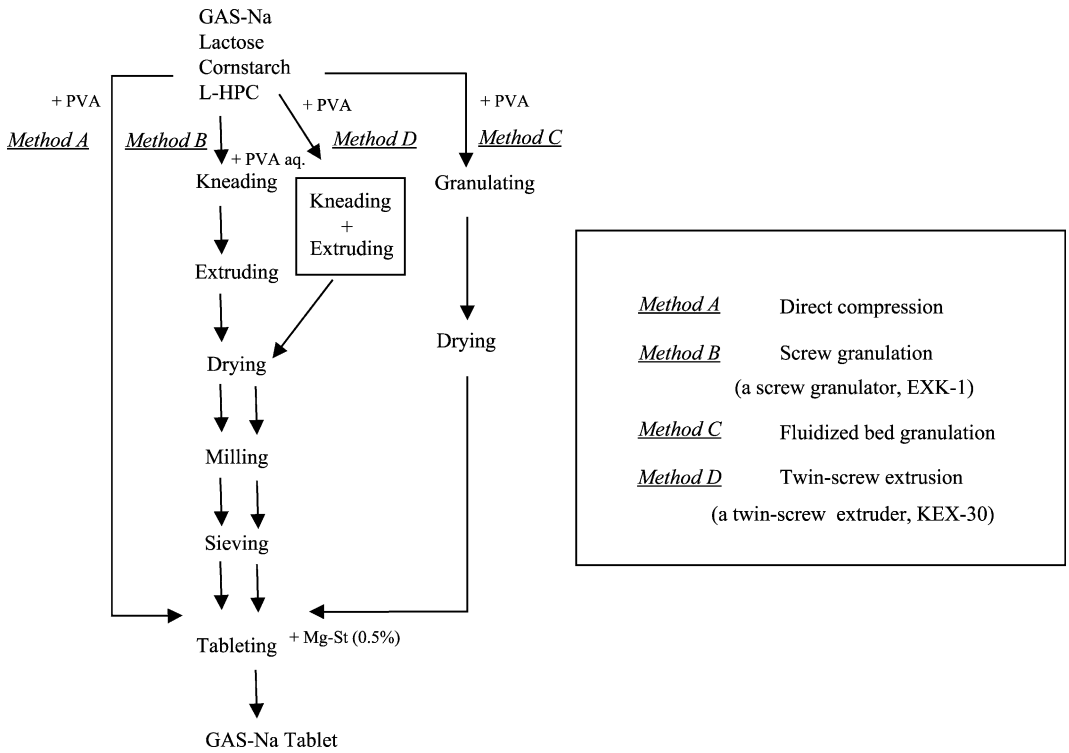

Fig. 2. Flowchart of preparation of various GAS-Na tablets.

of the kneading paddle elements, in which the extruder consisted of the feed screw elements alone without the kneading paddle elements.

2.3. Kneading in a mortar

A mixture of GAS-Na and an excipient (weight ratio; 1:250 (0.4 g:100 g)) was kneaded in a mortar, based on wet massing with water. The weight ratio of the purified water used was as follows: 20 and 50% for lactose and cornstarch, based on the weight of dry powder, respectively. As described above, after drying in a hot-air circulating oven, the material was crushed using a sample mill.

2.4. Extruding a mixture of GAS-Na and cornstarch

A mixture of GAS-Na and cornstarch (weight ratio; 1:20) was extruded using a twin-screw extruder to investigate the crystalline form of GAS-Na after processing. The experimental conditions were the same as in Section 2.2.3. After drying in a hot-air circulating oven, the material was crushed using a sample mill.

2.5. Coevaporation of a mixture of GAS-Na with a polymeric excipient

A mixture of GAS-Na and a polymeric excipient i.e. PVP and PVA (weight ratio; 1:5) was dissolved in ethanol and aqueous ethanol (ethanol:water = 4:6), respectively. This solution in a round type flask was evaporated at approximately 40 °C in a water bath (THB-7, Asahi Techno Glass Corporation) using a rotary evaporator (N-NK, Tokyo Rikakikai Co., Ltd.), with a circulator (CA-1100, Tokyo Rikakikai Co., Ltd.) and a diaphragm vacuum pump

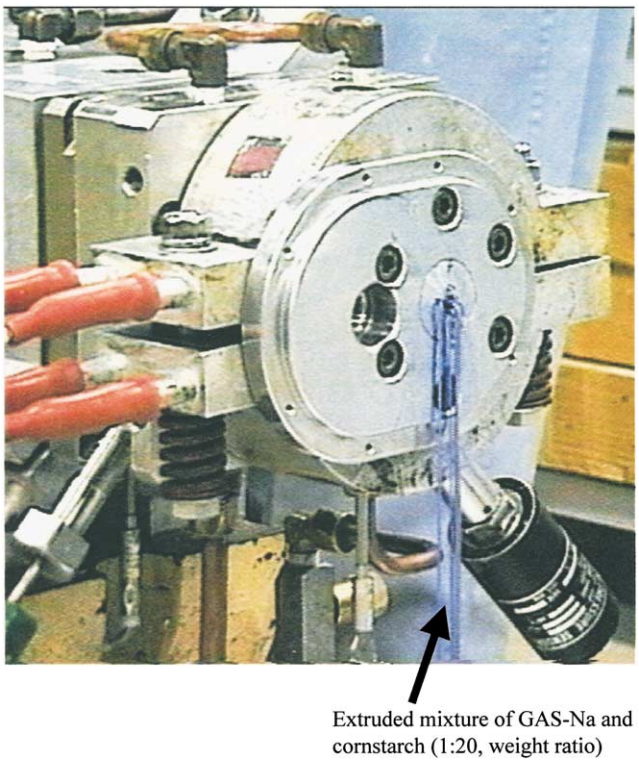

Fig. 3. Photograph of the outlet of the twin-screw extruder.

(MZ2C, Vacuubrand GMBH). After evaporating under reduced pressure, the coevaporated material was crushed using a small milling machine (Konishi Co., Ltd.).

2.6. Evaluation of stability of GAS-Na and physicochemical properties

The prepared tablets and the granules containing GAS-Na were stored under heated (40 °C 6% RH, 50 °C < 1% RH) and moist (40 °C 75% RH) conditions. The chemical stability was evaluated by measuring the content of GAS-Na and GA, i.e. the main decomposition product. A sample equivalent to 40 mg GAS-Na was added to 50 mL of the mixture of methanol and water (weight ratio; 6:4) to extract GAS-Na. An aliquot was filtered through a membrane filter (0.45 μm pore size, MILEX-HA, Millipore) and then added to a methanolic solution of internal standard (4 mg/mL, di (2-ethylhexyl) phthalate). The concentrations of GAS-Na and GA were measured by high-performance liquid chromatography (HPLC), using LC-10 AS and SPD-10A equipment (Shimadzu, Japan). The HPLC analysis conditions are as follows: mobile phase, methanol/water 17:3 (v/v) mixture containing 0.003 M tri-*n*-octylamine, adjusted to pH 6.0 with acetic acid; flow rate, 0.7 mL/min; reverse-phase column (Cosmosil 5C18-AR, 4.6 mm I.D. × 150 mm; Nakalai) at 50 °C; UV detector wavelength, $\lambda = 285$ nm.

The physicochemical properties of GAS-Na and two kinds of GAS-Na aqueous solution (purified water, 0.1 N HCl aq.) were also measured after a 4 week-storage. A 0.5 mL GAS-Na aqueous solution (20 mg/mL) was added to 0.5 mL 0.2 N HCl aq. or purified water to give a concentration of 10 mg/mL. The samples were then transferred to glass ampoules and sealed under nitrogen/air.

The moisture content of the powder was measured using a moisture analyzer (EB-280MOC, Shimadzu).

Powder X-ray diffraction patterns were obtained by a diffractometer (RAD-2B, Rigaku, Tokyo), using Cu-Kα radiation and a nickel filter. The operating conditions were as follows: voltage, 40 kV; current, 20 mA; and scanning speed, 4°/min.

3. Results and discussion

3.1. Chemical stability of intact GAS-Na

The stability of intact GAS-Na is shown in Fig. 4. Changes in the GAS-Na content in a temperature-controlled room are shown in Fig. 4 (1). Under heated conditions (40°C 6% RH, 50 °C < 1% RH), almost all the GAS-Na decomposed within 1 week. On the other hand, under moist conditions (40 °C 75% RH), no change in GAS-Na content was observed, and no GA was produced after 4 weeks.

The GAS-Na used is a hemihydrate and the water molecules play a role in the crystal formation, whereas the anhydrate has never been reported in the literature. Kitamura et al. [12] confirmed that cefixime trihydrate

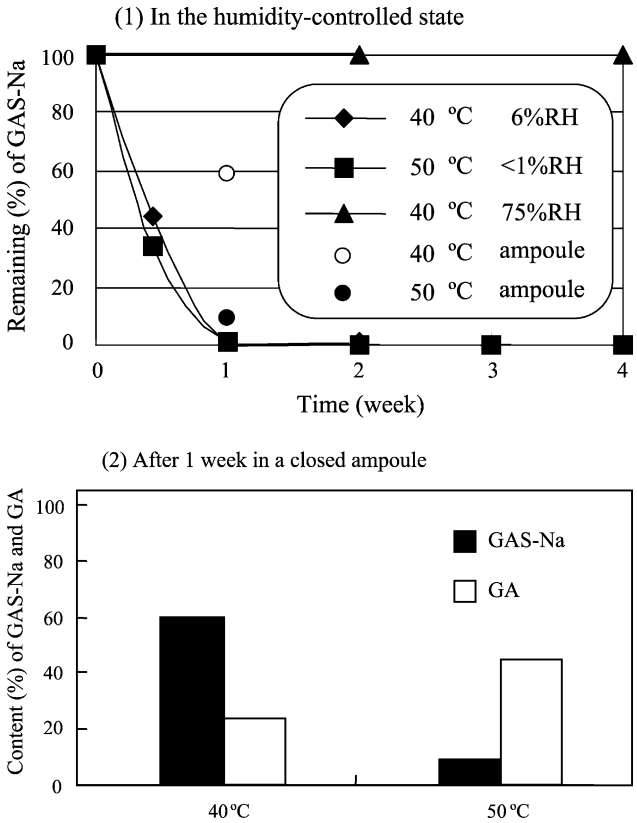

Fig. 4. Effect of heat stress on the stability of GAS-Na in the solid state. In the humidity controlled state (1); after 1 week in a closed ampoule (2).

becomes chemically unstable on storage below the critical relative humidity, because cefixime trihydrate is partly transformed into the anhydrous form by dehydration, which causes disorder of the crystalline structure and promotes decomposition. GAS-Na might have similar decomposition characteristics.

The GAS-Na and GA contents in a glass ampoule after 1 week are shown in Fig. 4 (2). As a result, GAS-Na remained and volatile GA was contained in the ampoule. It is likely that sealing a glass ampoule under nitrogen/air restricts the amount of oxygen to cause decomposition and moisture to stabilize GAS-Na retards the decomposition.

Changes in the GAS-Na content of the GAS-Na aqueous solution (10 μg/mL) put into a glass ampoule at 50 °C are shown in Fig. 5. This shows the stability of GAS-Na in two types of solution: purified water, 0.1 N HCl aq. Compared with the stability in the solid state, the decomposition was very slow in aqueous solution. Yuki et al. [13] showed that there is specific acid catalysis of GAS-Na. Similarly, under the acidic conditions in this experiment, decomposition was rapid.

3.2. Effect of conventionally used excipients on the stability of GAS-Na

Kneaded mixtures of GAS-Na and an excipient (lactose or cornstarch) in a mortar were stored at 50 °C

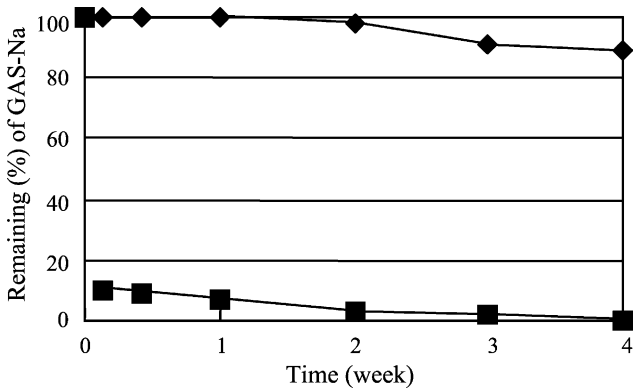

Fig. 5. Effect of heat stress on the stability of GAS-Na at 50 °C in the aqueous solution (10 μg/mL) (◆) and 0.1 N HCl aqueous solution (■).

and the stability was evaluated. The GAS-Na and GA content after 1 week in each excipient is shown in Fig. 6. In the case where lactose was used, almost all the GAS-Na decomposed while no decomposition took place when cornstarch was used. The moisture content of the cornstarch (11.9%) was higher than that of lactose (less than 0.1%). Considering the stability under moist conditions, it is possible that water in the sample affects the stability of GAS-Na. Accordingly, in subsequent experiments related to the stability of GAS-Na, the moisture content of the samples prepared was kept between 3 and 4%.

3.3. Stability of various tablets containing GAS-Na

Three kinds of tablets were prepared in a different manner: direct tableting (tablet A), tableting via screw granulation (tablet B), and tableting via fluidized bed granulation (tablet C). Changes in the GAS-Na content of these tablets under heated conditions are shown in Fig. 7.

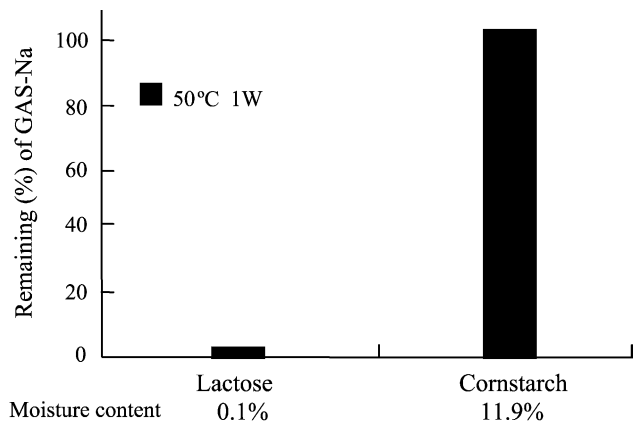

Fig. 6. Effect of excipients on stability of GAS-Na after 1 week at 50 °C (<1% RH).

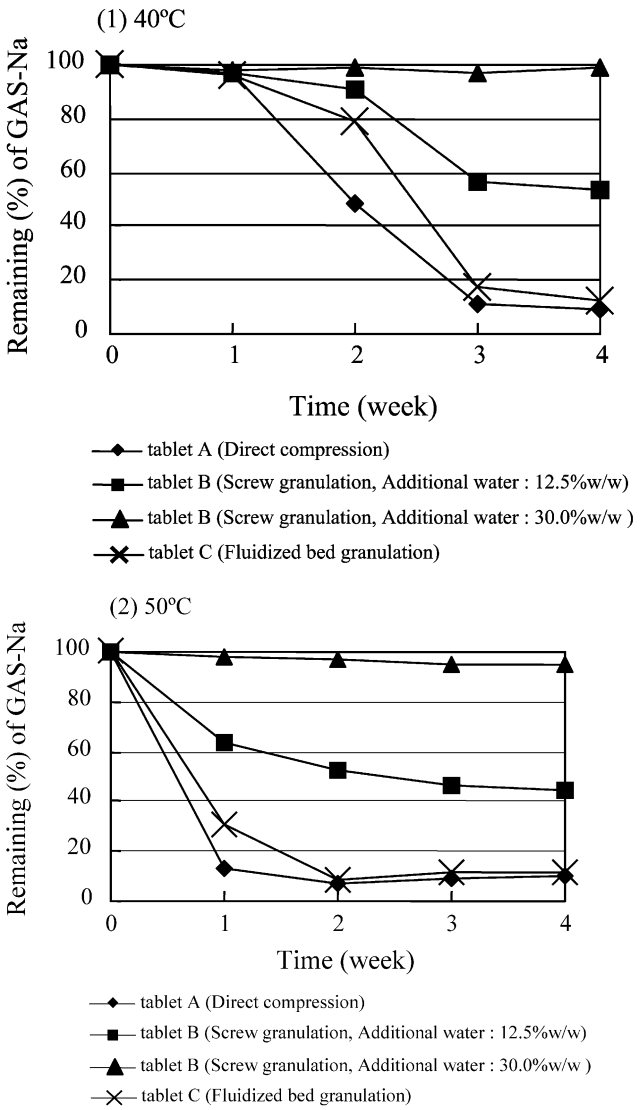

Fig. 7. Effect of heat stress on the stability of a GAS-Na tablet prepared by various methods. 40 °C (1); 50 °C (2). ◆, tablet A (direct compression); ■, tablet B (screw granulation, additional water: 12.5% w/w); ▲, tablet B (screw granulation, additional water: 30.0% w/w); ×, tablet C (fluidized bed granulation).

Tablet A (direct tableting) and tablet C (tableting via fluidized bed granulation) decomposed almost completely in 3 weeks, while tablet B (tableting via screw granulation) decomposed gradually. Furthermore, the stability of tablet B was affected by the amount of water added to the kneading materials. When adding a fixed amount of water (corresponding to 30% water), more than 95% of the GAS-Na remained after 4 weeks of storage. Direct tableting is conducted in a dry state. Also in fluidized bed granulation, water sprayed evaporates rapidly. Screw granulation, however, is conducted in a wet state. It is found that the production process (especially kneading and extruding using water) can affect the stability of GAS-Na in a tablet, which contains 3–4% water.

3.4. Stability of tablet D prepared through twin-screw extrusion (stabilization of GAS-Na with a twin-screw extruder)

The stability of GAS-Na in tablet B depends on the amount of water used for kneading and extruding. This could be related to the dispersibility of GAS-Na into an excipient during kneading and granulating. Therefore, a twin-screw extruder, which has an excellent kneading effect, was employed for stabilizing GAS-Na. Changes in the GAS-Na content of tablet D under heated conditions are shown in Fig. 8, where tablet B was used as references. It was found that tablet D was stable even when a small amount of water (corresponding to 12.5%) was added for kneading, while tablet B was unstable. In addition, when the kneading paddle elements were detached from the screws and only the feed screw elements were operated, GAS-Na was unstable. Yoshinaga et al. [14] reported that the screw disposition of the kneading paddle elements affected the residence time distribution, which was monitored by the marker tracking method. Tablet D prepared with kneading paddle elements is evenly vivid blue (reddish purple) colored, compared with tablet B. It is assumed that GAS-Na was uniformly dispersed due to the intense shear force caused by the kneading paddle elements during extrusion.

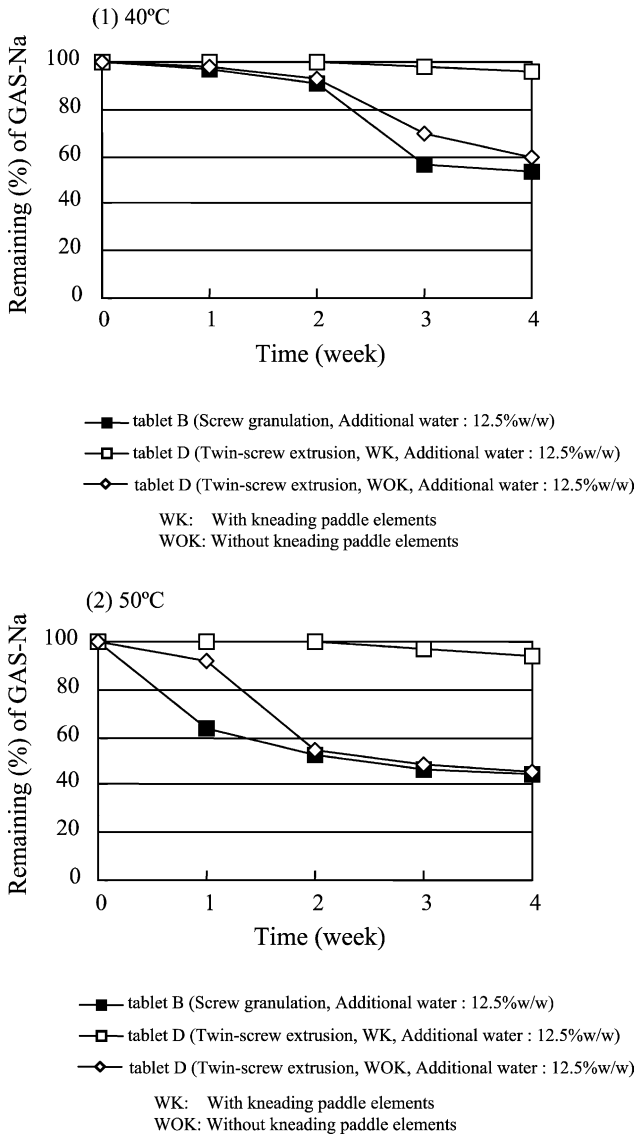

Fig. 8. Effect of heat stress on the stability of a GAS-Na tablet prepared with a twin-screw extruder. 40 °C (1); 50 °C (2). WK, with kneading paddle elements; WOK, without kneading paddle elements. ■, tablet B (screw granulation, additional water: 12.5% w/w); □, tablet D (twin-screw extrusion, WK, additional water: 12.5% w/w); ◇, tablet D (twin-screw extrusion, WOK, additional water: 12.5% w/w).

3.5. Discussion

It was found that a number of processes and conditions, such as the amount of water used, affect the stability of GAS-Na. To investigate the crystalline form of GAS-Na in kneading and granulating, a mixture of GAS-Na and cornstarch (weight ratio 1:20) was extruded using a twin-screw extruder (Fig. 3). The mixture kneaded in a mortar was also used as a reference. The powder X-ray diffraction patterns of recovered samples and their physical mixture are shown in Fig. 9. No crystalline peaks of GAS-Na were observed after twin-screw extruding. Meanwhile, crystalline peaks were observed after kneading in the mortar. Considering that the kneaded mixture was stable as shown in Fig. 6, it is thought that the water dispersibility in the mixture influences the stability much more than the crystallinity of drug. To examine the chemical stability of GAS-Na in a solid dispersion, two kinds of coevaporate were prepared and their stability was evaluated. The coevaporate of PVA and PVP contained 0.7 and 10.8% water, respectively. As shown in Fig. 10, in the case where PVA was employed, crystalline peaks of GAS-Na were observed in the powder X-ray diffraction experiment, and the GAS-Na decomposed under heated conditions (50 °C). On the other hand, in the case where PVP was employed, the crystalline peaks of GAS-Na disappeared in the powder

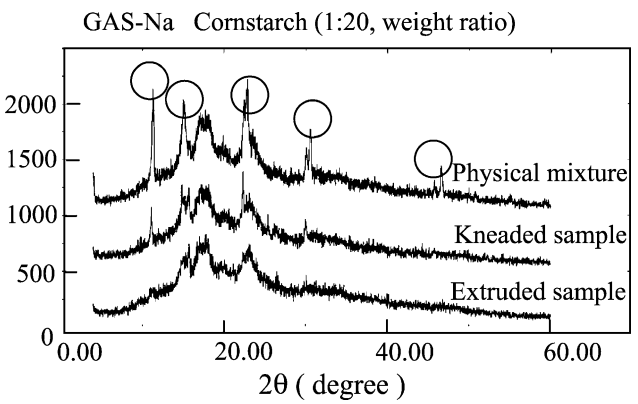

Fig. 9. Comparison of the crystallinity of kneaded/extruded samples with a physical mixture of GAS-Na and cornstarch.

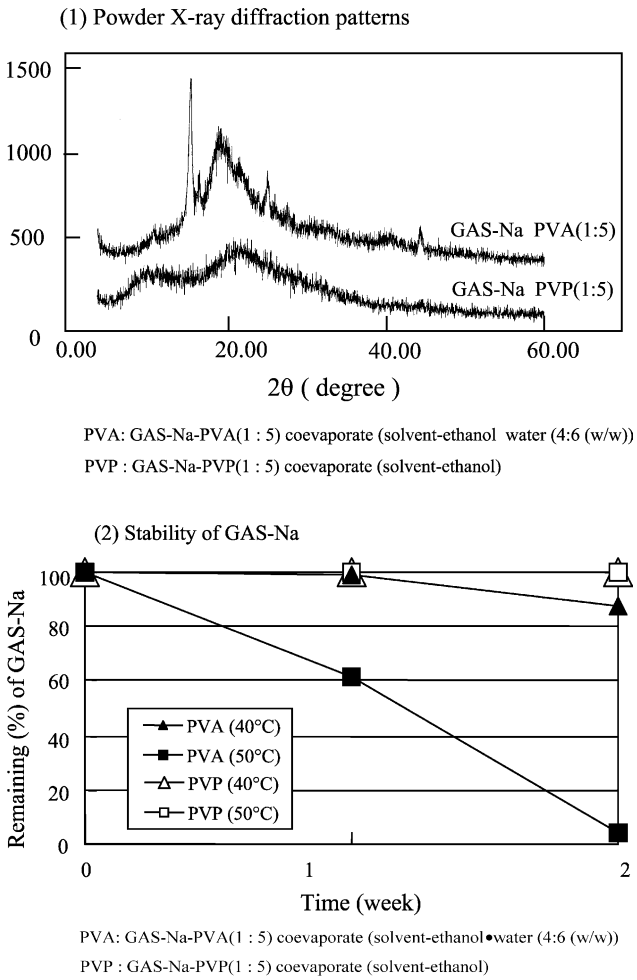

Fig. 10. Crystallinity and stability of GAS-Na coevaporate prepared by the solvent evaporation method. Powder X-ray diffraction patterns (1); stability of GAS-Na (2). PVA, GAS-Na-PVA(1:5) coevaporate (solvent—ethanol/water (4:6 (w/w)); PVP, GAS-Na-PVP(1:5) coevaporate (solvent—ethanol).

X-ray diffraction experiment, and GAS-Na was stable under the same conditions.

It is generally thought that a crystalline form is more stable than an amorphous form as far as the chemical and physical aspects of a compound are concerned, and Pikal et al. [15] demonstrated that the crystalline forms of β-lactam antibiotics are chemically more stable than their amorphous counterparts. However, GAS-Na has unique chemical stability characteristics in that the aqueous state is more stable than the solid state. In the case of a solid dispersion, where GAS-Na is stable, water molecules could be adsorbed or absorbed more uniformly to GAS-Na molecules than other states. Besides, polymer molecules could protect GAS-Na from reactants such as oxygen.

The decomposition reaction of GAS-Na is self-catalytic, and yields liquid products such as GA. Furthermore, various factors interact, and promote decomposition. Considering that a coevaporate with PVP and an extrudate with cornstarch were stable, it is assumed that, by forming an amorphous form and a solid dispersion, the moisture in the excipients readily acts as a stabilizing agent and combats the unfavorable of oxygen and some acidic products leading to decomposition. Even if GAS-Na is in an amorphous state, which is normally thought to be unstable thermodynamically, it is not always unstable. Therefore, in future, the twin-screw extrusion technique should be suitable for compounds with similar properties.

3.6. Conclusion

GAS-Na, which exhibits marked decomposition, is stabilized by the presence of water in excipients. Also, formation of a solid dispersion with specific excipients results in stabilized GAS-Na. Processes such as kneading and granulating with added water improve the stability of GAS-Na. Furthermore, using a twin-screw extruder, not a screw granulator, GAS-Na was stabilized even when a small amount of water was added. Kneading paddle elements in the twin-screw extruder are useful for reducing the amount of water added during the preparation of granules for tableting to maintain the stability of GAS-Na.

References

[1] E. Kohlstaedt, W. Schmidt, Verfahren zur Herstellung stabiler Praparate wie Puder, Tabletten, Dragees u.dgl.mit einem Gehalt an guajazulensulfosauren Salzen, Germany Patent 1034327, 1958.
[2] K. Ohara, Y. Tachibana, Manufacturing method of stable sodium guaiazulene sulfonate, Japan Patent S49-11219, 1974.
[3] M. Kawamata, K. Ushimaru, H. Gohshi, H. Miyasako, Stabilization method of azulene derivatives, Japan Patent H01-50225, 1989.
[4] M. Kawamata, K. Ushimaru, H. Gohshi, H. Miyasako, Stabilization method of azulene derivatives, Japan Patent H01-50226, 1989.
[5] K. Nakamichi, H. Yasuura, H. Fukui, M. Oka, S. Izumi, T. Andou, N. Shimizu, K. Ushimaru, Preparation of nifedipine-hydroxypropylmethylcellulose phthalate solid dispersion by twin screw extruder and its evaluation, J. Pharm. Sci. Technol. Jpn. 56 (1996) 15–22.
[6] K. Nakamichi, T. Nakano, H. Yasuura, S. Izumi, Y. Kawashima, The role of the kneading paddle and the effects of screw revolution speed and water content on the preparation of solid dispersions using a twin-screw extruder, Int. J. Pharm. 241 (2002) 203–211.
[7] K. Nakamichi, H. Yasuura, H. Fukui, M. Oka, S. Izumi, Evaluation of a floating dosage form of nicardipine hydrochloride and hydroxypropylmethylcellulose acetate succinate prepared using a twin-screw extruder, Int. J. Pharm. 218 (2001) 103–112.
[8] W. Mueller, R. Spengler, S. Grabowski, A. Sanner, Solid pharmaceutical retard form, European Patent EP 0544144, 1992.
[9] N. Follonier, E. Doelker, E.T. Cole, Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs, Drug Dev. Ind. Pharm. 20 (1994) 1323–1339.
[10] N. Follonier, E. Doelker, E.T. Cole, Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials, J. Control. Release 36 (1995) 243–250.
[11] F. Zhang, J.W. McGinity, Properties of sustained release tablets prepared by hot-melt extrusion, Pharm. Dev. Technol. 4 (1999) 241–250.

[12] S. Kitamura, A. Miyamae, S. Koda, Y. Morimoto, Dehydration effect on the stability of cefixime trihydrate, Int. J. Pharm. 59 (1990) 217–224.
[13] T. Yuki, K. Kakemi, I. Matsuura, M. Sugiyama, Stability of sodium azulenesulfonate and guaiazulene in solutions, J. Pharm. Sci. Technol. Jpn. 50 (1990) 89–93.
[14] M. Yoshinaga, S. Katsuki, M. Miyazaki, L. Liu, S. Kihara, K. Funatsu, Mixing mechanism of three-tip kneading block in twin screw extruders, Polym. Eng. Sci. 40 (2000) 168–178.
[15] M.J. Pikal, A.L. Lukes, J.E. Lang, Thermal decomposition of amorphous β-lactam antibacterials, J. Pharm. Sci. 66 (1977) 1312–1316.